NEURO-Oncology

Abstracts

ORAL PRESENTATIONS

EHI EANO HIGHLIGHTS

EHI.1 RESULTS OF THE INTERIM ANALYSIS OF THE EORTC RANDOMIZED PHASE III CATNON TRIAL ON CONCURRENT AND ADJUVANT Temozolomide in Anaplastic Glioma Without 1p/19q Co-deletion, An INTERGROUP TRIAL
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BACKGROUND: The benefit of adding chemotherapy to radiotherapy (RT) in newly diagnosed anaplastic glioma without 1p/19q co-deletion is unknown. The CATNON trial investigated the impact of adjuvant and/or concurrent temozolomide (TMZ) in these patients.

METHODS: Eligible patients were newly diagnosed WHO grade III glioma without 1p/19q co-deletion, ≥ 18 years, and WHO performance status (PS) 0–2. All patients received RT 59.4 GY in 33 fractions, and in a 2 x 2 factorial design were randomized to i. RT alone; ii. RT with concurrent daily 75 mg/m2 TMZ; iii. RT followed with 12 cycles of 150–200 mg/m2 adjuvant TMZ day 1–5/4 weeks; or iv. RT with both concurrent and 12 cycles of adjuvant TMZ. Stratification factors included O6-methyl-guanine DNA methyltransferase (MGMT) promoter methylation and PS. Primary endpoints were overall survival (OS). 748 patients and 334 events were needed to detect a HR reduction of 0.775 for both concurrent and adjuvant TMZ. An interim analysis was foreseen after 219 events (41%), and required a p value of 0.0084 for rejecting the Null hypothesis of no OS difference.

RESULTS: Between Dec 2007 and Aug 2015 748 patients were randomized. On Oct 6, 2015 the interim analysis was conducted based on 221 events (median follow-up: 27 months). The analysis showed a HR reduction for OS of 0.646 (95% CI 0.450, 0.926; p = 0.0014) after adjuvant TMZ (arms iii and iv). MGMT status could be determined in 74% of patients, and was found methylated in 42% of them. MGMT methylation was prognostic for OS (HR 0.54, 95% CI 0.38, 0.77; p = 0.001), but at this stage did not predict improved outcome to adjuvant TMZ. For progression free survival (PFS), the risk adjusted HR of adjuvant TMZ was 0.836 (95% CI 0.472, 0.727; p < 0.0001). OS at 5 years in the no adjuvant TMZ arm 44.1%, in the adjuvant TMZ arm 53.9%. With adjuvant TMZ median PFS increased from 19.0 months to 42.8 months.

EHI.3 EORTC 26101 PHASE III TRIAL EXPLORING THE COMBINATION OF BEVACIZUMAB AND LOMUSTINE VERSUS LOMUSTINE IN PATIENTS WITH FIRST PROGRESSION OF A GIOLOBLASTOMA
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BACKGROUND: Phase II data from BELOB suggested the combination of bevacizumab and lomustine to produce an overall survival (OS) benefit compared with either monotherapy for patients with progressive glioblastoma. Agnostic to the phase II data of the trial, EORTC 26101 investigated whether the combination of bevacizumab and lomustine improves overall survival (OS) in patients with first progression of a glioblastoma compared to monotherapy with lomustine.

METHODS: Patients with progressive disease after standard chemoradiation at least 3 months off the concomitant part were randomized 2:1 between lomustine 90 mg/m2 (cap. 160 mg) every six weeks plus 10 mg/kg bevacizumab every two weeks and lomustine single agent 110 mg/m2 (cap. 200 mg) every six weeks followed by best investigators choice at further progression. In the absence of hematological toxicity > grade 1 during the first cycle in the combination arms, the dose of lomustine could be escalated to 110 mg/m2 (cap. 200 mg) in the second cycle. Neuroimaging according to a standard protocol was assessed locally and centrally.

RESULTS: A total of 437 (288 and 149, respectively) patients were included. Median number of treatment cycles was 1 in the lomustine arm and 3 in the combination arm. With 329 OS events (75.3%) OS was not superior in the combination therapy arm (hazard ratio (HR) 0.95 (confidence interval (CI) 0.74, 1.21), p=0.630, analyses stratified by EORTC online randomization system), whereas locally assessed progression-free survival (PFS) was longer with the addition of bevacizumab to lomustine (HR 0.49 (CI 0.39, 0.61). Median efficacy outcomes were: OS 9.1 (8.1, 10.1) versus 8.6 (7.6, 10.4) months and PFS 4.2 (3.7, 4.3) versus 1.3 (1.5, 2.5) months in the lomustine arm versus the key combination arm. There was no expected range in median values in the combination arm being also longer on treatment. Crossover to bevacizumab occurred in 35.5% of patients in two-dimensional (2D) in vitro cultures might explain the observed discrepancy between pre-clinical and clinical responses to cytotoxic treatments. We developed a customised, 3D GSC culture system using a polystyrene scaffold (Abele-H Knopp) that recapitulates key histological features of GSCs including high cellularity and sparse extracellular matrix (ECM) and compared it to conventional 2D GSC cultures. 2D and 3D cultures of three different primary GSC lines exhibited similar radiation sensitivities as measured by clonogenic survival. Previous studies have demonstrated increases in the occurrence of gliomatosis in patients following anti-VEGF therapy in combination with radiotherapy. Bevacizumab enhanced the radiosensitivity of 3D GSC cultures in clonogenic and neurosphere formation assays, but had no effect on radiation responses of 2D GSC. Similar radiosensitising properties were observed by VEGF deprivation, with significant radiosensitisation of 3D GSC cultures but no effect on 2D GSC. Analysis of the DNA damage response after radiation treatment showed a correlation between radiosensitivity, increased double-strand breaks (γH2AX foci), increased non-homologous end-joining (NHEJ) repair protein phospho-DNA-PK nuclear foci and increased number of cells undergoing mitotic catastrophe or with micronuclei following radiation treatment. In contrast, increased numbers of foci of the homologous recombination (HR) repair protein Rad51 were observed in radioresistant populations after radiation. Our results show that in the 3D model, VEGF signalling is required for optimal NHEJ activation with fast kinetics. This effect allows access to HR repair proteins at the remaining unrepaired DSBs at late time points, facilitating their repair and conferring radioresistance. Detailed analysis of the signalling pathways involved in the radiation resistance conferred by VEGF signalling in the 3D model demonstrated a radioprotective role of the downstream signalling molecule Akt. Specific inhibition of Akt using the small molecule inhibitor MK-2206 increased radiation sensitivity to the same extent as VEGF deprivation in 3D cells, and no additivity was observed when these agents were combined. To our knowledge this is the first report demonstrating a role for VEGF in the regulation of the DNA damage response. Our results for anti-VEGF therapy in the 3D model recapitulate data from clinical trials and strongly support its clinical relevance and its potential value in preclinical GBM studies.

Glioblastoma (GBM) is the most common primary brain tumour with dismal prognosis. Tumours inherit inherent resistance to radiation and chemotherapy which has been attributed to a subpopulation of cancer cells termed ‘cancer stem-like cells’ (CSC) characterised by multipotentiality and potent tumorigenic capacity. The use of established cancer cell lines in simplified

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