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Does initial response to corticosteroids predict survival in primary CNS lymphoma (PCNSL)?

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Background: Corticosteroids alleviate symptoms from vasogenic edema in patients with PCNSL and have direct cytotoxic effects on tumor cells. It is not clear whether an initial response to corticosteroids predict patient outcome after definitive treatment.
Materials and Methods: Among 338 PCNSL patients treated in our institution since 1986, descriptive variables and impact of initial response to corticosteroids on OS and FFS were studied in 98 patients.
Results: The median age was 63 years and median KPS was 70. Men constituted 47% of the patients. Median follow-up for survivors was 30 months. Histologically, 69% had a diffuse large B cell lymphoma. Brain, CSF and ocular involvement were present in 100%, 22% and 15% of patients, respectively. We observed an objective radiographic response (CR plus PR) in 53% of patients after initial corticosteroids. Most patients were treated with MTX based regimens (85%), radiation therapy (61%) and high dose cytarabine (51%), independent of the initial response to corticosteroids. Five-year OS was 35% and five-year FFS was 26% for all 98 patients. There was no significant difference in OS and FFS between radiographic responders and non-responders after initial corticosteroids. There was also no significant difference in median age, initial KPS, time to definitive treatment between two groups.
Conclusion: A significant number of PCNSL patients had an initial response to corticosteroids. However, this response is not a good prognostic factor.

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Erlotinib (E) versus temozolomide (TMZ) or BCNU in recurrent glioblastoma multiforme (GBM): results from a randomized phase II trial (EORTC 26034)

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Background: Epidermal growth factor receptor (EGFR) is amplified in 40–50% of GBM cases and is often constitutively activated (EGFRvIII mutant), making it a potential therapeutic target. EGFR tyrosine-kinase inhibitors have shown promising activity in recurrent GBM, particularly in specific molecular subsets. We report results from a randomised phase II study of erlotinib (Tarceva®) in recurrent GBM.
Methods: Eligible patients (pts) had histologically proven GBM, recurrent >3 months after radiotherapy, Karnofsky performance status (KPS) $\geqslant$70, no prior chemotherapy for recurrent disease and an available tissue sample for EGFR analysis. Treatment was E 150 mg/day (300 mg/day if on enzyme-inducing anti-epileptic drugs [EIAEDs]), or control (TMZ 150–200 mg/m^2, day 1–5 q4wk or BCNU 60–80 mg/m^2 i.v., day 1–3 q8wk). E dose escalation to 200 mg (500 mg in pts on EIAEDs) was done in the absence of significant toxicity. Response was assessed using Macdonald's criteria, the primary endpoint was 6 months' PFS; P0 was set at 15% and P1 at 30%, sample size was 2 x 50 pts. EGFR amplification and expression of EGFR, EGFRvIII and PTEN were assessed by FISH and IHC, respectively. Adverse events (AEs) were monitored.
Results: 110 pts were randomised (54 E; 56 control: 27 TMZ; 29 BCNU), with a median age of 55 years and median KPS of 90. 109 pts commenced treatment, with E pts receiving a median 2 cycles of treatment, TMZ pts receiving 4 cycles and BCNU pts receiving 1 cycle. Few E-related grade 3/4 AEs were reported: 5 dermatological AEs and 1 haemorrhage, with only 3 pts discontinuing E due to toxicity. Grade 3/4 haematological toxicities were the most frequently reported AEs for control pts (3 with TMZ, 13 with BCNU). In the control group, 2 responses were observed, while the best response seen with E was SD in 6 pts. Six-month PFS was 12% for E and 24% for control. Similar 6- and 12-month OS were seen across both treatment arms (61% and 24% for E and 63% and 26% for control). Pts with EGFRvIII mutations (13 for E arm, 8 for control) had shorter PFS ($p = 0.007$) and OS ($p = 0.004$), irrespective of the treatment received. Neither EGFR expression, EGFR amplification nor EGFRvIII mutation status were correlated with response or PFS on E therapy.
Conclusion: The results of this randomised, controlled phase II study did not demonstrate sufficient activity for erlotinib in the general recurrent GBM population. EGFRvIII mutation status was not predictive of response to erlotinib.

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Networking of endogenous modulators of nuclear factor-kappaB in predicting outcome in high-grade gliomas

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Background: Nuclear factor-kappaB (NF-κB) is a eukaryotic transcription regulator at the crossroad of a cell's decision to live or die. Excessive and prolonged activation of NF-κB has been established as a principal mechanism of tumor chemoresistance, which is primarily mediated by its antiapoptotic activity. The activity of NF-κB is regulated by a complex network of endogenous pathway modulators, which under normal cell conditions keep NF-κB in an inactivated state. We have discovered alterations in several NF-κB pathway modulators in glioblastoma cells, which may act synergistically in activating NF-κB during resistance formation to temozolomide, including the TNFAIP3, NFKBIA, and TNIP1 genes.
Materials and Methods: We have evaluated the outcome relationship for these and additional endogenous modulators of canonical NF-κB activation in four independent high-grade glioma cohorts comprising more than 200 tumors.
Results: We here confirmed the putative importance of NF-κB pathway activation status in predicting high-grade glioma outcome. Our data indicate an increasing complexity and linkage of several modulatory molecules (TNFAIP3, NFKBIA, TNIP1, and TNIP2) to patient outcome that interact physical and functionally in a cooperative fashion to regulate NF-κB activation. We found that for many of these molecules combined predictor models outperform the predictive power of the individual molecules. This observation is consistent with recent evidence suggesting the cooperation of these endogenous inhibitors in a negative feedback regulation of NF-κB activation and a mutual facilitation of their repressive ability. In terms of outcome prediction, we found several of these inhibitors to outperform established clinical and morphological prognostic variables such as patient age and tumor grade (III vs. IV), as well as the O6-methylguanine DNA methyltransferase (MGMT) gene, the currently most established outcome marker in glioblastomas. We further found that treatment failure with temozolomide in initially sensitive tumors is associated with significant changes in the abundance of these endogenous modulators in such a way that we would predict the tumor to be resistant to the drug.
Conclusions: These findings raise the hope for this endogenous regulatory network as an amenable target to modulate NF-κB-mediated resistance in high-grade glioma cells, with the ultimate goal of increasing the efficacy of temozolomide in patients harboring these challenging tumors.

2505 ORAL

Abnormal expression of REST/NRSF and Myc in neural stem/progenitor cells causes cerebellar tumors by blocking neuronal differentiation

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Background: Medulloblastoma, one of the most malignant brain tumors in children, is thought to arise from undifferentiated neural stem/progenitor cells (NSCs) present in the external granule layer of the cerebellum; However, the mechanism of tumorigenesis remains unknown for the majority of medulloblastomas.
Materials and Methods: We used human medulloblastoma patient samples, mouse cerebellar stem/progenitor cells (NSCs) and mouse models to attain our objective.
Results: We found that many human medulloblastomas express significantly elevated levels of both myc oncogenes, regulators of neural