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A number of important studies were presented at the CNS tumors section of the 2011 American Society of Clinical Oncology Annual Meeting. There was particular interest in RTOG 0525, a Phase III study of newly diagnosed glioblastoma treated with different schedules of temozolomide. Prognostic factors for response, survival and chemotherapy-related toxicity in primary CNS lymphoma from the German randomized Phase III trial in newly diagnosed primary CNS lymphoma were also presented.

**Keywords:** biomarker • chemotherapy • glioblastoma • lymphoma • medulloblastoma • radiotherapy

The CNS tumors section of the 2011 American Society of Clinical Oncology Annual Meeting was notable for results of a large Phase III trial in patients with newly diagnosed glioblastoma (GBM) as well as therapies for other types of brain tumors, including medulloblastomas (MBs). In addition, the German investigators presented prognostic factors for response, survival and chemotherapy-related toxicity from a randomized Phase III trial in newly diagnosed primary CNS lymphoma (PCNSL).

In 2005, the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC; 22981/26981) landmark trial showed significant survival improvement in patients with newly diagnosed GBM treated with radiotherapy and temozolomide compared with those treated with radiotherapy alone [1]. Temozolomide is an oral alkylating agent that exerts its cytotoxic effect through methylation of the O⁶ position of guanine. The O⁶-methylguanine lesion is recognized by the DNA mismatch repair pathway, and failure of mismatch repair to repair the lesion that results in DNA double-strand breaks and apoptosis results in cytotoxicity [2]. O⁶-methylguanine-DNA methyltransferase (MGMT) is the enzyme capable of repairing the O⁶-methylguanine adducts, and the level of MGMT in cells correlates with effectiveness of alkylating agent [3]. In 2005 Hegi and colleagues showed that median survival was significantly improved in those patients treated with temozolomide in whom tumor MGMT was inactivated by hypermethylation of CpG islands in the promoter region [4]. One approach to inhibiting MGMT activity involves the delivery of temozolomide using dose-intense schedules that generate sufficiently large numbers of O⁶-methylguanine adducts such that total cellular MGMT is depleted. Depletion of MGMT activity in these tumors should result in enhanced sensitivity to temozolomide. Mark Gilbert (MD Anderson Cancer Center, TX, USA) presented the results of the Radiation Therapy Oncology Group (RTOG) 0525 trial, a randomized Phase III trial comparing standard adjuvant temozolomide given 150–200 mg/m² × 5 days every 4 weeks, with a dose-dense temozolomide 75–100 mg/m² × 21 days given every 4 weeks for 6–12 cycles in newly diagnosed GBM following 6 weeks of concurrent temozolomide and radiation [5]. A total of 833 patients were randomized from a total of 1173 registered patients to either receive standard adjuvant temozolomide or dose-dense temozolomide. No statistical difference was observed between the two arms in median overall survival (OS; 16.6
vs 14.9 months), or median progression free survival (PFS; 5.5 vs 6.7 months), or by methylation status. As expected, the MGMT methylation was associated with improved OS (21.2 months vs 14 months) and response. There was increased grade 3 lymphopenia and fatigue in the patients treated in dose dense manner. The study did not show any improved efficacy for dose-dense temozolomide for newly diagnosed GBM regardless of methylation status. The trial confirmed the prognostic significance of MGMT methylation in GBM in a prospective manner. Therefore the standard of care for patients with newly diagnosed GBM remains the presently used schedule of 6 weeks of concurrent radiation and chemotherapy with temozolomide followed by adjuvant temozolomide given days 1–5 every 4 weeks for 6 to 12 cycles.

Ken Aldape (MD Anderson Cancer Center) presented the molecular correlates from a RTOG 0525 Phase III trial of newly diagnosed GBM [6]. Four prognostic biomarkers consisting of an IDH1 mutation, the glioma-CpG island methylator phenotype, a microarray-based mRNA panel and a novel MGMT promoter methylation assay were evaluated from the formalin-fixed, paraffin-embedded tumor tissue from the patient samples from the RTOG 0525 trial. Each biomarker subgroup were defined based on associations with OS and all combinations of each of the four biomarker-derived subgroups were then defined and compared with survival data and consolidated into four risk groups. Application of the molecular risk classification to RTOG 0525 samples demonstrated a highly significant survival association (p < 0.001). When compared with the recursive partitioning analysis, this composite molecular classifier appeared to be a promising method to identify patients with long term survival and revealed an additional distinct risk group. However, there is a need to validate this composite panel prospectively.

The previously discussed landmark EORTC and NCIC 22981 study, also showed that patients with a hypermethylated MGMT promoter demonstrated survival rates of 49 and 14% at 2 and 5 years, respectively, when treated with concomitant and adjuvant temozolomide and radiotherapy [1,4]. By contrast, estimated 2- and 5-year survival rates were only 24 and 5%, respectively, in similar patients that were initially treated with radiotherapy alone. GBM patients whose tumors lacked MGMT hypermethylation demonstrated 2- and 5-year survival rates of 15 and 8%, respectively, when they received combined radiochemotherapy, which dropped to only 2 and 0%, respectively, when treated with radiotherapy alone [1,4]. Hence, there is an unmet need for improving therapy in GBM patients whose tumors lack MGMT hypermethylation. Preclinical data indicate potential activity of enzastaurin, an oral PKC-β inhibitor, together with radiation [7]. Wolfgang Wick (National Center of Tumor Disease, University Clinic Heidelberg, Germany) presented the results of a single arm Phase II study where GBM patients with an unmethylated MGMT promoter were treated with enzastaurin together with radiation [8]. A total of 57 patients with newly diagnosed supratentorial GBM received enzastaurin, 250 mg twice daily administered 7 days before, concomitant with radiation (60 Gy; five-times 2 Gy per week), and in the maintenance therapy until progression. The 6-month PFS (PFS-6) rate was 51.8% (95% CI: 38.1–63.9) and the study did not reach its primary end point of a PFS-6 of 55%. This is the first trial performed in patients with GBM that reported clinical data that limited entrance to the molecularly defined unfavorable subgroup of patients with unmethylated MGMT status. There are a number of ongoing studies and will help address the need for more effective therapies in this unfavorable patient population [10,11].

Primary CNS lymphoma (PCNSL) is a rare variant of non-Hodgkin’s lymphoma that involves the brain, leptomeninges, eyes, or spinal cord. Over the last 30 years, the treatment of PCNSL has evolved and numerous clinical trials have been reported including some with promising results. Therefore, it is imperative to develop a model that will serve as a guideline to determine patient prognosis and to help guide therapy in such patients. Currently the Memorial Sloan–Kettering Cancer Center prognostic scale is one of the most commonly used scale to make appropriate therapeutic decision making and determine patient prognosis [9]. The first ever large randomized Phase III trial in newly diagnosed PCNSL in immunocompetent patients was reported last year [10]. Kristoph Jahneke (Charité-Universitätsmedizin Berlin, Germany) presented the prognostic factors for response and survival in PCNSL from the same German randomized Phase III [11]. Patients on the study were treated upfront with high-dose methotrexate or high-dose methotrexate plus ifosfamide and received whole-brain irradiated thereafter if randomized to radiotherapy [10]. Patients with complete remission were observed while the patients who failed to achieve complete remission were treated with high-dose cytarabine. Multivariate logistic regression analyses was performed on the enrolled patients to identify prognostic factors for overall response and PFS and OS. Female gender, no steroids at study entry and having two or less tumor lesions were highly predictive for overall response. Age (≤60 years) and performance status were strongly associated with OS. In another presentation, the group reported prognostic factors for chemotherapy-related acute toxicity from same Phase III trial [11]. On multivariate analysis, age ≥60 years, performance status (Karnofsky Performance Scale [KPS] <70), and pulmonary disease were associated with greater hematological toxicity. Age ≥60 years, performance status (KPS <70), body mass index >25, elevated serum lactate dehydrogenase and preexisting cardiovascular disease were associated with greater chemotherapy related non-hematological toxicities [12].

Medulloblastoma is the most common malignant brain tumor occurring in children, comprising 40% of all childhood posterior fossa tumors [13]. Standard treatment of MB in older children consists of surgery followed by craniospinal irradiation and chemotherapy, with OS approaching 85% at 5 years for children with non-metastatic and near totally resected MB [14]. By contrast, the prognosis for infants and young children with MB treated with a similar approach remains poor [15]. Girish Dhall (Children’s Hospital Los Angeles, CA, USA) presented the data on the infants and young children with newly diagnosed MB treated on Head Start III protocol [16]. The study employed high dose chemotherapy with autologous hematopoietic cell rescue to manage the young children with MB to avoid radiation in children <6 years. A total of 92 children with newly diagnosed MB were treated with induction chemotherapy combination of vincristine,
cisplatin, cyclophosphamide, etoposide, high-dose methotrexate alternating with vincristine, cyclophosphamide, oral etoposide and temozolomide followed by consolidation with myeloablative chemotherapy and AuHCR. Children between 6–10 years of age or with those with residual tumor after induction received irradiation after consolidation. Impressive 3-year event-free survival and OS rates of 47 ± 6% and 65 ± 6% were seen in all patients. Patients with localized disease did better with 3-year event-free survival and OS rates of 63 ± 8% and 80 ± 7%. Patients with desmoplastic MB histology had better event-free survival than patients with classic tumors. These results appear to be promising while avoiding craniospinal irradiation in approximately half of the patients which may help preserve quality of life and intellectual functioning in such children. While the data presented in GBM studies did not have practice-changing implications, the promising results of the Head Start III study may help avoid craniospinal irradiation in select group of patients in MB.

Financial & competing interests disclosure
Manmeet Ahluwalia serves on the speakers bureau for Merck, has served on an advisory board for Elekta and is a consultant for Monteris Medical. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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