15140 Response-adapted sequential combination chemotherapy (CEBOPP/VIML) followed by radiotherapy for bulky and advanced-stage Hodgkin's disease  
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Introduction: To improve the results in patients (pts) with bulky or advanced-stage Hodgkin's disease, a combined modality treatment including a response-adapted sequential combination chemotherapy was used. O-CSF was additionally used in pts with severe or prolonged neutropenia or infection during CT.

Patients and treatment: From 11/96 to 1/98, 71 pts (42 males, 29 females) with a median age of 31 yrs (range 17-60) were treated. 7% of pts had stage I, 45% stage II, 35% stage III, and 13% stage IV disease. B-symptoms were present in 56% of pts, bulky disease (w > 5 cm) in 85%, extranodal involvement in 24%, splenic involvement in 20%, high ESR (≥ 30 mm) in 61%, and abnormal LDH (≥ 240 U/l) in 41%. CT started with a regimen consisting of cyclophosphamide (400 mg/m^2 d3), doxorubicin (40 mg/m^2 d1,2), bleomycin (30 mg d1, 10, only for the first two cycles), vincristine (2 mg d1, 10), prednisone (100 mg/m^2 d1-10), and procarbazine (60 mg/m^2 d1-10) (CEBOPP) repeated every 3 wks. In pts with residual tumor after a maximum of 4 cycles of CEBOPP, this regimen was continued for further 2 cycles. In pts with progressive disease or residual tumor, therapy was switched to a regimen consisting of VP-16 (130 mg/m^2 d1,3,5), ifosfamide (1300 mg/m^2 + mesna d1-5), methotrexate (70 mg/m^2 + leucovorin rescue d1,5) (VIML) repeated every 3 wks for 2-4 cycles. CT was followed by an adjuvant RT (30 Gy, 2 fractions) in stage I, II, and IIIA disease. In case of residual tumor or initially bulky disease, a higher irradiation dose (40 Gy) was given.

Results: Alopecia, leukocytopenia, and peripheral neuropathy were the most frequent toxicities of therapy. An overall response rate of 98% was achieved. The rate of complete response (CR) (no residual tumor or residual tumor of 2 cm or less) was 69% and the rate of partial remissions (PRs) (residual tumor larger than 2 cm) 29%. PRs were mainly seen in pts with bulky mediastinal disease. With a median follow-up of 54 months, the projected survival in the whole group of pts is 89% and 91% of pts with CR or PR are projected to be in continued remission at 88 months.

Conclusion: Based on these results, the therapeutic concept used appears to be highly effective in achieving remission, long-term relapse-free and overall survival in a large proportion of pts with bulky and advanced-stage Hodgkin's disease.

5150 Correlation between evolution of bcl-2/flg expression during treatment and outcome in follicular lymphomas (FL) with t(14;18)-bearing tumors P. Soubyeran, I. Hostein, M. Deblie, H. Eghbali, I. Soubyeran, F. Bonichon, T. Astrer-Gin, B. Horrm. Institut Bergonie, INSEMF 328, Bordeaux, France

Introduction: Follicular lymphomas (FL) are characterized by slow growing pattern, delayed responses and often late relapses. These features makes treatment decisions difficult. We worked on the hypothesis that, since bcl-2 is involved in resistance to chemotherapy, variations of its expression during treatment could predict for FL outcome.

Methods: We decided to use a RT-PCR assay able to detect bcl-2/flg mRNA in FL. A set of forward and reverse primers was designed on bcl-2 and flg. For this purpose, we analyzed 180 serial peripheral blood samples (PBS) in 34 treatment phases (TPh) of 25 patients (pts) with t(14;18)-bearing tumors. In all pts but 2, bcl-2/flg gene over-expression was demonstrated in pretreatment samples.

Results: During sixteen TPh (47%), bcl-2/flg expression converted to negative, although sometimes transiently (6 TPh). All but one were responders to chemotherapy, either partial (PR) (4) or complete (CR) (11). Bcl-2/flg expression remained detectable in 18 TPh; eight achieved PR and two CR while 8 failed to respond to treatment. We observed a significant correlation between RNA PCR results and response (p = 0.002). Three-year overall survival of patients with stable bcl-2/flg negative conversion was 100% compared to 54% for the remaining patients. Male stenlity could be managed by prior semen preservation (SP). However, semen quality in such circumstances could be poor with either a low amount of spermatozoid or functional abnormalities, and could not allow a successful insemination. In order to evaluate semen quality of male patients (pts) with HD and the outcome of insemination, we reviewed the spermogram of these patients who underwent SP just before cryopreservation. This cohort included 94 pts with following criteria. 1) age > 16 and < 50; 2) HD of any stage; 3) performance status (PS) of 0 to 2; 4) consent for SP. The more common presenting symptoms were: dyspepsia in 66 (20%), cough in 54 (28%), haemoptysis in 52 (27%) and hoarseness in 41 (21%). The diagnosis was established by histological examination in 118 (60%) and sputum cytology or FNA in 30 (15%). Both examinations were positive in 48 (25%) pts. Histological subtypes were estimated in 170/196 (87%) cases.


2-CdA (2-Chlorodeoxyadenosine) has been reported to be an effective treatment in previously treated low-grade lymphomas. Aim of the multicenter-study was to evaluate the rate and duration of remissions and to examine toxicity and immunosuppressive effects of 2-CdA in low grade lymphomas as first line therapy in first line setting. Data will be presented at this meeting.
Therapeutic management and results of 21 patients with post-transplantation lymphoproliferative disorders

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Introduction: PT-LP after solid organ transplantation (TX) is a serious complication and the third leading cause of death beyond the four postoperative weeks. No uniform treatment strategy exists.

Methods: From 410 to 1035 PT-LP were observed in 1695 patients (pts) after solid organ TX (heart=13; lung=1; liver=7). In 16 pts diagnosis was postmortem. 4 out of 17 pts presented in stage I and were treated with surgical extirpation +/- radiation. Three of these pts achieved complete remission (CR) but one pt relapsed and died PT-LP-associated. In the remaining 13 pts the immunosuppression was reduced. CR were obtained in 2 pts and progressive disease in 11 pts. These remaining 11 pts (stage II-IV) received cyclophosphamid- and adalimumab-based combination chemotherapy. Four pts achieved prolonged CR but 4 pts died: therapy- or PT-LP-related. Three pts got second line therapy with carboplatin and etoposid resulting in 2 CR and one early death in distinct partial remission.

Results: Thus 8 pts treated with cytotoxic regimens achieved long-lasting CR without a relapse (observation time after CR: 13+, 17+, 27+, 58+, 54+, 114+ months). In total 11 out of 17 pts (65%) which received PT-LP-specific therapy achieved a long lasting CR.

Conclusion: Pts with polymorphous hyperplasia and mononucleose-like illness may achieve long lasting CR through Rx. Pts with stage I PT-LP may achieve a long lasting CR through surgical tumorexstirpation +/- radiation. But in pts with stage II-IV cytotoxic chemotherapy may result in a long lasting CR, too. Cytotoxic chemotherapy-related complications are unacceptable high. As radiation in after CR were not observed in our pts, reduced dose-intensity should be considered. The optimal chemotherapy and dose have to be determined in multicenter trials.

5210 Molecular analyses of Castleman's disease

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Introduction: Castleman's disease shows characteristic morphologic features in the lymph node and laboratory findings, but patients with this disease have viable clinical courses. The disease may constitute a spectrum of benign to malignant diseases. Thus, the clinical nature of the proliferating lymphoid cells was determined to obtain further insight into the malignant potential of this disease.

Methods: A PCR panel for light and TCR β gene rearrangements was applied to 76 frozen specimens from non-Hodgkin's lymphoma (NHL), including 48 B-cell type and 28 T-cell type proved by Southern blot hybridization (SBH), and 19 frozen lymph node tissue samples from patients with reactive follicular hyperplasia to compare the sensitivity and specificity of PCR analysis. Then, using PCR technique, we detected 16 parafirmi encoded lymph node samples from 15 cases of Castleman's disease to assess the clonality.

Results: The light primers alone detected clonality in 92% of all B-cell NHL, and the TCR β primers detected in 39% of T-cell lymphomas. None of them showed false positive to reactive follicular hyperplasia. Furthermore, none of 15 hematologic patients of Castleman's disease had gene rearrangement of light and TCR β by PCR technique.

Conclusion: In spite of progressive clinical courses of some of our Castleman's disease, we failed to identify the clonality of this proliferative disorder.
Progress in the prognosis of adult Hodgkin's disease (HD) in the last three decades through clinical trials: A GATLA experience

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Introduction: Since 1966 a total of 996 previously untreated adult patients (pts) (> 15 years old) with HD were enrolled in 7 GATLA protocols. All pts were clinically staged without laparotomy. Up to 1986 the CVPP regimen included cyclophosphamide, (CPM) and vincristine (VBL) only on day 1, and thereafter, on days 1 and 8, both with prednisone and procarbazine on days 1 to 14. Radiation therapy (RT) was given to involved areas at diagnosis, 25 to 30 Gy. Pts with poor prognosis since 1987 were treated with a sequential regimen of CCOPP and CAPTe for six cycles, followed by RT to the remaining disease after the fourth cycle.

Results: In early stages with favorable prognosis, chemotherapy (CT) was similar to CT plus RT and similar results were seen for 3 vs 6 cycles of CT. In advanced stages, CT plus RT was superior to CT alone. CPM and VBL given on days 1 and 8 were superior to the same drugs given only on day 1. CCOPP and CAPTe were better than RT plus CT. The rates of complete remission (CR), event-free survival (EFS) and overall survival (OSV) at 72 months were:

<table>
<thead>
<tr>
<th>Period</th>
<th>Stages</th>
<th># Pts</th>
<th># CR</th>
<th># EFS</th>
<th># OSV</th>
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<tr>
<td>1968-1977</td>
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<td>87</td>
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<td>1978-1986</td>
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<td>132</td>
<td>119</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>1998-1997</td>
<td>III-V</td>
<td>225</td>
<td>154</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>1998-2001</td>
<td>II-V</td>
<td>218</td>
<td>150</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>2001-2003</td>
<td>III-V</td>
<td>155</td>
<td>120</td>
<td>66</td>
<td>81</td>
</tr>
</tbody>
</table>

Conclusion: In these three decades of randomized clinical studies there was a significant improvement in overall results in all stages of Hodgkin's disease.

Lymphoma

Treatment of Waldenstrom's macroglobulinemia with stem cell transplantation

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Introduction: Waldenström's macroglobulinemia (WM) is an incurable lymphoproliferative disorder. With conventional chemotherapy, the median overall survival is about 5 years. The purpose of this study was to investigate the role of autologous peripheral blood stem cell transplantation (PBSCT) for the treatment of WM.

Methods: Four male patients (age 44–56 years) with WM were treated with 1-2 cycles of the DEXA-BEAM regimen (dexamethasone, BCNU, etoposide, ara-C, melphan, G-CSF) for PBSCT mobilization followed by autologous therapy (TBU/CY) with PBSCT. Three patients were untreated, one had failed 1 line of previous chemotherapy. Prior to treatment, serum IgM levels were 17.4–67.7 g/L, and all patients had symptomatic disease due to lymphoma, hyperviscosity or B symptoms.

Results: 4–7.8 x 10^6/kg CD34+ cells were obtained after mobilization and subsequent immunomagnetic B cell depletion. Following PBSCT, engraftment was prompt, and procedure-related deaths did not occur. As all patients showed a complete remission of their infiltrations, we had evidence of clinical B cells in BM and or blood as demonstrated by PCR amplification of CDR3 rearrangements, the monoclonal M protein did not disappear completely (2.1–23.2 g/L at 3 months post transplant), suggesting persistence of residual disease. However, with 3–30 months of follow-up, all patients live progression-free and are asymptomatic.

Conclusions: Sequential intensive treatment including high-dose radiochemotherapy and PBSCT is effective and may improve the course of patients with WM, although a complete eradication of the disease does not appear possible with autologous PBSCT alone.

Hodgkin's disease: Survival outcome and excess mortality


Hodgkin's disease (HD) is now an example of curable disease. Nevertheless, a long follow up shows intercurrent deaths. We proposed quantify the risks of dying for patients with HD and to compare their survival with Spanish general population of the same age and sex.

Methods: Four male patients (age 44-58 years) with WM were treated with aortic perfusion of thorax performed by sequential Intensive treatment Including high-dose radiochemotherapy and PBSCT Is effective and may improve the course of patients with WM, although a complete eradication of the disease does not appear possible with autologous PBSCT alone.

Alumorph genotyping of low-grade extranodal marginal zone-B-cell lymphoma (MALT lymphoma)

F. Bertoni 1, R. Mullenbach 2, E. Zucca 1, C. Jones 2, E. Roggero 1, F. Cavalli 1, F. Cotter 3.

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Introduction: The t(11;18)(p12;q21) translocation and the trisomy 3 are the abnormalities most frequently reported in low-grade MALT lymphomas. However, for the majority the underlying molecular events are not understood. DNA amplification by polymerase chain reaction (PCR) with primers designed on the widely distributed Alu-repeat sequences permit the production of specific Inter Alu DNA-fingerprints (alumorph-PCR). Tumour and normal DNA from MALT lymphoma samples of each patient 500 ng of both Pb and neoplastic DNA were separately digested with ALU-I and RSA-I restriction enzymes to reduce the complexity of the fingerprint. The digested DNA samples were amplified by PCR with ALU-IV, ALU-V and BK-33 primers, Incorporating the segment of the Involved genomic region.

Results: In BM and or  Wood as demonstrated by PCR amplification of CDR3 rearrangements, the monoclonal M protein did not disappear completely (2.1–23.2 g/L at 3 months post transplant), suggesting persistence of residual disease. However, with 3–30 months of follow-up, all patients live progression-free and are asymptomatic.

Conclusions: In these three decades of randomized clinical studies there was a significant improvement in overall results in all stages of Hodgkin's disease.

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Conclusions: In these three decades of randomized clinical studies there was a significant improvement in overall results in all stages of Hodgkin's disease.

Thoracic perfusion with a cladribine-based regimen is very active in refractory malignant lymphoma (rML)


Division of Oncologic Haematology Nat Cancer Inst Naples, Italy

Six heavily treated cases of rML received conventional doses of cladribine-based regimen. Drugs were delivered via aortic perfusion of thorax performed by means of stop-flow technique. During the phase 1 of the procedure (the first 20 mins) drugs circulated in the thoracic district reaching very high concentrations as indicated by the calculations of Cmax and AUCs. In the phase 2 the same active substances distributed in the systemic circulation maintaining the well-known pharmacokinetics characteristics of standard treatments. Diagnoses included four advanced Hodgkin's disease, one primary mediastinal B-cell and one atrialplastic large cell lymphomas. Pts were aged 18-43 yrs; four presented with bulky mediastinum. They had never achieved a complete response (CR) as indicated by the calculations of Cmax and AUCs. In the phase 2 the same active substances distributed in the systemic circulation maintaining the well-known pharmacokinetics characteristics of standard treatments. Diagnoses included four advanced Hodgkin's disease, one primary mediastinal B-cell and one atrialplastic large cell lymphomas. Pts were aged 18-43 yrs; four presented with bulky mediastinum. They had never achieved a complete response (CR) as indicated by the calculations of Cmax and AUCs.
Lymphoma

to therapy was excellent. Hematological toxicity was mild and transfusional support was needed only in one course. Neither extrahematological toxicity, nor treatment related deaths occurred. At the last follow-up, four pts are alive (2CR and 2 PR); two have died, one from renal progression of lymphoma while still being in CR, and the other from thoracic PD. This new therapeutic approach seems feasible, well tolerated and very active in a cohort of pts with rML and may play an important role in this setting, alone or in combination with other therapeutic tools.

527P  Short Intensive treatment with high dose chemotherapy in patients with aggressive non Hodgkin's lymphoma (NHL) with 2 or 3 poor prognostic factors

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Introduction: Patients with NHL and 2 or 3 factors of the International Prognostic Index (IPI) have a poor prognosis. We performed a prospective trial of early intensification in such patients.

Methods: Thirty patients (pts) were included. The median age was 38 yrs (range 15–59). Fifteen pts had 2 IPI factors and 15 had 3 factors. Nine pts had bone marrow involvement. The patients received 2 to 3 courses of the ACE protocol (Adriamycin D1; cyclophosphamide D1-2; etoposide D1-3), with G-CSF support. Depending on the quality of remission after induction, patients then received one or two intensification courses with peripheral stem cell support.

Results: Twenty four patients received intensification, including 9 pts who received a second high dose treatment. Three patients relapsed after intensification Six patients did not proceed to intensification: one because of lethal fylsis syndrome during the first course of ACE, three because of progressive disease, and one because stem cells could not be collected and one because of altered performance status. With a median follow-up after first chemotherapy of 16 months, the overall survival was 77% with a tendency towards a plateau. All deaths and relapses have occurred within 7 months of the beginning of chemotherapy.

Conclusions: Early therapeutic intensification after intensive induction chemotherapy is feasible in patients with poor prognosis aclusive NHL and shows promising survival rates.

528P  Oxaliplatin (LÖHP): A new platinum analog active on refractory/relapsed non-Hodgkin's lymphoma

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Introduction: Non-hodgkin’s lymphoma (NHL) are chemosensitive but the majority of patients (pts) with advanced disease relapse and require salvage treatment, including new anticancer agents with different cytotoxicity spectra. We report the tolerance and activity of a new platinum analog, oxaliplatin in previously treated pts, non suitable for high dose chemotherapy.

Patients and methods: From 7/98 to 7/99, 22 pts (11 men, 11 women) were treated. Median age: 58 years (37–59). All were pretreated (median number of prior CT regimens: 2 (1–7)). Fourteen pts (63%) had refractory disease, while 6 pts had potentially sensitive tumors. Histological Diagnosis (REAL classification): 8 follicular, 5 mantle cell (MCL), 2 diffuse large cell, 2 MALT, 1 lymphoplasmocytoid, 4 others. Pts received LOHP 100–130 mg/m², iv over 2 hours with antemetic premedication, every three weeks.

Results: A total of 144 cycles were given (median number of 6 cycles (1–30) per pt). Objective response rate was 40%, including 1 CR (MCL) and 8 PRs (4 follicular, 2 MCL, 2 MALT). Five responses were seen in the 14 refractory NHL while 4/5 with relapsed NHL responded. Median follow-up: 80 months. Median response duration was 27 months (5–44). Median survival: 23 months (1–81) with 4 pts alive.

Toxicity: it was limited to grade 1–2 nausea/vomiting and reversible grade 1–2 cumulative peripheral neuropathy in the majority of patients.

Conclusion: Oxaliplatin is an active agent in refractory/relapsed NHL. Its safety profile makes this agent a good therapeutic alternative in heavily treated patients as well a candidate for the development of new combination salvage regimens. Further phase II studies are needed to confirm these preliminary results in other NHL histologic groups types.

529P  Study on Hodgkin’s lymphomas expressing P-glycoprotein and non-expressing

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Introduction: Over-expression of the MDR1 gene, which codes for P-glycoprotein, is thought to be an important mechanism in the drug resistance exhibited by a number of malignancies, especially those of the hematopoietic variety. This study was designed to assay the expression of P-glycoprotein in a series of Hodgkin’s lymphomas (HL) and compare biological features of lymphomas expressing multidrug-resistant phenotype and non-expressing.

Methods: 73 archival tumor specimens from patients with untreated Hodgkin’s disease were analyzed by Southern blotting using the MDR1 probe. Immunohistochemistry was performed on formalin-fixed and paraffin-embedded tissue sections. P-glycoprotein expression was scored on a 0 (negative) to 3+ (strong positive) scale.

Results: Thirty-three (45%) of the HL specimens expressed P-glycoprotein. There were no significant associations between the expression of P-glycoprotein and clinical stage, histological subtype, or other patient characteristics. However, patients with HL expressing P-glycoprotein had a higher risk of relapse than those without expression (p = 0.03).

Conclusions: These findings suggest that P-glycoprotein expression may be an important factor in the prognostic stratification of HL patients.
was: spleen in 15% p, liver in 13% p, pleural in 9%, p, peripheral blood in 4% p, peritoneal in 4% p and gastrointestinal in 2% p. Median follow-up time was 36 months (m) (range 0 – 204). Overall survival (OS) of the entire group was at 5 yrs 49%, at 10 yrs 35% and at 15 yrs 26%. Median survival was 58 m. Disease free survival (DFS) was: at 5 yrs 52%, at 10 yrs 44% and at 15 yrs 41%.

Prognostic factors in the univariate and multivariate analysis is showed in the table.

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;60 vs &lt; 60</td>
<td>0.0001 NS</td>
<td>0.0001 NS</td>
</tr>
<tr>
<td>Stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA vs IB</td>
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<td>0.00007</td>
</tr>
<tr>
<td>Stage IB vs IIA</td>
<td>0.0001 NS</td>
<td>0.00001</td>
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<tr>
<td>Stage IIA vs IIIB</td>
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<tr>
<td>WF</td>
<td></td>
<td></td>
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<tr>
<td>Normal spleen</td>
<td>0.0001 NS</td>
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<tr>
<td>Non-spleen</td>
<td>0.0001 NS</td>
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<td>ECGO normal/high</td>
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<tr>
<td>1.61 ±0.4</td>
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<td>Bulky disease</td>
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<td>&lt;2 vs 2</td>
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<td>Number nodal</td>
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<tr>
<td>&lt; 2 vs &gt; 3</td>
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<td>0.00001</td>
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<tr>
<td>The largest site</td>
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<tr>
<td>localization</td>
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<td>Involvement</td>
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<tr>
<td>Initial treatment</td>
<td>0.003</td>
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</table>

Conclusions: Our results about OS and DFS were similar to another report. To this known prognostic factors as histology and IPI we have found medastinal involvement and the largest site (the worst was mesenteric) also significant in the multivariate analysis.

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**535P** Is it worth doing bilateral bone marrow biopsies in non-Hodgkin’s lymphoma (NHL)?

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Examination of the bone marrow is routinely performed during the initial staging of NHL. The usefulness of doing bilateral rather than double unilateral posterior spine biopsies is controversial, consequently we designed a prospective study to solve this issue. We report here the results of 173 bone marrow biopsies (BMB), performed in 134 pts with NHL during initial staging or evaluation of residual disease. Bilateral BMB were done in the posterior iliac spine in 138 instances (Group A). 103 pts. Unilateral double biopsies were obtained in 35 instances in 31 pts (Group B). Histological diagnosis in lymph nodes in A were Indolent Lymphoma: 60 Aggressive Lymphoma: 78. In Group B 160/5 were Indolent and the remainder were diffuse aggressive histologies Of 134 pts with NHL, 50 had no evidence of lymphoma in the BMB. Lymphoma was found in the BMB in 74 pts, we found divergent histologies in 18% in Group A and 10% of Group B.Divergence consisted in positivity or negativity of the specimen in simultaneous biopsies.An additional finding was the disclosure of two different lymphoma subtypes in 4 instances in Group A A Large Cell Lymphoma on one side and a Small Cell on the other side (2/4) or a Large Cell on one side and Diffuse Mixed on the other side(2/4). We have never found these disparity in Group B. In conclusion: Doing bilateral trephine bone marrow biopsies in patients with NHL increases the yield of positive BMB. Our preliminary results showed and advantage in performing a bilateral procedure over a double unilateral one (18% Vs 10%) An additional benefit might be the potential finding of different lymphoma subtypes. We think that it is worth doing bilateral bone marrow biopsies in NHL.

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**535P** Ventricular diastolic function changes in patients with lymphoma undergoing high dose sequential chemotherapy and stem cell transplantation

F. Zappe, M. Ghielmini, R. Corti, F. Cavalli, A. Gallino. Department of Oncology, Rambam Medical Center, Haifa, Israel

Introduction: In patients (pts) undergoing high-dose chemotherapy (HDC), risk/benefit evaluation should include potential cardiotoxicity (CaT). Echocardiographic evaluation of diastolic function was suggested to be a sensible mean for detecting infra-clinic, presystolic early toxic cardiac changes.

Methods: In 20 pts with non-Hodgkin (12 pts) or Hodgkin’s Lymphoma (8 pts) (mean age 37) undergoing HDC (CTX 7 g/m2 iv day 1, MTX 180 mg/m2 iv days 1 to 5, Idarubicin 12 mg/m2 iv day 1, Prednisone 100 mg/m2, days 1 to 11, VP-16 100 mg/m2, days 11 to 20, every 28 to 35 days, up to 8 courses. Thirty previously untreated pts, 3 pts were included and evaluated for response: male=17, female=13, age=74 years (61-83), large-cell=13, mantle cell=3, immunoblastic=6, mixed follicular=8, stage II=7, III=13, IV=10; IPI: low=14, intermediate=4, high=5, LDH=620.

Results: Complete remission=14 pts (47%), partial remission=10 pts (33%); stable disease=3 pts(10%);progression=3 pts(10%). At three years event-free survival was 47% and overall survival 70%. Although the use of CSFs was not mandatory according to the protocol, 2900 pts were given prophylactic GCSF. Side effects and toxicity did not limit the use of HDC.

Conclusion: according to these results, an oral polichemotherapy regimen containing Ibradurbin may be useful to obtain significant remission rates in selected pts with NHL and should be considered an alternative to conventional intravenous therapy in this group of patients.

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**535P** Primary mediastinal diffuse large cell lymphoma (PMLCL): The experience of the Servizio Oncologico1 Cantonale and Servizio di Radioterapia2, Ospedale San Giovanni, Bellinzona


Introduction: PMLCL represents a distinct clinicopathologic entity. The data of 27 pts with PMLCL were reviewed in order to elucidate the clinical...
Lymphoma

Characteristics and prognostic factors for time to progression (TTP) and overall survival (OS).

Methods: The median age was 45 years (range: 21–87 years). Nineteen patients had stage I-II and 8 had stage III-IV disease. B-symptoms were present in 11 (46%). Patients and bulky disease was found in 10 (37%). All patients were given combination chemotherapy as initial treatment: doxorubicin-containing regimens in 23 patients (11 patients had CHOP, 12 a more intensive third generation regimens); 4 elderly (> 70 years) patients had CVP.

Eighteen responders were consolidated with irradiation (RT) as part of their initial treatment with a median total dose of 39 Gy (range: 30.6–45 Gy).

Results: Nineteen patients (70%) achieved clinical remission with initial therapy (15 CR and 4 PR). Forty-four percent of patients remained progression-free and 59% are alive at 3 years. The actuarial 10-years TTP and OS were 44% and 50% respectively. By univariate analysis (log-rank test), stage, bulk, B-symptoms, LDH, extranodal extension were not predictive of OS or TTP. Age > 60 years, performance status > 1 and IPI intermediate-high to high risk were significantly associated with the worse outcome. Additionally a better outcome was significantly associated with the use of the very aggressive third generation chemotherapy regimens or with the inclusion of RT in the primary treatment.

Conclusion: Despite the possible bias associated with a non-randomised study, our analysis appears to suggest that the combination-modality therapy (chemotherapy plus RT) should be considered as standard treatment for this disease entity.

537P Sequential evaluation of multiple cycles of high dose (H.D.CHE) chemotherapy and stem cell transplantation (S.C.T.) with PCR in lymphoma patients

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The aim of the study is to determine:
(1) If the H.D.S.CHE contributes to the eradication of the residual malignant disease from B.M. (2) If the P.B.S.C mobilization induces simultaneously mobilization of malignant cells.

Material and methods: 10 pts with NHL were enrolled in this study. 9 pts had disease in release and 1 pt at first diagnosis. The relapsed pts were introduced in this protocol of H.D.S.CHE and P.B.S.C while the first diagnosed pt was treated with conventional chemotherapy of 6 CHOP Samples of BM, peripheral blood and mobilized cells were studied by PCR in different times of the treatment protocol as seen on the table below.

Treatment protocol

<table>
<thead>
<tr>
<th>CTX</th>
<th>MTX</th>
<th>VCR</th>
<th>VP-16</th>
<th>PCR</th>
<th>PCR</th>
<th>PCR</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 gr/m2</td>
<td>8 gr/m2</td>
<td>16 mg/m2</td>
<td>2 gr/m2</td>
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</table>

Results: 4 out of 10 pts were and remained to be negative for malignant residual disease prior to chemo and post H.D.S.CHE and PBCST. 5 out of 10 pts were PCR positive prior to chemo and have been negative after been exposed to H.D.S.CHE and PBCST One pt PCR positive prior to chemo has been negative after 6 CHO.

Conclusions: The H.D.S.CHE contributes to the eradication of residual malignant disease of BM and to the collection of PBCS for transplantation without malignant contamination. The PBCS mobilization from PCR negative BM does not induce malignant cell mobilization and contamination of the transplant.

538P Valuation of a new regime in the treatment of histologically aggressive non-Hodgkin's lymphoma

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Introduction: We have evaluated the outcome and toxicity showed by patients (pts) with histologically aggressive lymphomas when increasing the intensity of dosages of the standard CHOP regime by shortening the time between cycles and hematological side effects. Acute toxicity is closely related to the radiation (RT) dose. Clinically WR has proven to be effective in preventing from AT in pts. irradiated for rectal cancer. Since WR is active in all organs responsible for the tumor of patients treated with CHOP.

Methods: 13 patients with NHL. 2 with ovarian cancer were treated. 10 patients previously had chemotherapy, and 11/15 patients had surgery. Daily dose was 1.8 Gy, 5 times/week, to a total dose between 18.9 – 25.2 Gy. Dependent from the extend of the disease 11/15 patients received local external beam irradiation with a mean dose given 30 mln before each track by iv. Treatments are common due to gastrointestinal side effects. Acute toxicity is closely related to the radiation (RT) dose. Clinically WR has proven to be effective in preventing from AT in pts. irradiated for rectal cancer. Since WR is active in all organs responsible for the tumor of patients treated with CHOP.

Results: 4 out of 10 pts were and remained to be negative for malignant residual disease prior to chemo and post H.D.S.CHE and PBCST. 5 out of 10 pts were PCR positive prior to chemo and have been negative after been exposed to H.D.S.CHE and PBCST One pt PCR positive prior to chemo has been negative after 6 CHO.

Conclusions: The H.D.S.CHE contributes to the eradication of residual malignant disease of BM and to the collection of PBCS for transplantation without malignant contamination. The PBCS mobilization from PCR negative BM does not induce malignant cell mobilization and contamination of the transplant.

539P Increased daily doses with radiation of the whole abdomen with Amifostine (WR) is feasible: Preliminary results

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Introduction: Patients suffering from cbc-on NHL. The whole abdominal irradiation (WAI) may be performed with curative intent when intrathoracal/ethe lymph nodes were involved. Treatment is often due to gastrointestinal and hematological side effects. Acute toxicity is closely related to the radiation (RT) dose. Clinically WR has proven to be effective in preventing from AT in pts. irradiated for rectal cancer. Since WR is active in all organs responsible for the tumor of patients treated with CHOP.

Methods: 13 patients with NHL. 2 with ovarian cancer were treated. 10 patients previously had chemotherapy, and 11/15 patients had surgery. Daily dose was 1.8 Gy, 5 times/week, to a total dose between 18.9 – 25.2 Gy. Dependent from the extend of the disease 11/15 patients received local external beam irradiation with a mean dose given 30 mln before each track by iv. Treatments are common due to gastrointestinal side effects. Acute toxicity is closely related to the radiation (RT) dose. Clinically WR has proven to be effective in preventing from AT in pts. irradiated for rectal cancer. Since WR is active in all organs responsible for the tumor of patients treated with CHOP.

Results: 4 out of 10 pts were and remained to be negative for malignant residual disease prior to chemo and post H.D.S.CHE and PBCST. 5 out of 10 pts were PCR positive prior to chemo and have been negative after been exposed to H.D.S.CHE and PBCST One pt PCR positive prior to chemo has been negative after 6 CHO.

Conclusions: The H.D.S.CHE contributes to the eradication of residual malignant disease of BM and to the collection of PBCS for transplantation without malignant contamination. The PBCS mobilization from PCR negative BM does not induce malignant cell mobilization and contamination of the transplant.

540P Value of International prognostic index (IPI) in low-grade non-Hodgkin's lymphoma (LG-NHL)


Introduction: The value of prognostic indicators in LG-NHL is controversial. The aim of this study was to analyze if the IPI was useful in identifying different risk groups of LG-NHL pts in our population.

Methods: 122 out of 145 evaluable pts included in Gatla LBG-87, with complete prognostic data, were analyzed. This protocol considered a watch and wait (WW) policy for favorable pts, and initial chemotherapy with CAVE (cyclophosphamide, Adriamycin, vincristine, prednisone and etoposide) and mantle field radiotherapy over residual masses, followed by interferon maintenance for unfavorable pts. Based on the IPI, pts were divided in two groups: low-risk group, scores 0-2 and high-risk group, scores 3-5.

Results: Complete response rates were similar for both groups. After a median follow-up of 5 years, survival probability was significantly higher for pts in the low-risk group.
Conclusions: Two different risk groups of LG-NHL could be defined by using the IPI score in our population. Future research should be focused in designing different treatment strategies based on this finding.

**543P**

**Hodgkin's disease: A flow cytometric study**

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**Introduction:** Anaplastic and S-phase fraction are well recognized prognostic features of solid tumors and non-Hodgkin's lymphomas. However, only limited data is available on Hodkin's disease. In these facts the frequency of DNA aneuploidy is low, and it hasn't correlated with known prognostic factors or survival, but the percentage of the S phase fraction (SPF) might turn out to be an indicator of patients who will have less favourable outcomes. The objective of our study was to analyse the nuclear DNA content from samples of Hodgkin disease and the relationship with the known prognostic factors.

**Methods:** The nuclear DNA content of 24 cases of Hodgkin's disease in relapse seen at Hospital La Fe (Valencia, Spain) was analyzed from paraffin-embedded tissue. Flow cytometry was performed using Multicycle software (Phoenix Flow Systems, San Diego, CA, USA). We studied the DNA ploidy status and the SPF.

**Results:** Twenty (83.3%) of the cases were diploid and the others (16.7%) aneuploid. The SPF ranged from 2 to 21.3% (mean 7.34%). The highest proliferative indices were found in the mixed cellularity (7.75%) and lymphocyte depleted (10.39%) histological subgroups. Aneuploid tumors were seen in 5 (20.8%) cases. Samples were analysed on an EPICS Profile II and EPICS elite flow cytometers (Coulter electronics, Inc., Hialeah, Florida, USA). Cell cycle analysis was performed using MultiCycle software (Phoenix Flow Systems, San Diego, CA, USA). We studied the DNA ploidy status and the SPF.

**Conclusions:** The overall percentage of DNA aneuploid tumours is low (16.7%), which confirms the results of the others studies. DNA aneuploidy was not associated with the histologic subtypes. However, our study showed a correlation between the less favourable histologic subtypes (MC and DL) and sex with a higher percentage of S-phase cells. These data suggest that the proliferative activity in Hodgkin's disease is linked to the histologic subtypes and then a high number of S-phase cells may indicate a more aggressive clinical behaviour.

**542P**

**A phase-II study with Idarubicin, Vepeside and predinilone (IDV/PVP), in patients with refractory or early relapsed intermediate and high grade non-Hodgkin's lymphoma**


**Introduction:** The prognosis for patients with non-Hodgkin's lymphoma (NHL) resistant to primary chemotherapy and those with early relapse is poor. The response rates to salvage regimens range from 20% to 60%, but durable remissions are rarely reported. The purpose of our study was to evaluate a regimen of Idarubicin, Etoposide and Prednisone (IDVP/P) in patients with refractory or early relapsed intermediate or high-grade NHL.

**Methods:** Eighteen patients, 8 men and 10 women, with refractory or early relapsed intermediate and high grade NHL, were entered. The median age of the patients was 63 years (40 to 72 years). At presentation 15 (83%) patients were in advanced stage III or IV and 14 (78%) were classified as high grade NHL (WF). All patients had been previously treated according to the protocol of remission study with either CHOP or CVP (cyclophosphamide instead of Etoposide) and for various reasons, mainly age-related, were not considered for megatherapy. After this first-line treatment, the disease was proven to be resistant in 14(78%) patients. In the remaining 4 patients the disease relapsed in 2-10 months after induced complete remission. The idar/VP/P regimen consisted of Idarubicin (10 mg/m² i.v. days 1-3), Etoposide (100 mg/m² i.v. days 1-3) and Prednisone (100 mg/m² p.o. days 1-7) to be repeated on day 21.

**Results:** Among our 18 patients, 14 received more than 2 (2-6) cycles of lda/V/P/P regimen. Four patients received only one cycle of chemotheraphy and were not evaluable. Six (43%) patients responded including 4 CR and 2 PR. Three patients are in complete remission for 16+, 26+ and 31+ months. All patients exhibited myelosuppression.

**Conclusions:** The lda/V/P/P regimen with an acceptable toxicity, is an alternative in the treatment of patients with early relapsed or refractory NHL. Its use may be important in the treatment of elderly patients not eligible for more intensive treatment modalities.

**545P**

**Epstein-Barr virus and Hodgkin's disease**

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**Introduction:** Epidemiologic, immunohistochemical and serologic data support an association between Epstein-Barr virus (EBV) and Hodgkin's disease (HD). The presence of EBV varied according to the histological subtype of HD. Mixed cellularity HD is more likely to be EBV-positive compared with nodular sclerosis HD. The presence of EBV has been correlated also with higher clinical stage and old age. This association between EBV and known prognostic factors of HD suggest a relationship between EBV status and survival. The purpose of our study was to analyse the prevalence of EBV in this disease and the association with prognostic factors.

**Methods:** Paraffin-embedded tissues from 27 HD cases were investigated for the presence of EBV using two methods: Immunohistochemistry (IH) for detection of latent membrane protein 1 (LMP-1) and polymerase chain reaction (PCR) for detection of a reiterated 110 base-pair EBV genomic sequence.

**Results:** Positive immunolocalization for LMP-1 was demonstrated in 21/28 (77.8%) of the cases examined, and EBV genomes in the Reed-Sternberg cell cytoplasm were detected by PCR in 23/27 (85.2%). We didn't find significant differences of LMP-1 positivity by histology (50% LP, 85.7% NS, 90% MC, 100% LD) and by clinical stage (100%-I, 83.3%-II and IV, 85.7%-II). The presence of LMP-1 didn't show a correlation with detection of LMP-1. When we compared the results with the two methods to demonstrate EBV presence (PCR and IH) there weren't differences.

**Conclusions:** The results of our study showed a high prevalence of EBV in HD. This association support a role of EBV in the pathogenesis of HD. The presence of EBV in HD patients is an important finding, which may be used to explore the impact of LMA on the progressive disease (PD) incidence in the course of induction chemotherapy (CT) for HD III/IV stages.

**Methods:** 123 cases of recrudescent HD in 642 pts allocated to 6 CO(V)PP cycles in 1976-97 years were analysed with regard to LMA (MMR > 0.35)
and general symptoms (A,B). Retrospective analysis served the bases of the two pilot trials initiated since 1989 with the aims to reduce PD incidence using between 2nd and 3rd CT cycles radiotherapy (RT) to LMA: (1) to 20 Gy; (2) to 40 Gy plus involved fields, with special attention to CT dose intensity.

Table 1: Number of patients with BM in LMA vs. non-LMA. In all patients the BM was detected by the bone scan. The CT dose intensity was calculated as the ratio of the total CT dose (in Gy) to the time interval (in months) between the induction CT and the final CT. The range of the CT dose intensity was 0.2-1.0 Gy/month.

<table>
<thead>
<tr>
<th>A pts</th>
<th>B pts</th>
<th>A/pts</th>
<th>B/pts</th>
<th>Total</th>
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<tr>
<td>9/408 (2%)</td>
<td>2/2 (100%)</td>
<td>5/7</td>
<td>45/408 (11%)</td>
<td>9/16 (56%)</td>
</tr>
<tr>
<td>16/100 (16%)</td>
<td>7/27 (26%)</td>
<td>11/43 (26%)</td>
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</table>

Conclusions: Monitoring of chemotherapy efficacy in patients with BM invasion by Hodgkin's disease (CR) may be a reflection of underlying malignancy and appears to be related to stage of disease, tumor burden and prognosis. Prognostic factors at diagnosis, clinical response, survival and CR were analyzed in 89 patients with Hodgkin's disease. All patients were newly diagnosed, in advanced stage, treated with Bleo-MOPP regimen. The median age was 40 years and 46% were under age of 45. Nodal sclerosis and mixed cellularity were the most common histology, 36% and 35% respectively. "P" BM lesions were present in 65%, bulky disease in 29% and bone marrow involvement in 4% of total. ESR was over 70 in 3% of patients and 27% had one or two extranodal localization. The median follow-up was 41 month. CIC were estimated by the polyethylene glycol precipitation test (100% complete resolution with CR) in all cases. The only factor influencing CR rate was the number of extranodal involvement (p < 0.05). The ten-year relapse-free survival (RFS) and overall survival (OS) are 63% and 83%, respectively. Nodal sclerosis was the favorable factor for RFS (p < 0.05). In univariate analysis OS was adversely influenced only by extranodal involvement (p < 0.001). Elevated CIC level was estimated in 58% of total. Patients with ESR over 30 had significantly higher values of CIC (p < 0.05). There were no significant correlation between level of CIC and the other prognostic factors. Survival was not influenced by CIC level. Qualitative analysis of CIC showed expression of PSGL-1 on monocytes/macrophages, GM and hepatitis B surface antigen. Surprisingly, C-reactive protein (CRP) was identified in 42% of all samples. CRP is an acute phase protein which show comformational similarity to Immunoglobulin molecule.
median in 4.5. Two pts missed the follow-up, 1 pt. is still alive (44 months) and 10 pts. died.

Conclusions: As described previously the supratentorial site, the B immunophenotype and a solitary lesion are characteristic features of the PLCNS. The prognostic of this tumour remains dismal, with a short survival despite the achievement of a CR, with the treatment of radiotherapy. The ch. as not shown any activity in our serie. There are no room for surgery other than biopsy in the treatment of this tumour.

551 Existent or not: Primary pseudolymphoma of the lung report of three cases

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Introduction: Pseudolymphoma of the lung is a rare and insufficiently investigated immunoproliferative disorder. It is characterized by lack or minimum of respiratory symptoms, with typical radiological pattern of solitary nodular peripheral shadows or diffuse bilateral interstitial infiltrates. Diagnosis is set by pathological studies of pulmonary infiltrates and is confirmed by immunohistochemical staining. Contrary to the lymphoma, which is a monoclonal disorder, pseudolymphoma is usually related to polyclonal gammopathy, which can be detected by immunofluorescent staining of the tumour tissues by specific antisera to light and heavy immunoglobin chains.

Methods: In this paper are presented 3 cases of this rare disorder, diagnosed in the period from 1977 through 1997. The disease was detected on routine chest radiography. In all cases lung biopsy with histological and immunohistochemical examination was performed.

Results: 1. Patient aged 69, male. The patient was repeatedly admitted to the hospital until he died of unrelated disease. First time he was admitted to the hospital with productive cough and abundant mucous sputum. After complete rest, at least 3 months, the symptoms ceased. After chest radiography was normal. The lesion was monoclonal (IgM, kappa). 3. Patient aged 64, male. During the five years prior to his admission for polycythemia rubra vera. Routine chest radiography detected an opacity in the right middle lobe. Lobectomy was performed, and histological investigation gave the diagnosis. It was confirmed by immunohistochemical staining, revealing polyclonality of the lesion. During the 5-year follow-up there was no relapse and the patient has been lost for follow-up.

Conclusions: Our experience in treating the patients with the pseudolymphoma of the lung confirms the accurateness of the recommendations for treatment of this disorder. Surgery is, where applicable, the treatment of choice. In our opinion, if there are no signs of progression with respiratory symptoms, immunosuppressive or radiation therapy is not necessary for the irresectable pseudolymphoma of the lung.

5520 Non-metastatic Ewing's sarcoma: Preliminary results of a protocol with ifosfamide since the induction phase added to vincristine, doxorubicin, actinomycin D, cyclophosphamide and etoposide

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From October 1991 and December 1996, 117 patients (median age 17 years, range 3-36) with non metastatic Ewing's sarcoma were treated according to a chemotherapy protocol with an Induction phase consisting of 2 courses of vincristine (VC), doxorubicin (AD) and cyclophosphamide (CP), alternating with one course of VC, actinomycin D (AC), and ifosfamide (IF). Tumor was locally treated with surgery (S) or conventional irradiation therapy (RT) with added S in case of inadequate surgical margin. When surgical resection was not feasible, RT alone was used for the local control of disease. In the maintenance phase, patients were given 3 courses of VC, AD, CP alternating with 2 courses of VC, AC, IF, followed by 3 courses of IF, etoposide alternating with 2 courses of VC, AC, CP.

Primary sites were: extremity in 72 (61%), pelvis in 24 (21%), other in 21 (18%). 88 patients (75%) were treated with surgery, 15 with irradiation (with addition of RT in 20), and 29 patients (25%) were treated with RT alone. In 79 of the 88 patients who underwent surgery, the histologic response to induction chemotherapy was evaluated: a good histologic response (no viable tumor cells or only small foci of tumor cells) was observed in 50 patients (75%), a poor histologic response was registered in 19 patients (25%). With a median follow up of 49 months (range 12-74), 90 patients were continuously free of disease, 25 patients relapsed, 6 with local recurrence, and 19 with distant metastases. Two patients died of chemotherapy related toxicity. The 5-years EFS and OS are 72% and 85% respectively. Site of the tumor, type of local treatment, age, serum level of LDH did not significantly affect prognosis. Patients with tumors < 100 mL had a better prognosis than those > 100 mL (5-year EFS 87% vs 55%, p = 0.02). The histologic response to induction chemotherapy was the main prognostic factor: patients with good response 5-year EFS 79%, those with poor response 44% (p < 0.002).