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Organizers: Carmine M. Carapella, Gaetano Finocchiaro, Giorgio Perilongo, Riccardo Soffietti
Glioblastoma multiforme is among the most devastating tumors, associated with a high rate of recurrence, despite intensive treatment regimens. Temozolomide (TM) is a cytotoxic alkylating agent currently investigated in clinical trials in the treatment of recurrent malignant gliomas. TM has shown antitumor activity in glioblastoma patients, in particular in patients with progression-free survival (PFS) and improving quality of life. A phase I study was designed in February 1998, for the treatment of adult patients (>18 years) with newly diagnosed supratentorial GBM: patients will receive surgery + radiotherapy (60 Gy-30 fractions-40 days) + TM, administered after two months orally in 5 day dose schedule (repeated every 28 days). Patients received for the first cycle 150 mg/m2/day p.o., and for the other cycles 200 mg/m2/day. The aim of the study was to determine the safety and efficacy of TM in this patient population. The study started on April 1998. We have enrolled 9 patients, mean age 60 years, who received 41 cycles. Two patients received one course, two patients two courses, four patients six courses. TM showed a low toxicity, without hematological adverse events, the most common ones being headache, fatigue, constipation, tiredness and malaise. We used a premedication with tropisetron, 1 mg/po, so we had no nausea or vomiting. Until now tumors progressed in three patients after 6, 10 and 14 months. One patient is alive with disease at 17 months from surgery, with partial response after 4 cycles, and progression of the tumor after 8 cycles.

2. PRIMARY INTRACRANIAL GERMINOMAS: OUR EXPERIENCE ON TWO CASES TREATED BY CHEMOTHERAPY

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Intracranial germinomas represent about two-third of intracranial germ-cell tumors. Their histology are similar to the germinal cancers located in extraneural sites. Commonly seen in the pineal region or in the suprasellar cistern, involvement of both sites, either sequentially or simultaneously, occurs rarely. Subependymal extension may occur, but if no evidence of cerebrospinal fluid (CSF) seeding has been shown, patients are considered to have synchronous lesions and not metastatic disease (multifocal germinomas). Standard treatment is focal irradiation and prophylactic craniospinal radiotherapy (RT). Recently, it has been attempted to use chemotherapy (CT) to avoid the late effects of craniospinal RT and to decrease the focal irradiation dose. Others used direct CT with a more intensive and prolonged administration. We present two patients affected by intracranial germinomas treated between 1998 and 1999. A 21-year-old male patient with a suprasellar tumor and multifocal extension was diagnosed by open biopsy (case 1). A 19-year-old male patient with a pineal and hypothalamic mass was considered as having germinoma on the basis of clinical and neuroradiologic signs (case 2). Staging included MRI craniospinal evaluation, chest X-ray, and bone scan. CSF markers level determination (o-FP, HCG). No patients had CSF or spinal dissemination. The first patient received 6 courses of CT with Cisplatin, Vinblastine and Bleomycin (DDP-VBL-BLM) with a nearly complete remission. At recurrence, a modified version of CT was administered with Cisplatin, Etoposide and Bleomycin (DDP-VPE6-BLM). The other patient was directly submitted to Etoposide therapy (2 cycles) with remission. In both, intraventricular administration of Methotrexate (MTX) and Ara-C (ARA-C) was performed. MRI evaluation at 15 and 3 months after diagnosis, showed a second (case 1) and a first (case 2) complete remission. This combined treatment represent an application of the successful strategy of extraneural germinomas. It may be considered a valid therapy to avoid craniospinal RT and to reduce focal irradiation.

3. ANALYSIS OF PROGNOSTIC FACTORS AND SURVIVAL TIME IN HISTORICAL GROUP OF 49 PATIENTS WITH LOW-GRADE GLIOMAS

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Between 1982 and 1996 49 patients were treated with radiotherapy for low-grade gliomas in our institutions. The average age was 39 years, the median KPS 80. Ten patients (20.4%) underwent biopsy for histological diagnosis, 33 pts (67.3%) had partial surgical resection and 5 pts (10.2%) gross total resection. Nineteen pts (38.8%) received total dose >50 Gy, 30 pts (61.2%) <50 Gy with conventional fractionation. Carmustine (BCNU 200 mg po every six weeks) was administered in 7 pts; in 3 pts six cycles of PCV (Procarbazine, Vin- cristine, Lomustine) were used. Eleven pts underwent second surgery at the time of tumor progression: histological diagnosis of low-grade glioma was confirmed in 5 pts, 2 pts had diagnosis of GBM, 1 pt diagnosis of anaplastic astrocytoma. Survival rates at 2, 5, 10 years were 68, 49, 20% respectively. Histological type (oligodystrocytoma vs astrocytoma) has been found as a prognostic factor. Age, extension of tumor to both hemispheres, tumor volume in pre- irradiation treatment (CT) and CT time to tumor progression. We observed no correlation between total dose of radiotherapy and overall survival time. Treatment of low-grade glioma remains controversial; new possibilities could be offered by the evaluation of proliferation index and in addition to histology rather than by clinical prognostic factors.

4. INTEGRIN ALPHAVBETA3 MEDIATES THE ADHESIVE, MIGRATORY, AND PROLIFERATIVE ACTIVITY OF FHF-2 AND PDGF-BB IN GLIOMA CELLS IN VITRO

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Integrins are cellular receptors mediating several cellular responses such as adhesion, migration, proliferation, cell survival and apoptosis. Integrins can collaborate or synergize functionally with growth factors in a variety of biological processes. This study showed that alphaBeta3 mediates the adhesion and the biological activity of FGF-2 and PDGF-BB in human glioma cells in vitro. Several adhesion assays were performed in which U87-MG, U373-MG and U118-MG cells were placed on 96 wells onto increasing concentration of FGF-2 and PDGF-BB were seed and the number of adherent cell quantified using a MTT assay. The number of adherent cells significantly decreased when the cells were rocked with increasing concentration of LM609, vitronectin and tenascin, but not by increasing concentration of fibronectin or a anti-alphaBeta5 antibody. The same findings were also observed when increasing concentrations of a anti-FG-2 or anti PDGF-BB blocking antibodies or FGF-2 and PDGF-BB were added to the media or to the cells. The activity of alphaBeta3 and CSF matrix was further confirmed in WB experiments. Increasing concentrations of LM609, but not of anti alpha5Beta1 antibody, were also able of significantly reduced the FGF-2 and PDGF-BB dependent migration of glioma cells through the Boyden Chamber assays. LM609 was also able of reducing the FGF-2 and PDGF-BB dependent proliferation in a dose dependent manner in the same cells in vitro. Globally considered, these findings suggest integrin alphaBeta3 as an alternative signaling pathway capable of mediating the proliferative, migratory and adhesive activity of growth factors in glioma cells.
1. Bello, R. Carroll, P. Marthyn, D. Nikas, G. Tomei

**INDUCED ANGIOGENESIS IN VITRO**

Recent experimental evidence shows that angiogenesis and invasion are strictly associated. Angiogenesis and invasion are regulated at least in part by common mechanisms. One of these mechanisms involves the functional interaction between alphavBeta3 and MMP-2. This interaction is regulated by PEX, a fragment of MMP-2 through its binding with alphavBeta3. In this study we initially showed that alphavBeta3 and MMP-2 were co-localized at the surface of tumor astrocytes and endothelial cells in glioma in vivo and PEX was expressed with gliomas tissues in vivo. Expression correlated with histological grade, tumor type and alphavBeta3 expression. Then we purified PEX from cultured media of U87-MG and U373-MG human glioma cells. On U87 and U373 cells in vitro, PEX expression was modulated by FGF-2 and PDGF-BB but not by FGF-4 or VEGF. Neutralization of PEX activity was able of reducing glioma induced angiogenesis in a dose dependent manner in in vitro migration assays with Boyden Chambers. The administration of purified human PEX was able of reducing glioma induced angiogenesis in a dose dependent manner in in vitro angiogenic assays. The administration of PEX was also able of reducing tel to block in a dose dependent manner the migration of U87 and U373 glioma cells in Boyden Chambers. These findings suggest PEX as a new therapeutic agent able of reducing both angiogenesis and invasion in glioma.

2. **PEX REDUCES GLIOMA CELL MIGRATION AND GLIOMA INTRACRANIAL TUMOR FORMATION IN SUBCUTANEOUS AND INTRACRANIAL HUMAN GLIOMA XENOGRAFTS**

L. Bello, R. Carroll, P. Marthyn, D. Nikas, G. Tomei, A. Bifulki, D.A. Cherevec, P. Mcl Black, and R. Villani

Intracranial xenografts strongly expressed alphavBeta3, alphavBeta5 integrins, as well as growth factors. Cells located at the invasive borders were strongly positive for alphavBeta3 and FGF-2 as well as, even if at a lower level, for alphavBeta5 and VEGF. No differences were observed for beta1 integrins expression in both tumors. As for extracranial matrix components, tenasin and vitronectin were stronger expressed in intracranial tumors, whereas no differences were noted for fibronectin and laminin. When cells took from subcutaneous tumors were implanted intracranially in the same animals, they formed rapid growing tumors highly expressing alphav integrins as well as, that of some angiogetic growth factors was influenced by local microenvironment. This was confirmed by the decrease in alphav integrin expression as detected by PAGS analysis when glioma cells were cultured in the absence of vitronectin and tenasin.

3. **GENE THERAPY OF GLOBLASTOMAS BY INTERLEUKIN-4 (IL-4): TOWARD A CLINICAL TRIAL**

S. Benedetti, B. Piorla, B.M. Merciai, M.G. Bruzzone, S. Benvenega, B. Pollo, L. Magrassi

Retroviral-mediated gene transfer of the IL-4 gene causes the rejection of a large fraction of rat experimental glioblastomas (GBM). These findings support the clinical use of this form of gene therapy for GBM. Toward this goal, we have checked the effects of dexamethasone (Dex) on IL-4 gene therapy by injecting intracranially Fischer 344 rats - with or without subcutaneous osmotic pumps releasing 100 microg/kg/die of Dex - with phosphate buffer saline (PBS), 9L + retroviral producer cells (RPC) transducing IL-4 and 9L + SBA (control RPC). After 4 months all PBS/dex and 5/6 9L + IL-4 RPC/no Dex rats were alive. Control rats injected with 9L + SBA + Dex with or without Dex were all dead by day 40. The survival of 9L + IL-4 RPC rats with Dex was significantly longer than controls (p=0.0039) but only 1/6 rats survived at 4 months. To test the safety of IL-4 gene transfer in the brain we also injected rats with 4.5 x 106 IL-4RPC, an amount three times higher than that to be used clinically. Rats treated with 9L + IL-4RPC+Dex survived longer than control rats, but this difference was not statistically significant (p=0.0612).

4. **6. DIFFERENTIAL EXPRESSION OF INTEGRINS, ANGIOGENIC FACTORS, AND EXTRACELLULAR MATRIX COMPONENTS IN TANDEM WITH SUBCUTANEOUS AND INTRACRANIAL HUMAN GLIOMA Xenografts**

L. Bello, R. Carroll, P. Marthyn, D. Nikas, G. Tomei, A. Bifulki

Intracranial xenografts were implanted intracranially in the right hemisphere and in the right flank of nude rats. These cells rapidly formed tumors. Tumors located in the right flank were strongly positive for alphavBeta3 and FGF-2 as well as, they formed rapid growing tumors highly expressing alphav integrins as well as, that of some angiogetic growth factors was influenced by local microenvironment. This was confirmed by the decrease in alphav integrin expression as detected by PAGS analysis when glioma cells were cultured in the absence of vitronectin and tenasin.

5. **7. GENE THERAPY OF GLOBLASTOMAS BY INTERLEUKIN-4 (IL-4): TOWARD A CLINICAL TRIAL**

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6. **8. SNC 91: COOPERATIVE STUDY ON MEDULLOBLASTOMA IN CHILDHOOD. RESULTS**

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The "SNC91 medulloblastoma protocol" was formed by: 1. Pre-RT CT: HD-MTX (8 gr/sqm), VCR (1.5 mg/sqm), CRDCA (550 mg/sqm), VP16 (130 mg/sqm); 2. Hyperfractionated RT: 66 Gy delivered to P.F., 30 to W.B., 30 to 36 to axia; 1 Gy twice daily with 6 hours interval; in case of positive CSF cytology 40 Gy, plus 8 Gy to the seeding site; 3. Post-RT CT: "8 in 1" (4 cycles). Between January 1991 and December 1996, 55 pts were enrolled, and 53 evaluated: 34 M, 19 F; age 40-216 months (median: 111); 33 pts had total resections, 15 subtotal. In 5/6 girls and 5/6 boys, Metastatic disease was partial. In 5/6 girls and 5/6 boys, Tumor progression or recurrence occurred in 19 pts, at a median time from diagnosis of 14 months (range: 6-61). At May 31st 1999, 16 pts died (20.2%), 37 pts (69.8%) are alive, 35 of whom without evidence of disease. The overall survival is 67% disclose any major alteration. These results suggest that IL-4 gene therapy is safe and effective for the treatment of rat GBM but that high levels of Dex may interfere with the treatment. We are now assembling a retroviral vector for clinical use that will transduce human IL-4 and the HSV-tk gene, to be used as a tassafe trigger if excessive inflammation is generated by IL-4.

7. **9. LOCAL DELIVERY OF CHEMOTHERAPY IN RECURRENT MALIGNANT GLIAL TUMORS IS EFFECTIVE**

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We evaluated the outcome of 60 patients operated on for malignant glial tumors. The Ommaya reservoir was positioned into the residual mass independently of its volume. 46 out of them were managed with an adjunctive chemotherapeutic delivery and 14 did not receive local chemotherapy, because the tip of the catheter was in communication with CSF. Out of the treated patients, 20 were primary GBM (group A), 10 secondary GBM arising from grade III gliomas (group B) and 16 recurrent grade III both at the beginning and after tumor recurrence (group C). All patients, treated with a standard protocol, at tumor recurrence were given locally delivered
chemotherapy (mitoxantrone or carboplatin) added to a second dose of chemotherapy systemically delivered. The mean age of (A) patients was 50.2 years, the initial median TTP was 8.7 months and after recurrence, during the local chemotherapeutic treatment, the adjunc- tive TTP was 24 months; the median ST was 17.8 months and 42% of patients were 2-year survivors. The median ST of 14 GBL patients untreated locally was 13.7 months and 22% of patients were 2-year survivors. 10 pts (B) (mean age 44.8 years) had initial median TTP of 24 months; the median ST of 8.5 months and 42% were 2-year survivors. Sixteen patients (C) (mean age 41.6 years) had the initial TTP of 23.3 months with adjunctive TTP during local delivery of 13.4 months. The median ST was not reached, most of the patients being still alive; 68%, 43% and 37.5% were long survivors at 3-4 and 3 years respectively. We can finally assume that local delivery of chemotherapy after recurrence of the tumor possibly extends patient survival, but certainly increases the number of long-survivors.

10. PRIMARY NON-HODGKIN’S LYMPHOMAS OF THE CNS (PCNSL) TREATED WITH HIGH-DOSE METHOTREXATE AND CYTARABINE BEFORE RADIOThERAPY: THE MATR Patients


Purpose: To assess the efficacy of a chemotherapy regimen including high-dose methotrexate and cytarabine before radiotherapy in PCNSL. Patients and methods. Twenty-four immunocompe­tent patients were accrued to a protocol (MATR) that included: intravenous methotrexate 3 g/m2 X 2 every 3 weeks for 2 courses; intra­venous cytarabine 3 g/m2 X 2 every 3 weeks for 2 courses; intra­thalidomide methotrexate and cytarabine (6 doses, days 1 to 20); WBRT delayed at tumor progression in complete responders; WBRT 45 Gy + 14.4 Gy boost in partial responders, stabilized or progressive patients. Results: Ten patients completed the chemotherapy protocol, with a response rate of 70% (CR 30% and PR 40%). TTP of the 3 patients who had no RT was 12-26 months. Six patients had tumor progression during chemotherapy, and 5 had severe toxicity (grade 4 neurotoxicity or piastrinopenia in 4, renal failure in 1). Seventeen patients underwent radiotherapy: CR in 8/17 (47%), PR in 6/17 (35%); SD in 1/17 (6%); PD in 2/17 (12%). Median TTP after RT was 8.5 months (2 to 22 months). Conclusions: 1) The MATR regimen has a limited activity in PCNSL. 2) Chemotherapy alone may result in long term remission in some patients. 3) Salvage radiotherapy is effective in about a half of patients unresponsive to or progressing after chemotherapy.

11. CHEMOTHERAPY WITH TEMOZOLOMIDE IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS: PRELIMINARY EXPERIENCE

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Temozolomide (TMZ) has shown significant activity in phase II trials against malignant gliomas with very favorable toxicity profile, also in pretreated patients with recurrent gliomas. We report our preliminary experience of the use of TMZ in the treatment of 12 patients affected by recurrent malignant gliomas, including 5 glioblastoma, 5 anaplastic astrocytoma, 2 mixed anaplastic oligoastrocytoma. All patients presented recurrence after radiotherapy and had received prior chemotherapy (CT) with PCV in 7 cases, with thalidomide in 1 case. Four cases had not received prior CT. Age ranged from 30 to 66 years, Karnofsky 70-100. TMZ was given at a dose of 150 mg/m2/day for 5 days repeated every four weeks. The dose was not increased in pretreated patients, while in not pretreated patients the dose was escalated, if not myelosuppression was observed, at 200 mg/m2. A total number of 27 cycles of TMZ was given; two patients completed 6 courses of therapy. All 12 patients are valuable for toxicity. The treatment was well tolerated; no signifi­cant gastrointestinal toxicity was observed in one case. The response was valuable after 3 courses only in 4 patients with 2 partial response, 1 stable disease and 1 progressive disease. The data analysis in the literature as well as the preliminary data confirm that TMZ is a safe drug in recurrent malignant gliomas and justify further evaluation on larger series and randomized trials.

12. NEUROPROTECTION OF NEUROTOXICITY INDUCED BY CISPLATIN: THE ROLE OF VITAMIN E

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Peripheral neurotoxicity is the main non-hematological side-effect related to cisplatin chemotherapy, sometimes requiring the dis­continuation of treatment. To overcome these neurotoxic effects, scien­tists have recently focussed their attention on the potential ben­efits of neuroprotective drugs such as radioprotective agents WR 2721, ACTH analog and neurotrophic factors. On the basis of the significant similarity between clinical and neuropathological aspects in peripheral neuropathy induced by cisplatin and neurologic syn­dromes due to vitamin E deficiency, we investigated the relationship between cisplatin neuropathy and plasmatic level of vitamin E (α­tocopherol). We measured vitamin E in the plasma of 5 patients (group 1) with severe neurotoxicity induced by cisplatin treatment. In another group of 5 patients (group 2) we analyzed the plasmatic level of vitamin E before and after 2 or 4 cycles of cisplatin treatment. Serum level of vitamin E measured after the treatment with cisplatin, when the peripheral neuropathy was clinically evident, was low in all patients (mean 6.8 ng/ml ± 1.9; normal range values 10-12). Before treatment the basal mean level of vitamin E was 10.28 ng/ml and after at least 2 cycles of treatment with cisplatin (range 2-4) mean level was 6.56 ng/ml (p<0.01). The results of this study seem to support our hypothesis that low serum vit E concentration is related with peripheral neurotoxicity. We believe that clinical trials to test neuroprotective effects of vitamin E should be started.

13. THE ACTIVITY OF GEMCITABINE (GEM) IN RAT C6 MALIGNANT GLIOMA: IN VITRO AND IN VIVO PRELIMINARY DATA

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Gemcitabine (2',2'-difluorodeoxycytidine) is a deoxycytidine analogue showing a broad spectrum of cytotoxic activity against different solid tumors, largely dependent on the administration sched­ule. In addition, GEM, through continuous exposure to non-cytotoxic concentrations, is a potent radiosensitizer of rodent and human tumor cell lines. Only few data are presently available in the litera­ture regarding its activity on primary brain tumors. We are presently studying its in vitro and in vivo effects of gemcitabine in C6 rat malignant glioma. The effects of GEM on cell cycle progression, growth inhibition and induced-apoptosis in C6 cells were evaluated in vitro by flow cytometry, using the IC50 dose of 0.0025 μM (calculated after 24 h of continuous exposure). Treatment of C6 cells with this GEM concentration induces an increase of about 30% in the G0/G1 cell cycle phase percentages. 24 h after the end of treatment, GEM-treated cells showed an apoptotic rate of about 15%, which increased up to approximately 40% 24 h later (48 h after the end of treatment). In vivo experiments have been performed on Wistar bearing brain tumors, obtained after stereotactic injection of 5x105 C6 tumor cells. The drug was administered ip at 120 mg/Kg every 3 days x 4 doses. Treatment was started when tumor volume, docu­mented by MRI, was in a range from 10 to 100 mm3. The treated/control volume ratio was calculated to quantify the antitu­mor effect. In different series of experiments we could not observe any complete remission of brain tumor; we detected a moderate decrease of tumor volume, evaluated with MRI sequential evaluations; this effect is more relevant after the second dose of GEM treatment. On this basis further studies are warranted because GEM might present relevant interest in the combined treatment strategies for malignant gliomas.

14. HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM-CELL RESCUE (ASCR) IN PEDIATRIC MALIGNANT BRAIN TUMORS


Between May 1991 and March 1999, high-dose chemotherapy and ASCR were administered to 24 children with malignant brain tumors: 17 had recurrent or progressive disease and 7 had newly
diagnosed disease. Diagnosis comprised 8 medulloblastoma, 5 supratentorial PNET, 3 glioblastoma multiforme, 2 ependymoma, 2 anaplastic astrocytoma, 1 oligodendroglioma, 1 pinealoblastoma and 1 germ cell tumor. 17 patients had measurable disease at the time of ASCR. Preparative regimen included BCNU 600 mg/m2 and VP16 1500 mg/m2 in the first 5 cases; thiopeta 900 mg/m2 and VP16 1500 mg/m2 in other 19 cases. Patients received hematopoietic support with bone marrow (BM) (n=13), peripheral blood progenitor cells (PBPC) (n=37). The 13 patients supported with BM received a median of 1.2 x 10^6 (range 0.7-4.7) total nucleated cells (TNC)/kg, the 11 patients grafted with PBPC ± BM received a median of 5.3 x 10^6 (range 3.3-3.7) TNC/kg and a median of 5.6 x 10^3 CD34+ cells/kg, 17.9 x 10^3 CD3+ cells/kg, 0.9 x 10^2 LTC-IC/kg. The 100 days toxic mortality rate was 4% (1/24). The overall incidence of severe toxicity (grade III/IV) was 54% and consisted of mucositis (n=13), liver toxicity (n=2) and coetaneous rash (n=1). The median time to achieve ANC> 0.5 x 10^3/L and platelet count> 50 x 10^3/L was respectively 9 and 11 days respectively. Time to ANC engraftment was significantly longer (p<0.01) in children receiving BM (median 13 days) than for PBPC (median 10 days). Nine of 24 (37%) patients (n=2 medulloblastoma; n=2 ependymoma; n=2 glioblastoma; n=1 supratentorial PNET; n=1 pinealoblastoma; n=1 germ cell tumor) are alive and disease free at the median of 25 months (range 3-98) from transplant; the 5-year overall survival and event-free survival rates are 37% and 28% respectively. 5 of 7 patients with no evidence of disease before the transplant survive progression free compared with only 4 of 17 patients with bulky disease.

15. INTRACRANIAL GERM CELL TUMORS: PRELIMINARY RESULTS OF SIOP CNS GCT 96 STUDY

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Objectives: The SIOP CNS GCT study aims to: standardize diagnosis and treatment of CNS GCTs. Secreting GCTs: combined treatment with 4xPET and irradiation (focal/craniospinal) is administered. Nonsecretors: Carboplatin-radiotherapy is compared to craniospinal irradiation only. Patients: 100 pts are enrolled (10/96 to 02/99), D 51, GB 27, 19, NL 6, other 7, 54 germinoma, 41 secreting tumors and 4 teratoma (Unclear diagnosis: 1 pt). Treatment: Germinoma: 33 received radiotherapy only and are discussed separately. 21 pts had combined treatment. 18/21 were protocol pts (chemo-focal/craniospinal irradiation) 6/18 received chemo-craniospinal radiation because of metastases. Secreting GCTs: 38/41 were protocol pts. 24 had chemo-focal radiotherapy (Option B), 14 received craniospinal irradiation (Option A) because of spinal mets and/or pos. CSF cytology. Results: Germinoma: 17/18 pts are in CCR, (EFS: 80% and 20% observation time: 1-18 mo). 1 pt is in CCR after additional therapy (local relapse). Secreting GCTs: 12/14 pts (Option A) are in CCR, (1 pt with progression and DOD, 1 pt DOF). EFS is 68%+ 25% observation time: 1-22 mo. 20/24 pts (Option B) are in 1 CCR (2 local rel, 2 local + distant rel), all pts DOD. p27 expression has been studied. In non-glial GCTs p27 was expressed in 26% of non-secreting GCTs, 85% of secreting GCTs and 95% of teratoma. In 72 non-secretors, p27 was not expressed. In medulloblastomas and other non neoplastic CNS pathology. In a multi-institutional study p27 expression in 26% of non-secreting GCTs, 85% of secreting GCTs and 95% of teratoma. In 72 non-secretors, p27 was not expressed. In medulloblastomas and other non neoplastic CNS pathology. In a multi-institutional study p27 expression was not present, suggesting that the real incidence of p27 mRNA expression was higher than that observed by in situ hybridization.
19. ADJUVANT HIGH-DOSE SEQUENTIAL CHEMOTHERAPY (CT) PLUS HYPERFRACTIONATED-ACCELERATED RADIOTHERAPY (HART) IN CHILDHOOD MEDULLOBLASTOMA

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Objectives: Conventional CT did not ameliorate significantly the outlook for medulloblastoma. Increased dose intensity has been correlated with response rate and survival in many solid tumors. To lessen the severe age-related sequelae from standard dose RT to neurosurgical care, we developed the in vitro efficacy to improve tumor control compared with standard dose RT recommendations. We employed the sequential high-dose and infusional high-dose chemotherapy regimen acceptable 40 Gy in children younger than 10 yrs, and 39 Gy in older ones. The posterior fossa always received 60 Gy during this pre-radiation phase. At the time of this analysis, 20/23 pts remained alive without progressive disease, with a median follow-up of 14 mos (2-yr EFS probability: 80%). The median duration of pre-radiation CT was 60 days. No CT course was complicated by neutropenia > 8 days; 70% of patients required antibiotic therapy and 60% transfusional support. Conclusions: The response rate to CT was very promising. The toxicity of this regimen was acceptable and administration of multiple courses of high-dose CT showed to be feasible within scheduled times. The planned HART program could be then delivered without delays or major complications. This approach is under investigation, as far as therapeutic results are concerned. Partially supported by Associazione Bianca Garavaglia, Busto Arsizio VA

20. DIFFERENT INTRACELLULAR MECHANISMS ARE AT THE BASIS OF APOPTOSIS INDUCED BY 2-CHLORO-ADENOSINE AND 2-CHLORO-2'-DEOXY-ADENOSINE (CLADRIBINE) IN HUMAN ASTROCYTOMA ADF CELLS

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The purine derivative 2-chloro-2'-deoxyadenosine (Cladrabine; 2-CdA) induces apoptosis of rar astrocytes [Abbacchio M.P. et al. (1995), Biochem. Biophys. Res. Commun. 213: 908-915; Ceruti S. et al. (1997), J. Neurosci. Res. 47: 372-383]. Thus, to further characterize the mechanism(s) at the basis of 2-CdA efficacy in inducing apoptosis, we tried to test whether 2-CdA could also modulate astroglial cell survival, we have tested these two compounds on an human astrocytoma cell line (ADF cells). Both derivatives induced apoptosis in a time- and concentration-dependent way, being 2-CdA more potent than 2-CdA; moreover, both compounds directly acted intracellularly and induction of apoptosis required the phosphorylation/activation of specific kinases, i.e. adenosine kinase for 2-CdA and deoxy-cytidine kinase for 2-CdA. Finally, only in the case of cladrabine, apoptosis was preceded by a marked increase of the nuclear area, due to a specific block of cells at the G2/M phase of the cell cycle. Taken together, these data clearly show that the apoptotic effects of cladrabine, previously demonstrated only on immune cells, can be obtained also on the cells of the central nervous system and that, in this experimental model, apoptosis is preceded by a specific modulation of cell cycle progression.

21. MODULATION OF CD95/CD95L EXPRESSION ON A HUMAN GLOBLASTOMA CELL LINE AFTER TREATMENT WITH PLATINUM COMPOUNDS, DNA TOPOISOMERASE INHIBITORS AND TAXOL


The CD95-mediated pathway could have relevance in regulating drug sensitivity of tumor cells because this system, consisting of a membrane-bound isoform and its natural ligand (CD95L), might be modulated in response to drug treatment. Thus, in this study, we investigated the effect of two different compounds, according to the CD95 and CD95L expression, using a CD95+ human glioblastoma cell line. A significant up-regulation of CD95 after treatment with topotecan, cisplatin and mitoxantrone was found, whereas taxol did not modify CD95 expression; the other two compounds had a significantly CD95 expression, while topotecan, cisplatin and mitoxantrone were ineffective. The observed up-regulation of CD95 might have important therapeutic implications because cells could be sensitive to specific DNA damaging agents through activation of the CD95 pathway. The profile of expression of these molecules might be a useful additional tool in the choice of the optimal chemotherapeutic regime in glioblastoma.

22. THYROID FUNCTION IN PEDIATRIC PATIENTS WITH MEDULLOBLASTOMA AFTER DIFFERENT IRRADIATION PROTOCOLS


We evaluated thyroid function in 32 prepubertal children treated for medulloblastoma. The children were grouped according to the type of radiotherapy (RT) they received. Group A consisted of 20 children treated with conventional craniospinal RT; cranial RT (CRT) 40-50 Gy, posterior cranial fossa RT (PCFRT) 35-66 Gy, spinal RT (SRT) 36 Gy (irradiation field C1-S5), with administration of 1.5 Gy per session. Group B consisted of 12 children given hyperfractionated RT: CRT 36 Gy, PCFRT 66 Gy, SRT 36 Gy (irradiation field C1-S5), with administration of 1 Gy per session. The age at diagnosis was 1.5-17 years, with a median follow-up period of 2-10 years. Every year the TSH, FT4, FT3 secretion and the antithyroid antibody titers in each patient were measured; every 2-4 months the thyroid was examined by ultrasonographic imaging. Results: in Group A 15/20 children present primary hypothyroidism (after 2-10.7 years) and 2/20 central (after 8-9 years) 7/20 reduced thyroid volume and 17/20 signs of hypothyroidism was confirmed after treatment had been discontinued. In Group B only 3/12 children present primary hypothyroidism (after 1.5-4.5 years), and 3/12 children show at thyroid sonographic examination features of the thyroid; none showed central hypothyroidism or reduced glandular size. No patients developed autoimmune or nodular thyroid diseases. The Kaplan-Meier analysis and a univariant comparison between the two groups showed that the children treated according to a conventional RT treatment were more likely to develop hypothyroidism than those treated with hyperfractionated RT (p<0.05). It can be concluded that the use of more moderate protocols can reduce compromised thyroid function.

23. OCULAR INVOLVEMENT IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS

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Ocular involvement is present at diagnosis in 12-18% of patients with primary central nervous system lymphoma (PCNSL), to 85% of patients, who initially present with ocular lymphoma, usually misdiagnosed as diffuse chronic uveitis, develop cerebral disease. Ocular radiation has been the most frequently employed, and few data are available regarding chemotheraphy. Since 1989 twenty patients with biopsy proven PCNSL were seen at the University Hospital of Turin. Four patients (20%) developed symptoms (blurred vision) and signs of ocular involvement. In one patient ocular symptoms developed one year before the diagnosis of PCNSL, whereas the other three patients had the ocular involvement after the diagnosis of
PCNSL, concurrent with a stable brain disease. Ocular disease was diagnosed with slit-lamp examination and indirect fundoscopy; two patients underwent a fluorangiography. All patients showed an involvement of the choroid; one patient, with additional vitreous involvement, was submitted to vitrectomy. The sight of the retina in both patients was initially unilateral and thereafter bilateral in two patients, bilateral from the onset in one patient and exclusively unilateral in the remaining patient. One out of the three patients who received steroids had a clinical benefit; the two patients, who were unresponsive to steroids, had an improvement after high-dose ARA-C (one patient) and vitrectomy (one patient). None of the patients were treated with ocular irradiation. Conclusions. Ocular involvement in PCNSL is frequent, and often misdiagnosed, so that an extensive ophthalmologic investigation is needed in asymptomatic patients. Chemotherapy with high-dose ARA-C may be useful.

24. CHROMOSOMAL CHANGES IN HUMAN GLIOMA PROGRESSION; A CYTOGENETIC STUDY OF 10 CASES

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Malignant progression of glial tumors has been associated with specific genetic events that seem to be correlated with various stages of progression. Cytogenetic abnormalities associated with PCNSL may prove to be of significant prognostic value as a sign of tumor progression. Cytogenetic analysis of 10 human gliomas, including 2 anaplastic oligodendrogliomas, 3 low-grade astrocytomas and 5 glioblastomas, was performed using the short-term tissue culture method. Low-grade astrocytomas only showed loss of chromosome Y. One anaplastic oligodendroglioma presented normal karyotype with trisomy 7 and 48, XX, +X, +X2 (1/10), whereas the other showed a normal karyotype and 45, X, Y (5/15). Among glioblastomas, in four cases the cells had 45, X, Y karyotype; one case had complex autosomal abnormalities, together with trisomy 7 and monosomy 10. Cytogenetically, the three low-grade gliomas are characterized by a simple numerical change (loss, gain, or a mix). On the other hand, anaplastic oligodendrogliomas and the most of glioblastomas displayed highly complex karyotype, with numerical aberrations (trisomy 7 and monosomy 10). These findings support the concept of progressive accumulation of chromosomal changes in human glioma progression.

25. CYTOGENETIC ANALYSIS OF PITUITARY ADENOMAS: STUDY OF EIGHT CASES AND REVIEW OF THE LITERATURE


We report the results of cytogenetic studies on specimens obtained from surgical removal of eight pituitary adenomas, using the short-term tissue culture method. Four cases were clinically non-secreting adenomas, three showed growth hormone production and one thyroid stimulating hormone. Seven cases presented a normal karyotype, whereas one case of non secreting adenoma was karyotypically characterized by a numerical aberration of chromosome 9. We compared our results with the data published in the current literature. It appears that trisomy 9 seems to be the best candidate for a primary chromosomal abnormality.

26. CYTOGENETIC ANALYSIS OF 10 CASES OF MENINGIOMA

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Although generally considered benign lesions, meningiomas have shown a significant rate of recurrence and malignancy, characterized by a clonal origin from benign tumors with monosomy 22 to aggressive forms with additional abnormalities. The aim of our study was to identify the most frequent karyotypic abnormalities associated with aggressive histopathology and poor behavior. Two intracranial meningiomas exhibiting histologically typical features and eight morphologically benign meningiomas were selected for cytogenetic studies at the time of intraoperative frozen section diagnosis. Chromosomal abnormalities were observed in 6 cases (60%), 2 of which were complex. Loss of chromosome 22 was the most frequently observed abnormality in benign meningiomas, with additional karyotypic and numeric aberrations of chromosomes 1, 2, 6 and 10. Two atypical meningiomas did not show loss of chromosome 22, but complex structural aberrations; in particular, one case presented a ring chromosome. These findings suggest that loss of chromosome 22 is associated with benign, non atypical histopathology. One histologically benign meningioma did not show loss of chromosome 22 but a (der)6. This tumor presented an aggressive biologic behavior. It suggests that this last abnormality might be associated with a more aggressive clinical course in otherwise morphologically benign meningiomas.

27. RESISTANCE TO ACTIVATED PROTEIN C NOT DUE TO FACTOR V R506Q MUTATION IN PRIMITIVE CEREBRAL LYMPHOMA

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Primary central nervous system non-Hodgkin’s lymphoma (PCNSL) represent a rare pathology. They are most frequently classified as B lymphoma. This histopathologically frequent complication and the second cause of death in patients with malignant disease. Recently, a new mechanism of hereditary thrombophilia characterized by a poor response to activated protein C (APC-resistance) has been identified. Resistance to APC is usually linked to a factor V (FV) gene mutation changing an Arg 506 to a Glu in the APC cleavage site. Therefore, APC-resistance may occur in other disorders associated with hypercoagulability such as lupus anticoagulant syndrome, systemic sclerosis, gastrointestinal cancer. In our study, we aimed at investigating the presence of APC-resistance and other markers of hypercoagulability in 11 selected patients with a diagnosis of PCNSL who had suffered from episodes of TIA and/or stroke. Twenty-two healthy subjects acted as control group. For laboratory investigations we measured resistance to APC, natural clotting inhibitions (AT III, PC and PS), prothrombin fragment 1+2 (F1+2) and fibrinopeptide A (FPA) according to international guidelines. Genomic DNA was extracted from peripheral white blood cells and PCR was performed to amplify genomic exon 10/intron 10 region of FV gene to search for Arg506 to Glu point mutation. Our result showed that 7 out of 11 patients had a poor response to APC (sapo < 0.70), whereas 3 normal patients (from our general population) without deficiencies in natural clotting inhibitors. All patients had high plasma levels of F1+2 and FPA compared to those found in healthy subjects (2.4±0.45 nM vs 0.40±0.35 nM; 3.5±0.35 nM vs 1.80±0.8 nM, respectively). Resistance to APC was not associated to a FV gene defect demonstrating that such phenomenon may be associated with other factors and other markers of hypercoagulability in our selected population.

28. INTERSTITIAL CHEMOTHERAPY FOR MALIGNANT GLIOMA: THE JOHNS HOPKINS EXPERIENCE

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Introduction: Interstitial chemotherapy with polymers releasing BCNU (Gliadel®) has been recently added to the neurosurgical armamentarium for the treatment of malignant gliomas, reducing systemic toxicity associated with traditional chemotherapy and improving the clinical experience. We present our experience at the Johns Hopkins School of Medicine. Methods: A total of 88 patients have been enrolled in multiple studies for treatment of malignant gliomas with BCNU polymers. Eight patients were enrolled in a phase I study, and 35 in a phase III, randomized, placebo-controlled study for recurrent gliomas; 35 were part of an additional safety-efficacy study for recurrent gliomas. Furthermore, 10 patients participated in...
a phase I study using the BCNU polymers at the time of initial treatment in combination with radiation therapy. Eligibility criteria for recurrent tumors included: histologic diagnosis of malignant glioma, previous external beam irradiation, Karnofsky Performance Status (KPS) 20-60, no chemotherapy within one month of surgery, and need for surgical debulking. Results: None of our patients showed evidence of the systemic toxicity usually associated with standard chemotherapy. Results of outcome or neurological examination at the end of phase III trial, there was a statistically significant improvement in median survival of the active group as compared to the placebo group (42 vs 21 weeks, respectively). Conclusions: Our data show that interstitial implantation of BCNU polymer is both safe and efficacious for the treatment of malignant glioma.

29. EXPRESSION OF NEUROTROPHINS AND THEIR RECEPTORS IN MEDULLOBLASTOMA AND OTHER CHILDHOOD BRAIN TUMORS
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This study was aimed to evaluate the expression of NTs and their receptors in a series of childhood brain tumors. Patients and Methods. Expression of NGF, TrkA, BDNF, TrkB, NT3, TrkC and p75NTR proteins was investigated in 41 brain tumors including 11 MBs, 3 primitive neuroectodermal tumors (PNETs), 15 pilocytic astrocytomas (PAs), 5 glioblastomas (GBs), 6 epidermoids (Eps) and 1 rhabdoid tumor (RT). Samples were obtained at diagnosis and evaluated by indirect avidin-biotin immunoperoxidase. Results. In MB, immunostaining was obtained in 10/11 cases for NGF, 9/11 for TrkA, 9/11 for BDNF, 9/11 for TrkB, 9/11 for TrkC and 2/11 for p75NTR. In PA, staining was found in 13/15 cases for NGF, 0/15 for TrkA, 15/15 for BDNF, 9/15 for TrkB, 12/15 for NT3, 4/15 for TrkC and 5/15 for p75NTR. Staining with a heterogeneous pattern was also obtained in PNETs, Eps, GBs and RT. In MB, transcripts corresponding to both the full-length and truncated forms of TrkC were detected by RT-PCR analysis. Regarding outcome for the 11 children with MB, 7 cases were positive for both NT-3 and TrkC and remained free of disease for a median follow-up of 36 mos (range, 10-45); of the 4 cases negative for one or both of the proteins, 2 died of disease (12 and 24 mos after diagnosis), 1 relapsed 3 mos after complete excision and is DF 10 mos after diagnosis, and 1 remains DF after 45+ mos (p<0.003). Conclusions. NTs and their receptors (apart from TrkA) are highly expressed in a wide range of childhood brain tumor histotypes. In MB, the concomitant expression of TrkC and NT3 is associated with a less aggressive tumor phenotype and better clinical outcome.

30. HISTOCHEMICAL PATTERN OF GLIOBLASTOMA AFTER POSTOPERATIVE IRRADIATION
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The pathological heterogeneity of glioblastoma multiforme is more and more expanded by radiotherapy and other ablative biological treatments (Giangaspero P and Buerguer PC, 1983). Modifications in extracellular matrix and receptors could play a role in the activity of radiotherapy, causing not only necrosis but also changes in proliferative potential and cell differentiation. In order to verify this hypothesis we have performed an histochemical and immunohistochemical analysis of two recurrent glioblastomas, operated on after postoperative irradiation, and three glioblastomas at the first surgical treatment. The immunohistochemical study focused on the following molecules: Standard CD44, GFAP, Ki-67 antigen (MB-1 antibody) and tenascin. Histochemical staining as Alcian blue pH 2.5 and Alcian blue pH 1.0 was also performed. Results: a) The study allowed us to conclude that significant differences between the two groups. Interestingly, CD44 expression in the same fields of serial sections did not correlate with GFAP expression, MB-1 labeling index, or intensity of Alcian blue staining. In conclusion these data confirm the opinion that interactions between cells and extracellular matrix play a major role in malignant astrocytic tumors (G. Donato et al., 1997).
ferent histological type of malignant gliomas; different histology could direct to different radiotherapy schedules. The AHF gives better results than MDF or CF. We have also observed that the dose-fraction value is able to influence significantly (p<0.02) the outcome of these patients. These conclusions could be considered a reasonable starting point for future trials for AA.

34. PRIMARY CNS LYMPHOMA (PCNSL): PRELIMINARY RESULTS OF A SINGLE-CENTER PROSPECTIVE TRIAL WITH HIGH-DOSE METHOTREXATE (HD-MTX), VINCRISTINE (VCR) AND PROCARBAZINE FOLLOWED BY RADIATION THERAPY (RT) WITHOUT INTRATHECAL CHEMOTHERAPY (CHT)

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Purpose: To assess the efficacy of chemoradiotherapy without intrathecal drug delivery in PCNSL. Inclusion criteria: histological diagnosis of lymphoma; disease limited to the CNS; untreated or resected pts; age ≥70 yrs; ECOG PS ≤3; normal hematological, renal and hepatic function. Treatment: Primary CHT: 2 courses of vincristine 1.4 mg/m2 d 1; MTX 3 g/m2 d 3 & 10; and procarbazine 100 mg/m2/d 1 to 14. Pts who achieved a CR underwent RT; pts in PR or SD received a 3rd course of CHT followed by RT; pts with PD were considered off study. Pts with solitary lesions (n=3) were irradiated to whole-brain with 40 Gy (1.8 Gy/d) plus a tumor boost of 10 Gy; pts with multiple lesions received 45 Gy to whole-brain. Results: Ten pts (6 males, median age 54) were registered (’97-’98). No pt had B symptoms or abnormal LDH. One pt had progressive CSF cytology, and 2 had ocular lesions. Four pts did not complete CHT because of lethal toxicity (n=1), renal failure (n=1) or PD (n=2). Six pts completed the planned treatment: 4 CR and 2 pts with no measurable disease (radical resections); 3 of them relapsed (8-24 mo), all within the boost area (median FFP: 11 mo). One pt underwent hepatic spread. The pt with positive CSF is relapse-free at 31 mo. Five pts are alive (median f-up: 12 mo). Conclusions: More pts and a longer follow-up are necessary to assess the relation between intrathecal CHT and meningeal relapse. The high frequency of treatment failures and local relapses underlines the insufficiency of performed CHT and RT. Improvements in primary CHT should be considered priority with respect to investigation of intrathecal CHT.

35. CANCER REGISTRY OF THE ISTITUTO NAZIONALE NEUROLOGICO “C. BESTA”

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The data collection, retrieval and analysis activities of tumour registries have long been accepted as essential by physicians and epidemiologists concerned with assessing cancer incidence, treatment and end results. Moreover, registries can assist hospital planners, administrators and the community. The Register of the Istituto Nazionale Neurologico “C. Besta” started its activity in 1997. The notification of cases is active and the registration techniques have been assessed. The regular sources of the Registry are the informatic system of hospital admissions, the clinical records and the surgical pathology files. Data are abstracted by one trained physician in conjunction with doctors, via a predesigned form. The data are coded by a trained physician and registered by an office worker. All tumors are classified in ICD-O through 9 digit codes by topography, morphology and behaviour. Demographic, clinical, radiological, surgical, histological and treatment data are available for each patient. Annual active follow-up of patients is done to determine vital status and disease status. Between January 1, 1997 and December 31, 1998, 1203 tumours were registered, 76% of whom were histologically verified. Gliomas were the largest group (38%) and with meningiomas (20%) accounted for 58% of all tumours in the Registry. Neurinoma was the third most common histologic type (9%), followed by pituitary adenoma (7%), metastases (6%) and angiomias (4%). The male/female ratio was 1.4 and 0.4 for gliomas and meningiomas respectively. The age-specific pattern shows a first “peak” in childhood, subsequently risk remains stable throughout life, to rise steeply after 35 years of age. Copies of the certification form including vital status are obtained from the municipalities. Survival analysis is ongoing.

36. DELETIONS OF CHROMOSOME 1P AND CLINICAL EVOLUTION OF OLIGODENDROGLIOMAS AND MALIGNANT GLIOMAS

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The loss of genetic material on chromosome 1p is a frequent event in gliomas. A high rate of loss of heterozygosity (LOH) in gliomas, was found in oligodendrogliomas and is associated with a more recent disease evolution compared to gliomas while LOH is less frequent in purely astrocytic tumors. Interestingly, a tight correlation has recently been found between sensitivity to chemotherapy and LOH on 1p in oligodendrogliomas (Grunewald et al., 1998; Ralou et al., 1998). The rate of sensitivity to chemotherapy of these malignancies may match the lower rate of 1p LOH. A panel of about one hundred oligodendrogliomas is presently available in our laboratory. We have started this analysis using marker D1S508. The initial result confirms the frequency of LOH in these cases. Investigations with other markers and correlation with therapy and survival rate are in progress. The results could be useful to assess the therapeutic approach for these malignant tumors and also to define more clearly the role of these losses.

37. MOLECULAR INVESTIGATIONS ON TUMOR SUPPRESSOR GENES ON CHROMOSOME 10Q

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Loss of one copy of chromosome 10 or of specific parts of chromosome 10q is a frequent event during the malignant progression of astrocytic tumors. During the last two years three novel tumor suppressor genes have been discovered on 10q: PTEN, DMBT1 and LG1. We are investigating the role of these three suppressors at different levels. First, we are studying the effects of the reintroduction of the wild-type PTEN gene in glioblastoma (GBM) cell lines. We have published a retroviral producer cell line for PTEN transduction into U-87 and U-373 cells. We are now characterizing the effects of this transduction with special emphasis on the possible effects on the expression of thrombospondin-1 (TSP-1), an important regulator of angiogenesis, and transforming growth factor beta, a cytokine that can be regulated by TSP-1 and that is partially responsible of the immunosuppressive effect of GBM. We also found that homozgyous deletions of sequence tagged sites internal to DMBT1 are present in about 13% of the GBM. In 24% of short-term cultures of GBM the expression of 3’ regions of DMBT1 is severely down-regulated. To investigate the structure of DMBT1 we have cloned genomic regions 5’ to the structural gene and we have also isolated different DMBT1 cDNAs from a human lung cDNA library that may result from the differential splicing of DMBT1. Finally we have looked for LG1 expression in GBM short-term cultures and found that in a fraction of them such expression is very low. The search for intragenic mutation is in progress. A retroviral vector for LG1 is also ready for expression studies in LOH-deficient cells.

Nonfunctioning adenomas (NPNA) are benign tumors with a high risk of recurrence because their surgical removal is often incomplete. The growth fraction of the tumor should be theoretically related to the likelihood and rapidity of recurrence. In the present study, we evaluated the usefulness of a proliferation index in 101 patients operated for a NPNA. There were 53 males and 48 females with a mean age of 52.0 ± 1.5 yrs. Eight patients had regrowth of residual tumor operated through a transphenoidal approach. All patients were treated with an extracranial macroadenoma and 44 showed MRI signs of sinus cavernous invasion. Immunohistochemical analysis was performed on paraffin embedded material, using a monoclonal antibody (MIB-1) directed against the proliferation associated nuclear antigen (Ki-67). MIB-1 index was estimated to be the number of MIB-1 positive cells in 1000 neoplastic cells. The mean Ki-67 LI in the 101 patients was...
2.4% ± 0.3%, ranging from 0% to 23.0%. Only age at operation was inversely correlated with Ki-67 LI, whereas sex, maximum tumor diameter, and invasiveness into cavernous sinus did not affect significantly the Ki-67 LI. The mean follow-up was of 39.7 ± 2.1 months. The first postoperative MRI did not reveal any residual tumor in 36 patients. During follow-up 23 patients had tumor recurrence after a mean period of 28.6 ± 4.8 months. Invasiveness of the tumor on preoperative MRI was the strongest predictor of late tumor recurrence followed by previous pituitary surgery, younger age, and lack of postoperative radiotherapy. The Ki-67 LI had no independent prognostic value.

39. TEMOZOLOMIDE IN RECURRENT MALIGNANT GLIOMAS: A PHASE II STUDY

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Temodal (T) is an oral alkylating agent and has shown significant activity in phase II study trials in malignant melanoma and gliomas (G) with good toxicity profile. We designed a phase II study to evaluate the activity and toxicity of T in patients (pts) with recurrent G. From July 1998 to May 1999 we included 17 pts with recurrent astrocytoma (8 pts), glioblastoma multiforme (8 pts) and anaplastic oligodendroglioma (1 pt), previously treated with radiotherapy (6 pts) and chemotherapy (5 pts). T was given at the dose of 300 mg/m² po daily × 5 to 28 days. Total number of the cycles was 53 (median number of cycles 3). Pts were evaluated every two cycles by TC or NMR imaging. Ten pts were valuable for response and 17 for toxicity. The objective responses were 6 (35%) with 4 PR (24%) (2 pts were pretreated with chemotherapy and radiotherapy) and 2 MR (11%) (all the pts were pretreated with chemotherapy and radiotherapy). Stable disease was present in 2 pts (11%) and 2 pts (11%) had progressive disease. T was well tolerated (grade 2 trombocytopenia and leukopenia occurred in one patient). Every patient has shown an improvement of Performance Status. Median survival as not reached yet. Conclusion: T is well tolerated and as been shown to produce significant response rates. The study is ongoing.

40. THE PIPERIDINE NITROXIDE TEMPOL INHIBITS IN VITRO AND IN VIVO GROWTH OF GLIOMA CELLS

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Malignant gliomas are highly aggressive neoplasms that are very resistant to current therapies. To improve the prognosis, it is essential to identify new agents for treatment. Recently, using cell lines of human and rodent origin, we have shown a cytotoxic activity for the piperidine nitroxide TEMPOL, with a significantly more potent effect against aggressive vs non-aggressive cells (Gariboldi et al., Free Rad Biol Med, 24:913-923, 1998). In the present study we evaluate the in vitro effects of TEMPOL against the C6 rat glioma cell line, the in vivo antitumor activity of the nitroxide is also assessed in a xenograft model from the same cells. Our results show that sub-millimolar TEMPOL inhibits the growth of C6 cells (IC50 96 h = 0.1978 mM); cytotoxicity data on the non-tumorigenic cell line, ST14A, derived from embryonic rat striatum (IC50 96 h = 4.9447 mM). Indicators of nitroxide toxicity for tumor and normal tissues are shown. Morphological features of apoptosis were apparent in C6 cells after treatment with TEMPOL. Cell death was preceded by a dose-dependent increase in p21Waf1/Cip1 expression, without apparent stabilization of the p53 gene product. For in vivo studies, nude mice were injected subcutaneously with C6 cells and treated with TEMOL. A significant dose-dependent decrease in tumor growth was observed in TEMOL–treated mice; upon treatment suspension tumor growth resumed with kinetics comparable to control mice. No sign of general and organ toxicity were observed in treated mice. Our findings suggest a potential use for TEMOL as a new antiproliferative agent, in combination with other drugs, for the therapy of gliomas.

41. RESULTS OF THE FIRST ITALIAN CO-OPERATIVE PROTOCOL FOR CHILDREN <3 YEARS AFFECTED BY MALIGNANT CNS TUMOURS


In 1995, a pilot trial was proposed in Italy for cases of malignant CNS tumors ≤3yr. of age; a protocol modified from the POG Study (Duffner et al. NEJM,1993) by the introduction of HDMTX, was adopted. The regimen consisted of: CDDP (120mg/m²), and VP16 (450 mg/m²) followed by the sequence AAB repeated times 4 where A was: VCR(1.3 mg/m²)/CTX(1.5 gr/m²)/MTX(1.3 gr/m²) and B: CDDP (90 mg/m²) and VP16 (450 mg/m²). Only 2 of 61 patients (M+) or metastatic disease (M+) were candidate to irradiation (RT). The first 39 consecutive cases enrolled are presented. Histology was Medulloblastoma (MB) 18 cases, Ependymoma (Ep) 8, AT 3, Cd Plexus Ca 3, Other 5; the tumor was completely removed in 18/39 cases; 21 were T+ and 6 of them M+: 21/39 (54%) had than measurable disease (MD+) before CT. Tolerance to CT was good without toxic deaths. Follow-up ranged from 16 to 43 Mos (median 25); 25 patients failed during (19 pts) or after CT (6 pts): 7 cases presented local failure (4 Ep, 3 others); 18 metastatic (11 Mb, 7 others); patients with MD+ did relapse more frequently than those MD-. Especially in Mb and in Ep the absence of Mb/MD+ had relapse early during CT while out of 10 cases MD-, 5 (50%) are still in first remission at 16, 27, 39, 43, 43 Mos. In MD+ cases: 4/12 with partial (pT+ or metastatic (M+)) or metastatic disease (M+) were candidate to irradiation (RT). Overall this CT regime failed in cases MD+ or with unfavorable histology; however our data suggest a possible role of HDMTX in reducing the frequency of leptomeningeal relapse in Mb/MD+ groups increasing than the possibility of long-term survival without RT; however these results should be confirmed after a more prolonged follow-up.

42. THE CLINICAL DIAGNOSIS OF PARANEOPLASTIC NEUROLOGICAL DISORDERS

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In patients with Paraneoplastic Neurological Disorders the detection of several autoantibodies reacting with neuronal antigens and tumors supports the hypothesis that autoimmunity plays a part in these diseases and gives impetus to the study of these neurological disorders. The relationship between detection of anti-neuronal antibody, clinical syndromes and certain types of tumors led to the recognition of the role of antibodies as a new tool for the clinical diagnosis, although their function in the pathogenesis of the various syndromes is still unclear. In the setting of anti-neuronal antibody detection in 862 patients, we found 18 cases positive for antineuronal antibodies related to paraneoplastic disorders; we reviewed the records and follow-up of 13 of these patients. Autoantibodies were detected by immunohistochemistry, Western Blot of gradient separated neuronal proteins and recombinant Yo and HuD proteins. In this study, the clinical data and antibody pattern are discussed and current opinions on the value of these antibody detection for establishing a diagnosis of paraneoplastic neurological disorders are reviewed.

43. IMMUNOHISTOCHEMISTRY MAY BE OF HELP IN IDENTIFYING A MALIGNANT LYMPHOMA AFTER STEROID-INDUCED REMISSION

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Marked and even complete remission of parenchymal brain lesions is seen in a significant number of patients with primary central nervous system lymphomas (PCNSL) after glucocorticoid treatment. The well known lymphocytolytic effect of glucocorticoids (GC) on a number of primary central nervous system (PCNSL) may obscure the neuropathological diagnosis. The stereotactic biopsy specimens of such cases shows a non-specific inflammatory picture that is common with other steroid-sensitive disorders (subacute or chronic encephalitis, granulomatous disease, progressive multifocal leukoencephalopathy). An immunohistochemical panel (Abs to LCA, L26, CD3, KP1, MIB-1, Bcl-2, GFAP) has been applied to stereotactic biopsy
samples of steroid-sensitive disorders. A pattern indicative of steroid-induced remission of malignant lymphoma has been identified: astroglial hypertrophy and perivascular infiltration of T-cells, accompanied by Bcl2-positive lymphocytes and with a small number of MIB-1-positive nuclei. GC-induced cytostasis is thought to be mediated by activation of apoptosis and may thus select lymphocytic clones expressing Bcl2.

44. INTRACRANIAL GERMINOMAS IN VITRO

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The origin of intracranial germinomas is still uncertain. Nowadays three predominant theories are proposed to explain the origin of extragonadal germ cell tumors, but there are no experimental data able to confirm the priority of one of them. Furthermore it is not demonstrated if these cells may undergo after migration to a neoplastic transformation. Such neoplasms are morphologically and histologically similar to tumors that arise in the gonads. Two primary cultures from intraoperative specimens of pineal tumors were obtained. Histological examination demonstrated that both were germinomas. Patient's preoperative melatonin circadian rhythm, tested with serial blood samples under controlled light-dark conditions, showed a disappearance of melatonin secretion with abolition of the circadian rhythm. The immunohistochemical investigation of the two germinoma cultures was performed using a panel of polyclonal antibodies against several neuroendocrine antigens (NSE), Vimentin, Class III beta-Tubulin, S-100, Neurofilaments, Melatonin, GFAP, CEA, PLAP, EMA. For the ultrastructural investigation the cells were rinsed in phosphate-glutaraldehyde. The immunochemical study showed that intracranial germinoma presented in vitro immunoreactivity for neuronal, glial and epithelial markers in the same cell. Even if the preoperative plasmatic level of melatonin in these patients was undetectable, the cell cultures showed in one case immunoreactivity for melatonin antigen. Ultrastructural study revealed dense-core vesicles considered neuroendocrine structures. This study suggests that extragonadal germ cell tumors could have different characteristics than gonadal tumors.

45. PHASE II STUDY OF TEMOZOLOMIDE IN RECURRENT HIGH-GRADE GLIOMA: PRELIMINARY RESULTS

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Temozolomide is a new oral imidazotetrazine derivative agent used in our department for treatment of high grade glioma. Between May 1998 to January 1999, 21 patients with recurrent high grade gliomas were entered into a phase II trial to evaluate the efficacy and toxicity of temozolomide. All patients with histologically confirmed grade III and IV glioma and measurable or evaluable lesions on CT or MRI scan, that had progressed after surgery and radiotherapy, were enrolled in this study. Other criteria, also, include KPS> 70, chemotherapeutic naive status, absence of prior therapy with alkylating agents. Temozolomide was administered orally as capsules at a dose of 200mg/m2 daily for 5 days every 4 weeks. No side effects occurred. Clinical and radiological controls by computerized tomography (CT) after contrast medium administration have been performed from 3 to 8 months after the treatment. Three patients died for tumor progression; among the other 9 alive patients the residual or recurrent tumor was unchanged in 4 cases and showed size increase in 3 and decrease in 2. The study continues by inclusion of further patients. Besides, we are performing a new protocol which combines Temozolomide with concurrent radiotherapy as initial treatment of patients with primary high-grade gliomas.

46. TEMOZOLOMIDE IN PATIENTS WITH GLIOMA: PRELIMINARY EXPERIENCE

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Temozolomide, a methylating imidazotetrazine, has antitumor activity against gliomas and seems to be efficacious both in patients with growth progression of residual tumors and in those with recurrent disease. This study reports the data of our preliminary experience in 12 patients with malignant gliomas of the cerebral hemispheres operated upon between February 1998 and February 1999 and treated by Temozolomide. The surgical removal was macroscopically complete in 8 cases and subtotal in 4. The histologic examination was in favor of glioblastoma in 7 cases, anaplastic astrocytoma in 4, anaplastic oligoastrocytoma in one. Postoperative irradiation was performed in 9 cases. Temozolomide has been administered to patients at a dose of 200 mg/m2/day for 5 days every 4 weeks. No side effects occurred. Clinical and radiological controls by computerized tomography (CT) after contrast medium administration have been performed from 3 to 8 months after the treatment. Three patients died for tumor progression; among the other 9 alive patients the residual or recurrent tumor was unchanged in 4 cases and showed size increase in 3 and decrease in 2. The study continues by inclusion of further patients. Besides, we are performing a new protocol which combines Temozolomide with concurrent radiotherapy as initial treatment of patients with primary high-grade gliomas.

47. PRIMARY CEREBRAL LYMPHOMAS IN IMMUNOLOGICALLY COMPETENT PATIENTS: CLINICAL, RADIOLOGICAL AND MORPHOLOGICAL FEATURES


Primary cerebral lymphomas are rare lesions accounting for less than 1% of all brain tumors. They present as single or multiple lesions located in the cerebral hemispheres, particularly in the basal ganglia and periventricular regions. These tumors are, especially, found in immunosuppressed patients, even if an increasing incidence is reported among immunologically normal people. This report describes clinical, radiological and morphological features of 25 immunocompetent patients with primary lymphomas, analyzing the different modalities of involvement in the Central Nervous System. The radiological pictures of these lesions are very polymorph because of their capacity of growing in different manners; indeed, it is possible to find both as localized tumor, resembling certain gliomas, either unique or multiple lesions with nodular or diffuse growth. Such pathological patterns result in different CT-features. Typical CT-finding of lymphomas is a slightly hyperdense, homogenous, contrast enhanced lesion. Moreover, it is possible to observe other cases with atypical CT features, similar glioma or abscess, or metastases or meningioma. Besides, we observed the occurrence of dissemination of the lesion and its contrast enhancement on CT-scan after corticosteroid therapy. This is another typical feature of cerebral lymphomas, important to differentiate them from other lesions.

48. INTRACRANIAL GANGLIOGLIOMAS: EXPERIENCE ON 14 CASES

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Gangliogliomas comprise 0.4-3.8% of primary brain neoplasms and typically occur in young patients. Surgical resection is considered in literature the most effective therapy.

We analyze retrospectively 14 cases (7 males - 7 females) of intracranial gangliogliomas operated on between 1993 and 1998 at our Institute. The mean age was 18.4 years (3 months to 51 years). Tumors were located in temporal lobe (8 cases), cerebellum (2 cases), corpus callosum, frontal lobe, hypotalamus, medulla oblongata (1 case each). A patient presented a second hypothalamic location. Clinical manifestations included seizures (9 patients), signs of intracranial hypertension (2 patients), gait disturbance, dizziness and blindness (1 cases each). Mean follow-up was 3.2 years (range 9 months - 7 years). Gross total resection was achieved in 8 patients,

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subtotal in 4 and partial in 2. After follow-up 9 patients showed a good outcome, 2 were moderately disabled and 3 were severely disabled. Among patients that underwent gross total resection only 1 patient showed a good outcome. Temporal gangliogliomas were found in 3 and 2 patients. Tumor location is the only relevant prognostic factor related to the possibility of radical surgery. Temporal gangliogliomas showed better outcome. Radiotherapy may be reserved for selected cases.

49. EFFECTIVENESS AND SIDE EFFECTS OF TREATMENT FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN IMMUNOCOMPETENT PATIENTS

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Introduction. The incidence of central CNS lymphoma has rapidly increased in the last few years. However, the radio-chemotherapy protocols are still limited to success. To improve the outcome, have been introduced, but the median survival time is still unsatisfactory. Material and Methods. From 1995 to March 1999, we treated 17 HIV-negative PCNSL. patients (aged 38-71, median 54.8 yrs; 8 man and 9 women). Histologically, all but one (T-cell) were B-cell lymphomas and all were verified either by biopsy (7) or on core-needle biopsies. Systemic chemotherapy and/or Herceptin and/or radiotherapy were used. Performance Status <2 and younger age (<50) were associated with better prognosis. Thromboembolism was a frequent complication (4 pts) adjuvant therapy. As to RT feasibility, HF-RT was not given in case of such a small lesion. This value is still no significant, but may serve in case of such a small subpopulation of patients. CT in affected areas may be useful to identify areas of solid and recurrent tumor or areas of delayed enhancement in cases that are ambiguous by MRI alone. H-MRSI showed no false positive, two false negatives and fewer ambiguous cases than MRI.

50. ROLE OF HIGH-DOSE HYPERFRACTIONATED RADIOTHERAPY (HF-RT) AND VINCristINE (VCR), VP16 AND CYCLOPHOSPHamide (CYCLO) CHEMOTHERAPY (CT) IN CHILDHOOD EPIDEMYODOMA (EPD): A STUDY OF THE ITALIAN PEDIATRIC NEURO-ONCOLOGY GROUP


In October '93, the Group initiated a study whose purposes were: 1) to stage and treat homogeneously the largest possible population of children with EPD; 2) to investigate the role of a) VCR, VP16 and CYCLO; b) VCR, VP16 and CT; c) VP16, CYCLO and CT following by HF-RT in improving disease-free survival in children with evidence of disease (ED) after surgery (S), and b) of HF-RT alone in those NED (no ED) after S. NED pts were submitted to involvement of 2cm margins field RT (2 fractions/day, 1.1 Gy x 2/d, total dose 70.4 Gy); those ED were to receive 4 monthly cycles of VEC (VCR 1.5 mg/sqm/d weekly, cyclo 1 and 3; VP16 100 mg/sqm d 1,2,3; CYCLO 3 g/sqm d 1) followed by the same HF-RT. Eligibility criteria were: age 3-17 yrs, no previous treatment but S, thorough tumor investigations (pre- and post-S head + spine MR, and CFS cytology). As of May 1999, 42 of the 53 patients enrolled in the study were eligible and evaluable. 12 EPD were supratentorial, 30 arose within the posterior fossa. After S, 27/42 eligible pts were NED, and 15 ED (1 with a metastatic spinal location). 21/27 (79%) NED pts were alive and disease-free (median f-up 17 mos), 6 progressed locally. In 11 pts evaluable for CT response, VEC obtained 7 PR and 4 SD. OS and EFS at 30 mos were 93% and 61% while EFS was 72% and 55% for NED and ED pts, respectively. CT acute toxicity was unremarkable, whereas S was followed by severe side effects that required to postpone or give up (4 pts) adjuvant therapy. As to RT feasibility, HF-RT was not given to 9/35 irradiated children due to technical problems. Good prognostic factors were microscopically observed and were associated with GFAP-positive neoplastic glial cell (astrocytic pattern in 13 cases) and a large tumor mass. In 12 patients with diffuse astrocytic gangliogliomas were found in 3 and 2 patients. Tumor location is the only relevant prognostic factor related to the possibility of radical surgery. Temporal gangliogliomas showed better outcome. Radiotherapy may be reserved for selected cases.

51. H-MR SPECTROSCOPIC IMAGING ADDS RELEVANT METABOLIC INFORMATION TO THE EVALUATION OF SUSPECTED RELAPSING BRAIN TUMORS

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Rationale and Purpose: Assess whether H-MRSI is reliable in detecting areas of recurrent tumor growth. The hypothesis that choline is highly increased in relapsing tumors and relatively low in residual and radionecrotic lesions was tested. Materials & Methods: 120 patients with progressive MRI and/or neurological signs and a history of brain tumor previously treated with surgery and radiotherapy, with or without chemotherapy were studied. The four categories were considered: prevalent recurrent tumor, prevalent radionecrosis, residual tumor, ambiguous. Results: twenty-two patients (9 AA, 3 GBM, 1 OA, 3 LGA, 1 MB, 1 gliosarcoma, 1 lymphoma, 1 metastasis, 2 atypical meningioma) were recruited in this study. Four patients had consecutive H-MRSI. Seven patients had FDG-PET and one had Sestamibi-SPECT. Surgery was recommended in 12/22 patients, nine of which underwent resection of the lesion, which showed a false negative rate of 2/21. 3/316 patients showed hypometabolism in 2/2. Conclusions: H-MRSI adds metabolic information that is helpful to identify areas of solid and recurrent tumor or areas of younger age (<50) adjuvant therapy. As to RT feasibility, HF-RT was not given in case of such a small lesion. This value is still no significant, but may serve in case of such a small
family as strong indication of a possible linkage of the tumor predisposing locus to this region. Additional LOH data on six sporadic chordomas allowed to define an SRO (the smallest region of overlap posing locus to this region). Additional LOH data on six sporadic chordomas involved in both inherited and sporadic chordoma.

53. SPATIAL DYSGRAPHIA AND OLIVO-PONTO-CEREBELLAR ATROPHY AS A PRECIOUS PARANEOPOLAMIC ASPECT OF CEREBRAL TUMOR
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We studied a 67-year-old patient with a cerebellar sporadic degenerative condition (multiple system atrophy of olivopontocerebellar type) and evidence of peripheral dysgraphia. Clinical examination showed a typical cerebellar syndrome with involvement of voluntary movements, dysmetria, ataxic wide-based gait, pyramidal signs such as increased reflexes at the lower limbs, harm weakness and Babinski sign were detected. Neuropsychological examination documented no cognitive deficit, but the presence of peripheral dysgraphia, a symptom previously described in subject with right supratentorial lesion, but more recently also in patients with primary cerebellar pathology. Three years after the onset of the cerebellar symptoms the patient developed a right temporoparietal glioblastoma. This is the first reported case of olivopontocerebellar atrophy documented in association with right supratentorial neoplasm and a possible incidental association with cancer is under discussion. We conclude that multisystemic atrophy can be considered as a special form of paraneoplastic syndrome, whose pathogenesis might be searched within the functional alteration of the crossed cerebellar diaschisis.

54. SECRETORY MENINGIOMA: CYTOLOGICAL AND HISTOPATHOLOGICAL FEATURES
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Secretory meningiomas represent a distinct subtype of meningioma, both pathologically and clinically. We report two cases in which the diagnosis of secretory meningioma was performed on crush preparations and on histologic paraffin sections. Hematoxylin and eosin-stained crush preparations showed the presence of two components: most of the cells formed sheets of loosely cohesive cells, while other formed irregular clumps containing variable numbers of intracytoplasmic inclusions with a well defined thin rim and an eosinophilic core. Histochemical light microscopic findings revealed multiple eosinophilic, hyaline, intracytoplasmic inclusions, known as "pseudopsammoma" bodies. Immunoperoxidase studies showed that the inclusions and the adjacent cells were strongly positive for pancytokeratin and for CEA, while the periphery of the inclusions were positive for EMA. The hyaline inclusions of secretory meningiomas have a distinctive appearance and their identification may improve diagnostic yield in defining this unique meningioma variant.

55. PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS (PCNSLs): HIGH RESPONSE RATE AFTER INTENSIVE PRE-IRADIATION CHEMOTHERAPY
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OBJECTIVE: to analyze the efficacy and feasibility of an ongoing phase II study using a high dose regimen based on two-drugs crossing the brain blood barrier Methotrexate (MTX) and ara-C. METHODS: the results of 22 consecutive immunocompetent patients (median age 61 years, range 28-83) have been reported. Histological diagnosis was obtained by stereotactic biopsy (11/22) or open microsurgery (11/22). Pretreatment neurological performance status was 3-4 in 10 patients. The cycle of chemotherapy (CT) administered every 3 weeks on an in-patient basis included: MTX 1 g/m2 iv over 24 hours (d 1) with leucovorin rescue, followed by 4 doses (d 2-3) of ara-C 2 g/m2 iv every 12 hours. In the 10 patients under 60 years, MTX and ara-C doses were increased to 2 g/m2 and 3 g/m2, respectively. CT was followed by whole brain irradiation (30 Gy plus 5-10 Gy boost). Three cycles of CT were planned for patients in partial response (PR) after the initial cycle, and 2 cycles for those in complete response (CR) or near-CR (i.e., PR>90%). RESULTS: forty-nine cycles were administered with treatment completion achieved in 18 patients. The mean dose intensity was 85% of that planned. Hematological toxicity (grade 4 neutropenia and thrombocytopenia) was minimal (mean 7 days). Neutropenic fever occurred in approximately 50% of the cycles. In 4 patients, all over 60 years, CT was interrupted after the initial cycle due to severe infectious complications (2 cases) or toxicity (2 cases). At autopsies, one patient was found to be in CR and the other in near-CR. Overall response rate to CT was 86%; 15 CR or near-CR, and 4 PR. To date, at a median follow-up of 15 months (3-38), 13/15 alive patients are in continuous CR. CONCLUSIONS: this study demonstrated: 1) this specific high dose intensity protocol was feasible despite the advanced age of the series; 2) a high response rate was achieved; 3) extended follow-up periods are required to evaluate the impact of high response rates on long-term survival.

56. GAMMA KNIFE RADIOSURGERY AS PALLIATIVE TREATMENT IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS (PCNSLs)
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OBJECTIVE: to evaluate the outcome of gamma knife (GK) radiosurgery in 9 clinically compromised patients with primary central nervous system lymphoma (PCNSL) ineligible for chemotherapy or who refused further treatments. METHODS: at the Department of Neurosurgery in Verona, 9 patients (4 males, 5 females; mean age of 65.5 years, range 34-73) were affected with PCNSL. All patients underwent GK radiosurgery from December 1993 to December 1998. The patient population included: 5 patients with AIDS, 2 elderly patients (70 years, with concomitant platelet deficit in one case and the other in general deterioration); one patient, 12 years old undergoing transplantation, and 1 who refused WBRT/chemotherapy. Histologically confirmed diagnosis was obtained by stereotactic brain biopsy (8/9) or open surgery (1/9). Due to the short life expectancy in these patients and the high radiation sensitivity of PCNSLs, larger tumor volumes (mean 11.9 cc, range 0.7-45.0 cc) were accepted for GK treatment. The mean and range dose planning values were as follows: edge isodose (40.7%, 30-50%), edge dose (20.2 Gy, 13.3-25 Gy) maximal dose (50.4 Gy, 40-70 Gy), average dose (32.3 Gy, 29.9-38.2 Gy), and number of shots (4.4, 1-10). GK treatment was performed under local anesthesia in all cases, and patients were discharged within 24 hours from radiosurgery. In 2/9 cases, WBRT was administered following GK. RESULTS: the follow-up period ranged from 4.3 to 45.4 weeks (mean 20.0 weeks). The mean and median survival times were 23.6 ± 4.8 weeks and 21.9 weeks, respectively. Tumor growth control was obtained in all tumors (GK: 50% since 4 weeks; 2/11 cases). Neither early complications nor GK-related deaths were observed, and only 1/9 cases of symptomatic transient radionecrosis was reported. At the end of the study, 3 patients were still alive, and the causes of death in all deceased patients was determined to be unrelated to PCNSL progression (3 AIDS, 1/6 sep ticemia). CONCLUSIONS: in this study, an acceptable level of tumor growth control was achieved in PCNSLs treated with radiosurgery with very low complication rates. These data suggest that GK may be considered a valid palliative treatment modality in elderly and/or clinically compromised patients affected with such brain tumors.

57. THE ROLE OF GAMMA KNIFE RADIOSURGERY IN THE TREATMENT OF LOW-GRADE NEUROEPITHELIAL BRAIN TUMORS
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OBJECTIVE: to assess the efficacy of gamma knife (GK) radiosurgery in the treatment of low-grade neuroepithelial brain tumors (LGNTs). METHODS: between February 1993 and April 1999, at the Department of Neurosurgery in Verona, 32 patients affected with 36 LGNTs (grade II according to WHO classification) were treated with a 201-source cobalt-60 Leksell gamma unit. The results
of this study are based on available follow-up (FU) of 28 patients - 13M/15F; mean age 33.9 (5-72) years - with 29 treated tumors who did not undergo RT/chemotherapy (CT) before or after GK. Most tumors (21/29) were surgical remnants, while pathological diagnosis was obtained by stereotactic biopsy before radiosurgery in the remaining 8/29 cases. Tumor pathology included: 22 low-grade gliomas, 4 central neurocytomas, 2 choroid plexus papillomas, and 1 pineocytoma. GK was considered in the following cases: unacceptable risk associated with surgical removal, neoplasm volume < 20 cc (mean 6.4 cc), open surgery or additional microsurgery refused, and/or medical conditions precluding general anesthesia. Radiosurgical treatment was performed under local anesthesia (excluding 5 pediatric patients), and patients were typically discharged 48 hours after hospitalization. Clinical and MR FU was scheduled every 6 months. RESULTS: the minimum FU period was 6 months. The overall median survival was 32.8 (4.1-68.8) months, with actuarial survival rates at 2 years and 4 years of 96% and 85%, respectively. Tumor growth control rate was achieved in 26/29 (90%) tumors. Post-GK surgery was required in 2/3 failures. To date, no recurrences or tumor malignant transformations have been reported. From a neurological point of view, 26/28 (93%) patients were stable/improved. No early post-GK complications have been observed. Delayed side effects due to radionecrosis occurred in 3/28 cases, 2 transient and 1 permanent. At the end of the study, 26/28 (93%) patients were still alive; one patient died due to a polytrauma, and the other due to a post-surgical complication, after a procedure performed for the occurrence of radionecrosis. CONCLUSIONS: this study suggests that GK, alone or combined with surgery, may be considered a valid primary treatment choice for LGNFBs in selected patients, achieving the high rate of severe side effects reported after RT in this relatively young adult patient series. The authors recommend limiting RT and/or CT for high surgical risk recurrences or tumor malignant transformations.

58. SALVAGE CHEMOTHERAPY WITH CARBOPLATINUM FOR RECURRENT OLIGODENDROGIAL TUMORS
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Purpose. A phase II study of carboplatinum as second-line chemotherapy was performed in adult patients with recurrent oligodendrogial tumors. Patients and methods. Seventeen patients with recurrent oligodendrogialomas and oligoastrocytomas after first-line PCV received carboplatinum 450 mg/m2 iv (10) or 600 mg/m2 (7) at 4-week intervals. Response was evaluated on CT/MRI according to Macdonald's criteria. Results. A median of 3 cycles of carboplatinum (range 2 to 6) were administered. Among patients receiving carboplatinum 450 mg/m2, no responses (CR or PR) were observed (0/10), whereas 3/7 (43%) of patients receiving carboplatinum 600 mg/m2 had a partial response. Median response and stable disease duration was 6 months with a greater myelotoxicity was observed among patients receiving the higher dosage. Conclusions. Carboplatinum at a dose of 600 mg/m2 has some activity on oligodendrogial tumors recurrent after PCV.

59. TEMOZOLOMIDE AND RADIATION THERAPY IN PATIENTS WITH UNRESECTABLE Glioblastoma OR WITH GROSS RESIDUAL MASS AFTER SURGERY

Temozolomide has been utilized as a single agent in patients with relapsing glioblastoma multiforme. In the present study, we report the results obtained by temozolomide associated with radiation therapy in 7 patients with unresectable glioblastoma multiforme or with gross residual mass after surgery. All patients with histologically proven glioblastoma multiforme were included in the study. Treatment schedule consisted of external beam radiation therapy with a Planning Target Volume (PTV) that includes a 1 cm margin around perilesional edema. Beams were arranged so that the PTV was included in at least 90% of the normal volume. A treatment-related side effect of 5,000 cGy in 5 weeks followed by a boost of 1,000-1,400 cGy with a reduced field on residual tumor, utilizing kinetic techniques when appropriate. After having delivered a dose of 5,000 cGy, the patient was discharged for 48 hours. In 5 days. We administered 2 additional cycles of temozolomide every 3 weeks in patients who did not show disease progression. Only one patient experienced WHO grade III thombocytopenia. In 2 patients, treatment was withdrawn after the first and the second cycle, respectively, because of disease progression. In the remaining 5 patients, there was a significant reduction of neurological symptoms and improved performance for both pain and intracranial pressure. In conclusion these preliminary data suggest that the association of radiation therapy and temozolomide is well tolerated. Although a significant reduction in tumor mass has not been documented, this regimen improved the quality of life in patients with inoperable glioblastoma multiforme or with gross residual mass after surgery. A higher dose regimen should be investigated in the future.

60. CELL KINETICS EVALUATION IN MENINGIOMAS PATIENTS
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Introduction: Meningiomas generally are benign in nature, but sometime can recur showing aggressive behavior. Pathological classification is considered not sufficient to predict recurrence and biological aggressiveness. Cell kinetics data can evaluate tumor growth rate. Some authors referred a relationship between bromodeoxyuridine (BrdU) labeling index and tumor recurrence. In these cases IV infusion to the patient prior to surgery was performed. Our cell kinetics evaluation is possible without IV administration of BrdU, but directly on surgical specimens. Results: 23 patients affected by meningioma and operated on were studied. The autoradiographic method of 3H-thymidine labeling index (TLI) and the flow cytometric evaluation of S-phase fraction of DNA ploidy were employed. In these patients TLI was 0.92 ± 0.72, mean value + S.D.; S-phase fraction was 2.3% as median value (4.7 + 0.47, mean value + S.D.); DNA index was 1 as median value (1.14 + 0.32, mean value + S.D.); of 23 samples appeared aneuploid. Conclusions: These data were not related to pathological classification, but cell kinetic values can be predictive of different growth rate. Further analysis on larger series is necessary to establish the role of cell kinetics parameters in the selection of patients with increased risk of recurrence, or regrowth after incomplete tumor removal.

61. 111-IN-OCTREOTIDE SCINTIGRAPHY IN HUMAN MENINGIOMAS: COMPARATIVE STUDIES IN VIVO AND IN VITRO

Purpose: This study correlates 111-In-octreotide uptake index (UI-OCT) with somatostatin receptors (Ssr) distribution observed in tissue samples and cultures of meningiomas and investigates the relationship between Ssr scintigraphy and the histologic and immunohistochemical markers of malignancy of the tumors. Methods: 47 patients with meningiomas underwent CT or MRI and 111-In-octreotide scans before surgery. A semi-quantitative UI-OCT index was computed on all studies. All surgical samples underwent pathological and immunohistochemical assessment. Cell cultures were obtained from 22 surgical specimen of patients. Results: UI-OCT was significantly correlated with presence of Ssr un-bound (p = 0.02) but non-significantly with Ssr-bound (p = 0.56). Ssr localization in meningiomas was significantly correlated with Ki-67 and expression was significantly correlated (p = 0.04 and 0.02 for Ki-67 and p = 0.43 and 0.13 for PCNA, respectively). Conclusion: The higher UI-OCT score predicts a high presence of Ssr in tissue sample and in cell cultures of meningioma and correlates with histologic and immunohistochemical markers of malignancy. UI-OCT may serve as a useful adjunct in presurgical evaluation of meningioma proliferative potential and influencing a clinical planning therapy.
62. INTRA-ARTERIAL CISPLATIN-RESCUE (AMIPHOSTINE AND SODIUM THIOSULPHITE) IN THE TREATMENT OF MALIGNANT GLIOMAS

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The Neuro-Oncology Group of Ancona - Regional Hospital has been in 1988. An important field of activity is the treatment of malignant gliomas. Our standard therapy is: radiotherapy plus intra-arterial chemotherapy with ACNU (hydrorosoluble nitrosourea). The aims of this trials are: 1) to ameliorate with cisplatin the good results obtained with ACNU intra-arterial chemotherapy; 2) to evaluate the reduction of treatment toxicity using a rescue with amiphostine + sodium thiosulfate. We know that the limiting factors of cisplatin administered as single agent via intra-arteral infusion are: neurologic toxicity in 30-50% of patients, ophthalmic toxicity in approximately 20%. Schedule: cisplatin mg 80/m in 20 min infusion in internal carotid or vertebral artery; amiphostine mg 1,500 in 15 min infusion starting 30' before cisplatin infusion; sodium thiosulphite mg 12,000/m in 45 min infusion after cisplatin administration.

Nine patients with recurrent malignant glioma were admitted to the study. Results: 1 pt presented a complete response, 3 pts stable diseases and 5 pts progressive diseases. Toxicity: 3 pts stopped the treatment for neurologic impairment; confusion and psycho-motor deficit in the first patient, empiareesis in the second patient, cephalgia and confusion in the third patient. One patient stopped the treatment for ophthalmic toxicity (amaurosis ipsilateral to arterial infusion). We can consider treatment safe as for systemic toxicity. Conclusion: the study was stopped definitely because of too high regional toxicity. We need more trial to improve the above mentioned results, using different schedules (doses and timing of both cisplatin and amiphostine-sodium thiosulfate).

63. RADIOTHERAPY + INTRA-ARTERIAL CHEMOTHERAPY WITH ACNU + ESTRAMUSTINE (EM) IN THE TREATMENT OF MALIGNANT GLIOMAS

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The Neuro-Oncology Group of Ancona - Regional Hospital has been in 1988. An important field of activity is the treatment of malignant gliomas. Our standard therapy is: radiotherapy plus intra-arterial chemotherapy with ACNU (hydrorosoluble nitrosourea). This report regards preliminary study on Estramustine + Radiotherapy (RT) + Intra-arterial Chemotherapy (IAC) for the treatment of malignant gliomas. EM is a derivate of beta-oestradiol + anotized mustard already used in prostate carcinoma. EM has antimitotic and radio-sensitizing activity on glioma cells, both in vitro and in vivo. This activity seems to be correlated to the Estramustine Binding Protein (EMBP), receptor present in high concentration in malignant glioma cells. Treatments: 1) RT, primary or following surgery, 60 Gy; 2) IAC with ACNU mg 100/sm every 6 weeks, 4 courses; 3) EM mg 360/die starting at the beginning of RT and ending 15 days after last course of IAC. Fifteen patients entered the study. All were treated with RT +/- IAC. Eight patients received EM too. The study was discontinued because of important vascular toxicity (thrombosis of deep venous system) in half of patients with EM. Of the other four patients treated with EM, two discontinued the treatment (one for remarkable water retention - one young female - the other for gastric intolerance). No toxicity in the seven patients treated without EM. Conclusion: EM in association with RT + IAC with ACNU gives an important toxicity that can limit the good response rate obtained with RT + IAC (ACNU) in the glioma treatment.

64. PCV CHEMOTHERAPY IN RECURRENT MALIGNANT GLIOMAS

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The present effectiveness of chemotherapy in the treatment of patients affected by malignant gliomas has remained limited and it is still debated the inclusion of CT in the first line therapeutic strategies. It is an emerging concept that chemo-sensitive gliomas represent a defined subset with clinical and bio-molecular specific characteristics. For this reason we retrospectively tried to correlate clinical-radiological response to PCV (procarbazine, lomustine and vin-cristine) chemotherapy with clinical neuro-imaging and biopathological characteristics. We treated sixty-nine patients affected by histologically confirmed malignant gliomas with PCV schedule, at recurrence after surgery and radiotherapy (30 anaplastic astrocytoma, 3 anaplastic oligo, 9 oligo-astrocytoma, 27 glioblastoma). For each patients we collected data about age, presenting symptoms, location of tumor, entity of surgical removal, MR aspects (volume, enhancement, necrosis ratio, edema), proliferation index measured with PCNA LI and p53 expression. Clinical and hystopathological data were analyzed in correlation with the response to the PCV treatment. Mean age was 62 years (range 24-73); Karnofsky status range 70-100. The response to chemotherapy was defined according to McDonald’s criteria. Follow up evaluation was performed each two months. 12 patients affected by anaplastic glioma (6 AA, 2 AO, 2 O-A) presented a complete response, 12 a partial response, 11 a progressive disease. No patients in the group affected by glioblastoma showed response to chemotherapy. The results showed that age, KFS and necrosis/tumor ratio are significantly correlated with the response to chemotherapy. Our data suggest that prognostic factors, in particular age and extent of necrosis, should be taken into account in clinical decisions concerning whether to treat patients affected by malignant gliomas with chemotherapy. Potentially chemoresistant patients should be considered only for experimental protocols with the purpose of evaluating new drugs and unconventional treatment modalities.

65. RADIOGUIDED SURGERY AND CEREBRAL NEOPLASM: METHODOLOGICAL ASPECTS AND PRELIMINARY RESULTS

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Surgical cytoreduction is the first step in the treatment of cerebral gliomas. Although the advancement of neuro-imaging in specifying the preoperative localization of the lesion facilitates the surgical approach and the preservation of functional brain areas, radical tumor removal is still a problem. Intraoperative ultrasonography is easy to be performed, but limited for quality of imaging and resolution. Neuro-navigation is a more innovative technique and the potential for a more accurate tumor localization. This technique is based on the use of a gamma probe for intra-operative detection of necrotic tissue, which was previously labeled with a radioactive tracer. The protocol consists of two steps: 1) a scintigraphic study of the brain at the iv administration of an oncotropic radiopharmaceutical (99mTc-tetrofosmin) for mapping the proliferative areas of the tumor; 2) the surgical procedure (within 24 hours from the scintigraphic scan), guided by a collimated gamma probe that may guide the surgeon to remove the radiolabeled necrotic tissue, even if it appears macroscopically intact. We observed a good correlation between CT and scintigraphic scans performed pre and postoperatively. The intraoperative detection by the surgical gamma probe was easy to perform and useful to distinguish tumor remnants from normal brain tissue.
66. CHEMOTHERAPY (CT) FOR CHILDHOOD LOW GRADE GLIOMAS (LGG); EFFECTIVENESS OF SINGLE DOSE CARBOPLATIN AND VINCRISTINE (VCR) PRELIMINARY REPORT: A COMBINED STUDY OF THE BRAIN TUMOUR SUB-COMMITTEE OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY (SIOP) AND OF THE GERMAN PAEDIATRIC ONCOLOGY AND HAEMATOLOGY GROUP (GPOH) - PRELIMINARY DATA

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Study Aim: to investigate the efficacy of one year CT with Carboplatin and VCR in delaying radiotherapy (RT) in children <5 years of age with a non-resectable, progressive LGG. Results: from 7/93 to 4/99, 124 eligible children were intended to be treated with CT (median age 34.7 m; M/F=69/55). The main patients’ characteristics are: NFl status 28 (22.6%); histology: Astrocytoma (A) no.s. 15 (12.1%); juvenile pilocytic A 63 (50.8%); clinical diagnosis 39 (31.5%); others 7 (5.6%); primary site: cerebral hemisphere 54; mid-line 49; resectable, progressive LGG.

67. "MULTICENTRIC" JUVENILE PYLOCITIC ASTROCYTOMA (JPA) STILL A CLINICAL AND THERAPEUTIC DILEMMA

G. Periélongo, M.L. Garré, L. Cordero, D. Walker, A. Gneckow, and I. Zanetti, for the Low Grade Glioma (LGG) Study of the International Society of Paediatric Oncology (SIOP). Trial centre: Division of Pediatric Oncology, Department of Paediatrics, University of Padova, Padova, Italy

Aim: To describe clinical characteristics and treatment outcome of 15 children who presented with a biopsy proven "multicentric" JPA entered into the SIOP-LGG Study (1994’98). Results- 11 were boys; age ranged from 4 to 193 months (median 11 months); the primary sites were: hypothalamic-chiasmatic region 11, cerebellum 2, basal ganglia 1 and medulla 1. All patients had an Gadolinium enhanced spine MR (not for protocol guidelines but for physicians’ decision). The "multicentric" nodules were located in the brain only in 1, in the spine only in 1, in the brain and spine in 4; in 5 it was unknown. They were located in sub-arachnoidal space, into the ventricles; areas of diffuse leptomeningeal enhancement were reported. The spinal nodules were always asymptomatic. Surgery at diagnosis consisted of biopsy in 9, partial resection in 4, near total resection in 2. None “multicentric” nodules were biopsied. 14 children were initially treated with Vincristine and Carboplatin as per protocol guidelines; one is presently only “observed.” 7 children are alive on first line treatment (median follow-up 7 months), 3 are alive with progressive disease at +15, +35, +41 months from diagnosis and 4 died of disease at 12, 16, 16, and 27 months, respectively. The one “observed” is alive with stable disease at +6 months. Conclusions- "Multicentric" JPA seem to affect preferentially, but not exclusively, young boys with an hypothalamic-chiasmatic primary. The natural history and the response to treatment of these tumours are far to be understood; despite an indolent course, they seem to bear a much worse prognosis than “classical” JPA.

68. LONG-TERM SURVIVORS AMONG PATIENTS WITH GliOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is still almost incurable despite every therapeutic effort. Median survival time is about 10-12 months in most series. Only a minority of patients survives more than 5 years, most of them actually dying from tumor recurrence or progression. In a retrospective analysis of patients with glioblastoma multiforme operated on during the 9-year period 1985-1993 in the Department of Neurosurgery of Verona, 13 patients were found, out of 437 harboring a GBM (3%), who survived more than 5 years. Four out of five died of radiation-related adverse events. At the moment of the diagnosis. Three of the latter patients had a second operation for tumor recurrence. One patient died from unrelated causes 87 months after diagnosis with recent radiological evidence of no tumor recurrence. One more patient, who sustained repeated surgery for tumor recurrence, was alive 11 years after initial operation but still bearing a recurrent tumor. The remaining 6 patients constitute a very unusual and peculiar group. All are alive from 7 to 14 years after diagnosis and treatment of Neure for follow-up controls. MRI scans showed no evidence of disease in all patients and this lack of recurrence of a tumor otherwise fatal may suggest their inclusion into a separate GBM category. Patients’ files and pathological specimens were reviewed in an attempt to identify distinctive features. Not unexpectedly, clinical data were not different from those of long-term survivors who had recurrences. Genetic analyses on blood leucocyte DNA (obtained in 5 patients) and DNA extracted from tumor at the time of the disease diagnosis, as well as the detection of viral sequences (SV40, BKV, JCV) in tumor and blood cells are currently under way. Although the preliminary results are conflicting, it is our opinion that the clues of potential GBM cure resides in these investigations. To support this hypothesis it is worth noting that one of these 6 patients underwent a bowel resection for colon cancer 4 years after GBM surgery. The diagnosis of Turcot syndrome was therefore established, a rare genetic disease which is known to be linked to unusually long survival of associated GBM.

69. PLEOMORPHIC XANTHOASTROCYTOMA: REPORT OF 17 CASES

G. Pinna, P. Cecchi, A. Alfieri, P. Iuzzolino*, and A. Bricolo, Department of Neurosurgery and "Service of Pathology, University City Hospital, Verona"

Pleomorphic xanthoastrocytoma (PXA) is an uncommon astrocytoma of childhood or young adults characterized by marked cellular pleomorphism and variable degree of intracytoplasmic lipid accumulation. It is generally regarded as a benign lesion, most frequently affecting adolescent and young adults. However, malignant progresses have been described and to date no clear guidelines exist to predict an aggressive behavior have been established. Survival rates are not clear as well due to the rarity of this lesion and the short follow-up of the reported cases. A series of 17 patients (7 male, 10 female) with PXA observed since 1986 in a single institution is described. Age ranged from 12 to 64 years (mean 29.8) with 4 patients over 50 years. A cystic component was present in 10 cases. Supratentorial lobar was the most common location but in 3 patients the lesion occurred in unusual sites (hypothalamus, quadrigeminal plate, cerebellum). Gross total removal of the lesion was achieved in 15 out of 17 patients; in 2 a subtotal and a partial excision was feasible. Postoperative adjuvant therapies were not considered in all cases. Only one patient, with an initial misdiagnosis of GBM, received postoperative radiotherapy. An additional case, with a very long history, received RT 22 years before surgery. Pathological findings included low or absent mitotic figures despite striking cellular pleomorphism in most cases (16/17). One case with increased mitotic activity and another with presence of necrosis were classified as WHO grade III. Spotty necrotic foci and leptomeningeal invasion were observed in two additional patients. All these patients had uneventful courses. Survival data are valuable in this series (mean follow-up 5,7 years). One patient had a fatal outcome due to a subtotally removed PXA (low mitotic figures, no necrosis) 10 years after first operation: GBM features were observed at recurrence. All the other patients are alive: 2 after 11 years, 7 after at least 3 years and 7 after at least 2 years, without evidence of disease in all patients and this lack of recurrence of a tumor otherwise fatal may suggest their inclusion into a separate GBM category. Patients’ files and pathological specimens were reviewed in an attempt to identify distinctive features. Not unexpectedly, clinical data were not different from those of long-term survivors who had recurrences. Genetic analyses on blood leucocyte DNA (obtained in 5 patients) and DNA extracted from tumor at the time of the disease diagnosis, as well as the detection of viral sequences (SV40, BKV, JCV) in tumor and blood cells are currently under way. Although the preliminary results are conflicting, it is our opinion that the clues of potential GBM cure resides in these investigations. To support this hypothesis it is worth noting that one of these 6 patients underwent a bowel resection for colon cancer 4 years after GBM surgery. The diagnosis of Turcot syndrome was therefore established, a rare genetic disease which is known to be linked to unusually long survival of associated GBM.
70. GENE THERAPY OF 9L GLIOSARCOMAS BY RETROVIRAL-MEDIATED GENE TRANSFER OF THE INTERLEUKIN 12 (IL-12) GENE

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IL-12 is a cytokine with a strong anti-tumor activity based on stimulation of natural killer (NK) cells, activation of cytotoxic T lymphocytes and an anti-angiogenic effects mediated by the IP-10 protein. We previously showed that 9L gliosarcoma cells transduced in vitro with the IL-12 gene may stimulate a relevant anti-tumor effect when injected into the brain of syngeneic Fischer 344 rats. We now evaluated the effects of the in vivo gene transfer of IL-12 into 9L tumors. 9L cells were co-injected in a 1:1 ratio with IL-12 retroviral producer cells (RPC) into the left striatum of Fischer 344 rats. 9L cells only (n=11) rejected the tumor; while the rats injected with 9L cells and control RPC died in one month. Survivors injected with 9L cells only into the right striatum rejected this second tumor challenge in 75% of the cases. MRI with a 1.5 T equipment confirmed histologically. Inflammatory cells were mostly macrophages, not T lymphocytes. We are now evaluating the effects of the injection of IL-12 RPC into established tumors. Further studies are also requested to test the efficacy of the system in other tumor models and to study the effects of systemic vaccination with gloma cells overexpressing IL-12.

71. DEVELOPMENT OF A NOVEL EXPERIMENTAL MODEL OF MURINE CENTRAL NERVOUS SYSTEM TUMOR AS A PROPEDEUTIC TOOL FOR AN IN VIVO GENE THERAPY APPROACH USING HERPETIC VIRAL VECTORS

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During the past few years many different immunomodulatory therapeutic strategies have been developed for the treatment of parenchymal brain tumors. However, the still poor availability of mouse models of central nervous system tumors, hampers the assessment of efficacy of these new therapeutic strategies. We have established a novel in vivo mouse model of brain tumors using low-grade astrocytoma cell lines obtained from previously developed GFAP-v-srsc transgenic mice (Weissenberg et al., 1997). We selected 3 out of 7 cell lines derived from these mice on the base of their growth kineric (low, moderate and high) and transplanted them stereotactically (50x106 cells in 5 µl) in the frontal lobe (x=-1.8, y=+1.6, z=-3) of Nude mice (CD-1 np). At the time of sacrifice (4 weeks p.i.) the mice developed tumor like lesions at the site of cell injection. The microscopic tumor analysis revealed cell phenotype resembling those of schwannomas. In order to test the potentiality of this model to be used for an in vivo gene therapy approach using non replicative herpetic vector (HSV) containing a reporter gene such as β-Gal gene, we tested the efficacy of HSV1-derived vectors to in contrast with the low-grade astrocytoma cell lines. All cell lines showed to be efficiently infected by the HSV1-derived vectors and no cytotoxic effects have been recorded with the infection doses of the vector used (1, 3, 5, MOI). Our results show a novel mouse model of brain tumor, which seems promising for experimental therapies based on the administration of non-replicative HSV1-derived vectors containing immunomodulatory molecules.

72. CLINICOPATHOLOGICAL CORRELATIONS IN PINEAL PARENCHYMAL TUMORS: STUDY OF 11 CASES IN PEDIATRIC AGE


We report a series of 11 pineal parenchymal tumors (PPT) in children (1982 and 1997). The patients included 5 boys and 6 girls, with mean age 10.3 years (range, 4 to 17 yr), with a prevalence of pilocytomas (9) versus pineocytomas (2). All the cases were investigated immunohistochemically, in order to characterize cell differientation and to find some correlation with the prognosis. The immunohistochemistry was performed using antibodies against: neuronfilaments (SMI32), synaptofilin, MAP2, N-CAM, chrogranin A, S100, GFAP, vimentin, PCNA and MiB1. Four patients had biopsies only; four biopsy and surgical removal; the resection was partial in 2 cases, subtotal in 2 and total in 3. All the patients affected by pineoblastoma received radiotherapy and 4 also chemotherapy. At neuropathological study neuronal differentiation was demonstrated in 3 pineoblastomas. Six patients with pineocytomas had tumoral progression and died in the disease. In these cases neoplastic dissemination was fatal. Both the patients with pineocytoma and three with pineoblastoma are still alive. Two survived patients presented a pineoblastoma with neuronal differentiation. The four cases with dissemination were negative for neuronal markers, and two showed strong immunoreactivity for N-CAM. The children with pineoblastoma who received radio and chemotherapy had a better prognosis. These results suggest that pineoblastoma is a rarer phenomenon, recently showed an increased incidence associated with worse prognosis. Materials, Methods and Results. Among 161 ovarian cancer patients admitted at our Institution during the period January 1992-December 1998, eight (5%) developed brain metastasis. According to the FIGO classification 6 patients were period January 1992-December 1998, eight (5%) developed brain metastasis. According to the FIGO classification 6 patients were
tomy, hysterectomy, selective lymphadenectomy and partial omen-
tectomy followed by chemotherapy was performed. Because of
advanced abdominal disease six patients underwent chemotherapy
and then a second look cytoreduction. In all cases cisplatin was
administered. Pathological examination disclosed a serious papillifer-
ous adenocarcinoma in seven cases and a poorly differentiated car-
cinoma in the remaining one. Considering 7 patients, brain metas-
tases occurred after a medium disease-free interval of 18.9 months.
Intracranial hypertension by a solitary cerebellar lesion constituted
the clinical onset in the last one. Four cases with solitary metastases
were submitted to surgery (1.9% of all treated intracranial metas-
tases) followed by whole-brain irradiation and focal boost. Radio-
therapy alone was reserved to multiple lesions. The combined treat-
ment compared with radiotherapy alone led to better results (median
survival, 14 vs 7 months). Conclusions. Up till now the majority of
ovarian cancer patients die for extracranial disease progression.
However incidence of brain metastasis is increasingly being
reported, as result of effective systemic chemotherapy and improved
locoregional surgical control. Their management presents no specific
therapeutic problems: surgery plus radiotherapy is the best option.
Neuroimaging surveillance should be performed in ovarian cancer
tumor survivors even in absence of local recurrence or systemic
dissemination.

75. NEUORADIOLOGICAL FINDINGS OF PRIMARY CEREBRAL NON-HODGKIN’S LYMPHOMAS IN IMMUNOCOMPETENT AND HIV-POSITIVE PATIENTS
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INTRODUCTION: Primary central nervous system lymphoma (PCNSL) has rapidly increased also in immunocompetent patients. Radiologically, PCNSL has no highly specific features. MATERIAL AND METHODS: From 1995 to 1998, CT and MR examinations of 34 AIDS-related PCNSL and 16 immunocompetent patients were analyzed. All were histologically verified. RESULTS: In 13/16 immunocompetent patients, well-demarcated iso-hyperdense lesions, with small rim of surrounding hypodense area (edema? infiltration?) were analyzed. On enhanced CT scan, 12 out of 16 presented dense and homogeneous enhancement. In AIDS-related lymphomas 11 showed ill-defined, hypodense lesions with patchy or slender ring-like enhancement. The enhancement was usually less intense (1 non-enhancing) than in immunocompetent group, but peritumoral hypodensity was larger. More frequent (10 vs 4) and massive was the subependymal infiltration, as well as central necrosis (18 vs 5). In both groups there was disproportion between size of the lesions and mass effect. MRI generally better detailed contrast-enhanced CT, in addition to the detection of subarachnoid diffusion (2 cases) and other atypical sites of involvement (2 cases). Basal ganglia were the most common sites of involvement in PCNSL, but we observed some atypical locations (cavernous sinus, ponto-cerebellar angle, diffuse involvement?) were found. On enhanced CT scan, 12 out of 16 presented dense and homogeneous enhancement. In AIDS-related lymphomas 11 showed ill-defined, hypodense lesions with patchy or slender ring-like enhancement. The enhancement was usually less intense (1 non-enhancing) than in immunocompetent group, but peritumoral hypodensity was larger. More frequent (10 vs 4) and massive was the subependymal infiltration, as well as central necrosis (18 vs 5). In both groups there was disproportion between size of the lesions and mass effect. MRI generally better detailed contrast-enhanced CT, in addition to the detection of subarachnoid diffusion (2 cases) and other atypical sites of involvement (2 cases). Basal ganglia were the most common sites of involvement in PCNSL, but we observed some atypical locations (cavernous sinus, ponto-cerebellar angle, diffuse microcerebral subependymal spreading, and gliomatosis cerebri like). Two patients had transient symptomatic contrast enhancing lesions. These “serotonin” lesions recurred spontaneously or with corticosteroid treatment. CONCLUSION: PCNSL is a disease with increasing incidence. Atypical presentations are becoming more frequent. Reliable distinguishing features of PCNSL were not found, but some findings were very suggestive. There were quite evident radiological differences between the two groups.

76. TREATMENT OF MEDULLOBLASTOMA IN POOR PROGNOSIS PEDIATRIC PATIENTS
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Medulloblastoma is a cerebellar midline tumor and accounts for
10% to 20% of primary CNS neoplasms in children and 40% of pos-
terior fossa tumors. We present 3 cases of poor prognosis medul-
loblastoma (according to Chang criteria) admitted to our Institu-
tions and treated with surgery and adjuvant therapies. At admission
all children had intracranial hypertension and cerebellar symptoms
in one case. Surgery was radical in all the cases (post operative MR).
Additional treatment consisted of post operative chemotherapy
(21 patients) according to AIO protocols plus 1 or 2 cycles of MEGA-CHT with autotransplantation of stam-
cinal cells in patients with poor prognosis medulloblastoma.

77. THE ROLE OF GLIAL FIBRILLARY ACIDIC PROTEIN IN THE DEVELOPMENT OF GLIOMAS
Inst., Milano; 4Univ. Wisconsin, Madison, WI, USA; 5Univ. Zurich, Switzerland

Extracellular matrix (ECM), integrins, or cytoskeleton constitute
primary molecules in development and regulation of tumors. Tumor
Cell proliferation and invasion require complex interactions between
the neoplastic cells and the surrounding matrix. Integrins behave as
intermediate molecules that transduce signals between ECM and and the
cytoskeletal compartment. Downstream events after integrin activa-
tion due to ECM-binding may include interaction with intermediate
molecules and cytoskeletal reorganization. Either ECM or integrins
are reported abnormally expressed in gliomas, and influence prolifer-
ation and migration of glioma cells in vitro. For example, we described the overexpression of the laminin-receptor integrin alpha-6 beta-4 in spontaneous gliomas in human and in chemically-induced
gliomas in rats. It would be, therefore, intriguing to interfere with
more downstream substrates of the ECM-integrin-cytoskeletal pathway
and evaluate neoplastic behavior. In glioma cells in vitro, over-
expression of stretch translation of the glial-fibrillary-acidic-protein
(GFAP), an intermediate filament of the astrocytic cytoskeleton,
respectively inhibits or favors growth and invasiveness. To address
the role of GFAP in the development and behavior of gliomas in vivo
and to test if GFAP could be a good target to interfere with
tumorigenesis, we decided to explore this question in transgenic
mice. Carrying the oncogene v-src under the control of GFAP
promoter develop astrocytomas in 30% of animals. By breeding
this transgene into the GFAP-null background we will estimate the
role of GFAP in the pathogenesis of gliomas.

78. UP-FRONT CHEMOTHERAPY (CHT) CONTAINING HIGH-DOSE METHOTREXATE (HD-MTX) FOLLOWED OR NOT BY RADIOTHERAPY (RT) IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS (PCNSL): A CRITICAL REVIEW OF PROSPECTIVE TRIALS
M. Reni, A.J.M. Ferreri, S. Dell’Oro, and E. Villa, Dept. of Radiotherapy, S. Raffaele H Scientific Institute, Milan

Aims: To identify the optimal RT following primary HD-MTX-
containing CHT for PCNSL and to analyze the impact on survival
(OS) of RT dilation at recurrence in complete responders to up-front
CHT (CRs). Methods: Intent-to-treat analysis was performed on 10
published prospective trials (186 pts) and 13 pts treated at our insti-
tution.

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<th>Patients' characteristics</th>
<th>WB dose (Gy)</th>
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<td>age PS Therapy n° &lt;60 / &gt;70</td>
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CHT-RT 165 60/116 51/77 68 89 3 30 40 93
CHT 34 15/34 11/18

Results:

| CHT-RT CRs Pts median 3 yr alive OS (%) TTF DFS OS |
|-----------------|-----------|---|---|---|---|
| CHT-RT 52 81(49%) 24 mo. 53 5 21mo. 9 6 71 6 |
| CHT 82 2 6(62%) 21 mo. 65 10 13mo. 33 12 77 10 |

p-level 0.001 0.11 0.09 0.44
Pts treated with WB < 40 Gy (p=0.06) or with 40-50 Gy (p=0.03) survived longer than those irradiated with > 50 Gy. Tumor doses of 40-50 Gy were associated to similar OS than < 40 Gy (p=0.09) and to a longer OS than > 50 Gy (p=0.03). Conclusions: WB irradiation with 30-36 Gy seems to be the optimum RT after HD-MTX-containing CHT. CHT alone was related to a higher a longer OS than > 50 Gy (p=0.03). Conclusions: WB irradiation with

97. RETROSPECTIVE ANALYSIS OF POSTSURGICAL THERAPY IN LOW GRADE (LG) AND ANAPLASTIC (AN) OLIGODENDROGLIOMAS (O) AND OLIGOSTROCYTOMAS (OA) M. Reni1, A. Franzin1, R. Moscioni2, A.J.M. Ferreri2, G. Truci1, C. Ferrari2, N. Canal1, and E. Villa1, Dept. of Radiochemotherapy, Neurosurgery and Clinic of Neurology-Centro M. Magueris University of Milan, S. Raffaele H Scientific Institute, Milan, Italy

Retrospective series reported contradictory results about the impact on survival of postsurgical radiotherapy (RT) in O and OA and anecdotal cases treated with postsurgical chemotheraphy (CHT). Thirty-four LG (29 O and 32 AN tumors (18 O) were treated between 1982 and 1998. Characteristics of patients and treatment performed are reported on table.

Grade treatment num age FS O frontal radical biopsy Gy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
<th>Age</th>
<th>FS</th>
<th>O</th>
<th>Frontal</th>
<th>Radical</th>
<th>Biopsy</th>
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<td>17</td>
<td>41</td>
<td>100</td>
<td>16</td>
<td>10</td>
<td>7</td>
<td>1</td>
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<tr>
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<td>surg RT</td>
<td>17</td>
<td>43</td>
<td>90</td>
<td>13</td>
<td>10</td>
<td>8</td>
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<tr>
<td>AN</td>
<td>surg RTCH</td>
<td>21</td>
<td>48</td>
<td>90</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>5</td>
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<tr>
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<td>11</td>
<td>42</td>
<td>90</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>60</td>
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</tbody>
</table>

In LG tumors, 5-year survival was 77 ± 15 % for patients receiving adjuvant CHT and 43 ± 13 % for patients treated alone (p=0.18). In AN tumors, CHT prolonged 5-year survival as compared to RT alone (54 ± 17% vs. 20 ± 10%, p=0.004). Multivariate analyses, stratifying patients according to age, FS (both as continuous variables), site of surgery and RT use (LG) or CHT use (AN) confirmed the independent positive impact on survival of frontal lobe location and higher PS for LG tumors and of frontal site and CHT use for AN tumors. In both analyses, younger age was nearly significantly related to better survival (p=0.06). Our findings raise doubts on the efficacy of postsurgical RT in LG patients and provide further signs of the chemosensitivity of AN tumors.

80. EARLY RESULTS OF A PHASE II STUDY OF TEMOZOLOMIDE IN CHILDREN WITH HIGH GRADE GLIOMA R. Riccardi, G. Cefalo*1, M.L. Garze1, A. Ruggiero, V. Riodola, and C. Di Rocco*, Division of Pediatric Oncology, Section of Pediatric Neurosurgery, Catholic University, Rome; *Division of Pediatrics, Istituto Nazionale dei Tumori, Milan; **Division of Pediatric Oncology, Istituto G. Gaslini, Genova

Temozolomide (Temo) is an orally active alkylating agent with antitumour activity in high grade astrocytoma. Phase II study suggested dose is approximately 200 mg/m2 x 5 d in children. We undertook a phase II study in refractory or relapsed high grade gliomas, heavily pretreated with radiotherapy and chemotherapy. Temo has a short half-life and multiple daily dosage may keep drug plasma concentration. Phase II study suggested dose is approximately 200 mg/m2 x 5 d in children. We undertook a phase II study in refractory or relapsed high grade gliomas, heavily pretreated with radiotherapy and chemotherapy. Temo has a short half-life and multiple daily dosage may keep drug plasma concentration.

81. PROGNOSTIC CONSIDERATIONS OF PROLIFERATIVE INDEX, PROGESTERON AND ESTROGEN RECEPTOR STATUS IN MENINGIOMAS F. Riccio, M. Del Basso De Caro, B. De Divitiis*, F. Cappabianca, and G. Petrinati, Department of Science Biologiche e Funzionali - Sez. di Anatomo Patologica, [Cattedra di Neurochirurgia, Università di Napoli; *Servizio di Citogenetica - Ospedale E. D’Aosta - ASL NA1, Napoli

The behavior of meningiomas and the risk of recurrence cannot be predicted by clinical and histopathological features alone. The purpose of this study was to correlate the biological behavior of a series of 17 meningiomas to one or more risk factors. The current study was compared to a second control group of 30 patients without recurrence. The prognostic value was based on the analysis of clinical data, histopathological subtype, tumor grade, proliferative index (using mitotic count and the Ki-67 antigenic index from immunohistochemistry with Ki-67) and on determination of female sex hormone receptor status (ERs and PRs). Among clinical parameters, the extent of surgical resection was the only one with prognostic value. Moreover, although the meningioblastomatous and transitional meningiomas (grade I) have a more prolonged disease-free survival compared to atypical meningiomas (grade II), tumor grade and histopathological subtype had no significant effect on recurrence rate, indicating that the proliferative potential of the tumor cannot be determined only by histology. These data, statistically analyzed by the X2 test, the Pearson’s coefficient and Mantel-Haenszel for linear associations test, appear to support the good correlation between the proliferative index and a shorter progression-free survival. About PR status, the estrogen receptor for their role in meningiomas seems to be significant in both groups. These data indicate that the presence of PR status is a favorable prognostic factor for meningiomas.

82. MULTICENTRIC GLIOMA IN A 12-YEAR-OLD BOY F. Rychlicki, N. Zamponi1, A. Ducati, L. Regnicolò*, and R.A. Ricciucci, Departments of Pediatric Neurology, Children's Hospital G. Salesi, Ancona 2Department of Neuroradiology, University of Ancona

Introduction. In the literature single cases or short series of multicentric gliomas (M.G.) are reported, quite adults patients. We report the case of a child with Multicentric anaplastic glioma and discuss some diagnostic and pathogenetic problems. Case report. In August 1988, a 12 years old boy was admitted to the Pediatric Intensive Care Unit with a three days history of fever, partial seizure and comatous state. CT scan and EEG were consistent with a right temporal encephalitic lesion. Serum examination detected positively for EBV infection. (sternal treatment internal, anti-convulsive, antiepileptic drugs) produced a gradual improvement of neurological status, but three weeks later the child was readmitted for fever, headache, vomiting, seizure and left hemiparesis. CT and MRI revealed an increase of the right hypodense temporal lesion and a new left frontal lesion with a strong contrast enhancement. A right temporal lobectomy with a large tumor excision followed by a subtotal resection of the frontal mass was performed. They were both anaplastic glioma but the frontal one showed a more aggressive picture. The post-operative neurological status improved but 15 days later the child was detected two other lesions, bilaterally in the retrotrigonal region. Discussion. Owing to the first incorrect diagnosis we observed the natural history of a true multicentric glioma. We could not identify a single case in the medical literature. The clinical picture completely different from the first one but was well explained by the hystological pattern of the two tumors. It seems pathogenetically interesting to stress the presence of positivity for EBV reinfection markers and the acute varicella zoster infection closely related in time to the appearance of tumoral masses.

83. STEREOTACTIC RADIATION THERAPY IN CHILDHOOD BRAIN TUMORS: PADOVA EXPERIENCE G. Scarzello*, G. Petrinati, B. De Divitiis*, and G. Faggian†, Departments of Department of Radiation Oncology, Pediatric, Neurosurgery and Physics, Azienda Ospedaliera, Università di Padova

From October 1997 to May 1999, 26 selected children with intracranial neoplasms underwent SRT at the Radiotherapy Depart-
adapted 6-MV linear accelerator equipped with the XKnife Stereotactic Radiotherapy System. Treatments were given everyday by 3 to 5 arcs, median 4, with fractions of 1.8-2 Gy, till a dose ranging from 16 to 54 Gy, median 54 Gy. The collimators size ranged from 25 to 47.5 mm, median 37.5 mm. A Gill-Thomas-Cosman or a Boston Children' Hospital relocatable frames were used during planning and treatment, respectively for collaborative or non collaborative children, the compliance to both was good. 6 children were treated under anesthesia. With a follow-up ranging from 2-16 months from the end of RT with a median of 9, 3 children, 2 with high grade glioma and 1 with relapsed ependymoma died of disease progression. The remaining 23 children are alive in complete remission or stable disease. All our patients had at least one follow-up radiographic study. Our preliminary results demonstrated 3 tumor progressions respectively at 3, 4 and 6 months from the end of therapy affecting the respective mentioned patients. Two children showed a radiological progression one of these complete. All other patients have a stable disease. All children tolerated the treatment well and no acute complications were seen. Our preliminary results are encouraging and the study is continuing to determine whether this regimen improves tumor control without increasing the complication rate.

84. SOMATOSTATIN RECEPTORS SCINTIGRAPHY IN CHILDREN WITH CNS TUMORS
A. Schiavetti, P. Maurizi, G. Varrasso, R. Massa, G. Trasimeni, C. Carabella*, and M.A. Castello, Pediatrics Department and Radiology Department, University of Rome “La Sapienza,” * Dept of Neurosurgery, Inst Regina Elena – Rome

INTRODUCTION: Somatostatin receptors (SR) are surface markers characterizing not only neuroendocrine tumors but also malignancies without neuroendocrine expression. In111-pan-tetrotide is a new radiolabeled somatostatin analog introduced for the in vivo imaging of SR positive tissues. METHODS: In an attempt to evaluate the clinical usefulness for tissue characterization in brain tumors, somatostatin receptors scintigraphy (SRS) was performed in comparison with contemporary RMI in 9 children affected with brain tumors. The patients (pts.) were affected by medulloblastoma (MB), 1 low grade astrocytoma (LGA), 1 germ cell tumor (GCT) and 1 ependymoma (EP). RESULTS: In three relapsed MB with MRI positive, SRS was performed at relapse and it was positive in all cases. The presence of tumor was confirmed at surgery in one case; in the other two cases both MRI and SRS were repeated after chemoradiation (CRT) and both imaging techniques showed a shrinkage of tumor. In these patients SRS was useful to elucidate the presence of tumor recurrence before surgery and CHI. In two MB patients at onset, MRI and SRS were performed after total surgery and after total surgery and radiotherapy (RT) respectively. In both pts. MRI was negative while SRS was positive. After CRT one in case and after surgery the other one, SRS became negative. In one other case of MB off-therapy MRI was uncertain for residual tumor but SRS was negative; this patient was well at longer follow-up. In three pts. (LGA, GCT, EP) with MRI positive for gross residual tumor after partial surgery, SRS was negative in all cases. EXCLUSIONS: In our small series SRS allowed a differential diagnosis of MB versus other CNS tumors. In MB, SRS was useful to confirm the presence of tumor in macroscopic disease while it seems more sensitive than MRI in microscopic disease. In one MB case SRS was useful to differentiate disease from post-therapy effects. Further evaluation is needed to establish the sensitivity and the specificity of this new-imaging technique in children with CNS tumors. The goal is to differentiate between various CNS lesions before surgery, to evaluate the response to treatment, and to elucidate the differential diagnosis between tumor recurrence, necrosis and edema, in the postsurgical and post RT/CHT evaluation.

85. POSSIBLE PROGNOSTIC SIGNIFICANCE OF CHANGES OF GENE PROTEIN REGULATING THE CELL-CYCLE IN GLIOMAS
D. Schiffer, P. Cavalla, S. Bortolotto, L. Chiadò-Piat, and N. Di Vito, Department of Neuroscience, University of Turin

Deregulation of cell cycle is an important event in the tumor transformation. In malignant gliomas, it becomes evident when astrocytomas transform into anaplastic astrocytomas and glioblastomas. At least one of the following components of the cell cycle regulation is altered: CycD1, CDK4, pRb, CDKN2/p16, p27/Kip1. These genes/proteins have been studied by immunohistochemistry and PCR technique in a series of 70 astrocytic and oligodendrogliocytic gliomas. Their labeling indexes (LI) were compared with malignancy grades and evaluated as possible prognostic factors. Even though their changes correlate with histological malignancy, only p27/Kip1 could be discussed as a possible prognostic factor. The other proteins showed an overlapping of their LI ranges in different malignancy grades. Defective correlation of immunohistochemistry with molecular genetics, regional variability, heterogeneity of tumor cells for the proteins and tumor cellularity made the recognition of the above mentioned proteins as prognostic factor difficult. For CDKN2/p16 the possibility must be considered that cases negative for the protein do not show homozygous deletion, but methylation of CpG islands promoters. Supported by AIRC, Milan

86. MULTILOBATED LYMPHOMA OF B CELL TYPE: REPORT OF ONE CASE OF (CNS) CENTRAL NERVOUS SYSTEM
A. Siciliano, P. Riccio, A. Monticelli, B. De Divitiis*, F. Pappabianca, and G. Pettinato, Dipartimento di Scienze Biomorfologiche, cliniche e Funzionali - Sez. di Anatomia Patologica, [Cattedra di Neurochirurgia, Università di Napoli; * Servizio di Citogenetica - Ospedale E. D’Aosta - ASL NA1, Napoli

Malignant lymphomas with multilobated nuclei are rare neoplasms of the immune system, initially thought to be of T-cell type. Actually, they represent a somewhat heterogeneous group of lymphoid tumors displaying different morphological, clinical and immunophenotypic features. We report a case of a 70 years old woman affected by non-Hodgkin's lymphoma of CNS, composed of large, polymorphous cells, characterized by multilobated nuclei, sometimes with prominent nucleoli and distinctly basophilic cytoplasm, intermingled with scattered small lymphocytes and rare histiocytes. Mitotic index resulted elevated. A battery of immunohistochemical stains intended to detect epithelial and lympho-reticular antigens, was employed in this study, as well as ultrastructural examination. Neoplastic cells stained positively with CD43, a pan-leukocyte marker, and with L26, a B-cell marker. Negative were the immunoreactions with CK, EMA, VIM, Cromogranin, Ki-1 and UCLH-1 (T-cell marker). The ultrastructural study showed a monomorphous proliferation of large cells with irregularly shaped, frequently multilobated nuclei and one or more peripherically located prominent nucleoli. The cytoplasm was abundant and contained several ribosomes and sparse cisternae of rough endoplasmic reticulum and a well developed Golgi complex, with many vesicles. All these features were consistent with a B-cell non Hodgkin's lymphoma, with large multilobated cells.

87. PROGNOSTIC VALUE OF THE PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA) AND THE Ki-67 IN 34 CASES OF OLIGODENDROGLIOMAS
A. Siciliano, M.L. De Caro, A. Monticelli, B. De Divitiis, and P. Pappabianca, Dipartimento di Scienze Biomorfologiche e Funzionali - Sez. di Anatomia Patologica, [Cattedra di Neurochirurgia, Università di Napoli; *Servizio di Citogenetica - Ospedale E. D’Aosta - ASL NA1

Thirty-four pure supratentorial oligodendrogliomas were investigated using proliferating cell nuclear antigen (PCNA) and Ki-67 immunohistochemical analyses. The percentages of immunoreactive cells (Labeling Index - LI: positive nuclei/total number of counted nuclei x 100%) were compared with the clinical features and outcome of these patients. The PCNA LI had a range of 0.70% (mean, 38%, SD=64.01). The mean survival time of patients was 5.38 years. The data were statistically analyzed by the Kruskall-Walls test to define the correlation between the different variables. Ki-67 and PCNA staining indicated that patients with a high LI had a significantly higher survival, with mean survival time of 3.27 years and 3.38 years, respectively. No significant correlation between LI and tumor size, central location of the lesion total or incomplete resection, radiation, sex age or preoperative Karnofsky rate was found. The data obtained in this study show that the use of immunohistochemistry for cells cycle related antigen, especially for the Ki-67, is a tool in predicting clinical outcome of patients with supratentorial oligodendrogliomas, especially for well differentiated oncocyttes, in order to identify those which are disposed to rapid recurrence.
88. SYSTEMIC TREATMENTS FOR GLIOMA: A SYSTEMATIC REVIEW OF THE RANDOMISED CLINICAL TRIALS

A. Silvani, A. Solari, M. Pozzi, A. Boiardi, and G. Filippini, Istituto Nazionale Neurologico "C. Besta" - Milano

The objective of this systematic review is to assess the outcome benefits from the use of systemic therapies in gliomas. Included interventions are randomized controlled trials (RCT) of adults with high-grade malignancies or low-grade glioma in which chemotherapy has been compared with neurosurgery followed by post-operative radiotherapy (hyperfractionated or conventional). The outcomes assessed in the review are local tumor control, recurrence and survival. Treatment related toxicity using common toxicity criteria (NCI/WHO/EORTC/MRC) is also assessed. RCT are identified from multiple databases (MEDLINE, EMBASE and CCTR/CENTRAL). References, conference proceedings, and Science Citation Index searches are also used to locate trials. Statistical estimation and assessment of methodological quality are done by two independent reviewers. Data extraction forms are used including specific assessment of the 4 main sources of bias, selection, performance, attrition and detection. 31 articles have been included up to now. Where clinically and statistically sensible, raw data are pooled and statistically analyzed. Heterogeneity will be assessed and, when it can be explained on the basis of differences in methodological quality or study characteristics, we will consider presenting the results in a series of sub-group analyses. If this is not the case consideration will be given to calculating an "effect size" using an appropriate statistical model (e.g. fixed effects, random effects).

89. M-BACOD CHEMOTHERAPY IS EFFECTIVE AS FIRST TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

A. Silvani, M. Eoli, A. Salmaggi, L. Fariselli, and A. Boiardi, Istituto Nazionale Neurologico "C. Besta," Milan

The optimal treatment of PCNSL has yet to be defined, but several studies show that the addition of high-dose methotrexate based chemotherapy before radiotherapy has increased median survival time about 40 months. In this study, the M-BACOD scheme was delivered prior to irradiation in a group of 20 PCNSL patients, other 8 PCNSL patients underwent radiotherapy only and the overall survival was evaluated. NMR scan images in the group of patients treated with chemotherapy, displayed 70% of CR, 15% of PR and 15% of PR. Half of the CR patients were scheduled for radiotherapy only at tumor recurrence. The TTP and ST of the whole group treated with early chemotherapy followed by radiotherapy, were 24 and 32 months respectively, but in the subgroup of CR (75%) taking into account also the patients not yet receiving radiotherapy it was 38 and 48 months respectively. The TTP and ST in the group of CR (75%) of patients treated only with radiotherapy was 13 and 18 months respectively. Patients CR to chemotherapy at tumor recurrence had a second disease-free period longer than two years after radiotherapy. Our data support the knowledge that in scheduling the treatment of PCNSL after histological diagnosis, the first step is delivering high-dose chemotherapy with doxorubicin, bleomycin, etoposide and procarbazine; blood-brain-barrier. Our primary approach with early chemotherapy in PCNSL, corroborates a consensus to continue chemotherapy until tumor recurrence, and only at that event initiate radiotherapy.

90. TEMOZOLOMIDE IN ASTROCYTOMAS AND OLIGODENDROGLIOMS

R. Soffietti, A. Cucatto, M. Nobile, and R. Ruda, Division of Neurology, Department of Neurosciences, University of Torino

Background: Temozolomide (T) has shown significant activity in phase II trials against malignant melanoma and gliomas, with a very favorable toxicity profile. We designed a phase II study to evaluate the activity and toxicity of (T) in pretreated patients (P) with recurrent (G). Methods: from January to July 1998, 21 (P) with recurrent anaplastic astrocytomas (12), glioblastoma multiforme (8) and oligodendroglioma (1), previously treated with chemoradiotherapy (17) or radiotherapy alone (4), were given (T) 150 mg/ms po daily x 5 q 28 days (median number of courses 4). (P) were evaluated every 2 courses by MRI. Results: all 21 (P) are still alive at this moment. (T) is an active and safe drug in recurrent (G) and deserves further evaluation in the treatment of this disease.

91. RESULTS OF COMBINED TREATMENT OF POSTERIOR FOSSA EPENDYMOMA IN CHILDREN

D. Spagnoli, G. Ceccarelli, G. Tomei, N. Grimoldi, L. Bello, D. Portaleone, E. Veggetti, A. Sergio, M. Moioli, and R.M. Villani, Institute of Neurosurgery, Ospedale Policlinico, IRCCS and Dept. of Pediatric Hemato-Oncology G. e D. Marchi, Milan

This study investigated the relevance of prognostic factors and the impact of histological features in posterior fossa ependymoma in children. The charts of 15 patients (aged 1-14 yrs, mean 6.1 yrs) operated on between January 1983 and December 1994 were reviewed and the patients followed up. A gross total resection was performed in 9 patients (60%) a subtotal in 6 patients (40%). One patient developed respiratory complication and died (6.6%). Out of 5 children less of 2 years, 4 initially received chemotherapy and then radiotherapy only when at least 3 years old. Ten patients underwent posterior fossa radiotherapy (mean dose 50 Gy) after surgery and 3 patients lower doses (35 Gy), because younger than 4 yrs old. Slides were reviewed and classified according to WHO classification. The global 5 years survival rate was 71.4% (mean follow-up 93 months). This review suggests the following conclusions: a) younger patients (3 years old or less), despite of multimodality treatment, have a poor prognosis; b) tumors arising from lateral recess are more likely to be subtotal resected and are related to a shorter survival; c) longer survivals are associated with a complete removal (p<0.05); d) the histological feature most related to a poor prognosis is a high mitotic index (p<0.05), whereas vascular proliferation, necrosis, nuclear atypia and high histologic grade do not affect survival; e) histological diagnosis of ependymoma or anaplastic ependymoma (WHO classification) is of no prognostic relevance.

92. ACTIVITY OF TEMOZOLOMIDE IN RECURRENT MALIGNANT GLIOMAS: A PHASE II STUDY


Background: Temozolomide (T) is an active and safe drug in recurrent (G) and deserves further evaluation in the treatment of this disease.
94. ON THE PARANEOPlastic ORIGIN OF CANCER-ASSOCIATED MOTOR NEURON DISEASE (MND)
M.C. Vigliani, P. Polo, A. Chio², B. Giometto¹, M.L. Mazzini², and D. Schiffer, Dept of Neuroscience, Univ of Turin; ²Neurology Clinic, Univ of Padua; ³Maugeri Centre, Veruno

A possible paraneoplastic origin of MND has been suggested, but it is still controversial. To address this issue, we have examined a series of patients affected by both MND and cancer to evaluate whether: i) some forms of cancer-associated MND can be considered as a distinct clinical entity; ii) anti-neuronal system antibodies are present in these patients; iii) cancer-associated MND can benefit of the oncological therapy. Four cases of ALS associated with other neurological signs (ALS plus) showed anti-HU-antibodies, suggestive of a paraneoplastic origin, but they were eventually classified as paraneoplastic encephalomyelitis. Twelve cases of pure ALS associated with a solid cancer resulted indistinguishable from classic ALS, did not bore anti-neuronal system antibodies and did not benefit of cancer treatment. Similarly, in two cases of pure ALS associated with lymphoproliferative diseases, no anti-neuronal system antibodies were found and MND symptoms did not improve after cancer therapy. All these patients fared worse than ALS cases without cancer and all of them died as a consequence of the neurological syndrome. These observations indicate that, except for those cases of ALS plus, in which MND symptoms can part of a paraneoplastic encephalomyelitis, a cancer-associated MND cannot be considered as a distinct clinical entity of paraneoplastic origin. In addition, these patients do not benefit of oncological treatment and their neurological syndrome progresses at a faster pace.

95. MALIGNANT ANGIOENDOTHELIOMATOSIS, A PRIMARY INTRAVASCULAR (ANGIOTROPIC) LYMPHOMA. HISTOPATHOLOGICAL, HISTOCHEMICAL AND ULTRASTRUCTURAL FEATURES: CASE REPORT
F.S. Zeppetella Del Sesto, A. Monticelli, A. Siciliano, P. Cappabianca, and G. Pettinaro, Dipartimento di Scienze Biomorfologiche e Funzionali - Sez. di Anatomia Patologica, [Cattedra di Neurochirurgia, Università di Napoli

Malignant angioendotheliomatosis (MAE) is an uncommon, controversial disease characterized by a disseminated intravascular proliferation of atypical mononuclear cells within the lumina of venules, arterioles, capillaries and small arteries, mainly in the skin and the central nervous system. The histogenesis of neoplastic cells has been the subject of long-standing controversy. Early investigators concluded that this entity represented a neoplasm of endothelial cells but, last evidence has suggested a lymphoid origin. We report a case of a 61 years-old woman, with a MAE sited in the rolandic area. A battery of immunohistochemical stains, intended to detect epithelial, endothelial and lympho-reticular antigens, was employed in this analysis, as well as an ultrastructural observation, the result of which constitute the basis of this report. Neoplastic cells stained positively with CD45, a pan-leukocyte marker, and with L26, a B-cell marker. Negative was the immunoreaction with factor VIII-related antigen, an endothelial cell marker. Furthermore, the ultrastructural study disclosed a predominant cell type lacking features both of epithelial or endothelial differentiation. These results provide additional evidence that malignant angioendotheliomatosis is a diffuse intravascular malignant lymphomatosis.

96. ISOLATED CENTRAL NERVOUS SYSTEM RELAPSE IN ADVANCED AGGRESSIVE NON-HODGKIN’S LYMPHOMAS
P.L. Zinzani, M. Magagnoli, E. Barbieri*, C. Cellini, V. Stefoni, L. Babini*, and S. Tura, Institute of Hematology and Medical Oncology “Seràgnoli”, *Institute of Radiotherapy “L. Galvani,” University of Bologna

Isolated central nervous system (CNS) relapse was evaluated in terms of incidence, risk factors, and outcome in a consecutive cohort of 202 patients between 1991-1997 with advanced aggressive non-Hodgkin’s lymphoma in which no case of lymphoblastic or Burkitt’s lymphoma was encountered. All these patients had obtained a complete remission with first-line treatment and none had received prophylactic CNS treatment at diagnosis. Eleven patients (5.4%) developed isolated CNS relapse after a median of 8 months from diagnosis. CNS involvement was documented by cerebrospinal fluid (CSF) cytology in 4 patients and on the basis of radiological and clinical features in 7 others. Factors significantly associated with a greater likelihood of CNS relapse were advanced stage, B symptoms, bone marrow involvement, and high LDH levels in univariate analysis, with only advanced stage being of significance in multivariate analysis. All relapsed CNS lymphoma patients died within a median time of 6 months from the disease recurrence, confirming the poor prognosis after CNS relapse and stressing the need to develop new treatment strategies for patients at high risk of CNS recurrence.