JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of CNS oncology

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Wick W, Platten M, Meisner C *et al.* Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, Phase 3 trial. *Lancet Oncol.* 13, 707–715 (2012).

The authors report results of a randomized trial of patients older than 65 years with glioblastoma ($n = 331$) or anaplastic astrocytoma ($n = 40$), randomly assigned to radiotherapy (60 Gy in 1.8–2.0 Gy fractions) or dose-dense temozolomide (100 mg/m²/day, 1 week on, 1 week off, continued for 6 months). The median survival was 9.6 months in the radiotherapy group and 8.6 months in the temozolomide group. Thirty nine randomized patients who did not start treatment were excluded from analysis. Methyl guanine methyl transferase (MGMT) promoter methylation (MGMT⁺), present in 35% of 209 patients tested, was strongly associated with longer survival (hazard ratio: 0.62). MGMT⁺ patients treated with chemotherapy had longer survival (hazard ratio: 0.69) and MGMT[−] patients had shorter survival (hazard ratio: 1.34) compared with patients treated with radiotherapy (hazard ratio: 1.0 for both MGMT⁺ and MGMT[−] patients). The authors conclude that temozolomide is not inferior to radiotherapy in elderly patients with radiotherapy, and that MGMT promoter methylation status could be considered in deciding between these treatments.

– Written by Larry Junck

Malmström A, Grønberg BH, Marosi C *et al.* Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, Phase 3 trial. *Lancet Oncol.* 13(9), 916–926 (2012).

In a trial conducted in seven European countries, 291 patients aged 60 years and older were randomized to temozolomide (200 mg/m²/day for 5 days, every 28 days), hypofractionated radiotherapy (34 Gy in ten fractions of 3.4 Gy), or standard radiotherapy (60 Gy in 30 fractions of 2 Gy). An additional 51 patients were randomly assigned to temozolomide or hypofractionated radiotherapy. In the three-way randomization, temozolomide (median survival: 8.3 months) was superior to standard radiotherapy (6.0 months), but not to hypofractionated radiotherapy (7.5 months). For patients older than 70 years, compared with standard radiotherapy, temozolomide ($p < 0.0001$) and hypofractionated radiotherapy ($p = 0.02$) provided superior survival. In patients treated with temozolomide, those with MGMT promoter methylation had superior survival (9.7 months) compared with those without methylation (6.8 months). The authors conclude that temozolomide and hypofractionated radiotherapy should be considered standard treatments in elderly patients with glioblastoma, and that MGMT status may be helpful in predicting benefit from temozolomide.

– Written by Larry Junck

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Peyrl A, Chocholous M, Kieran MW et al. Antiangiogenic metronomic therapy for children with recurrent embryonal brain tumors. *Pediatr. Blood Cancer* 59, 511–517 (2012).

While the standards of care for non-metastatic medulloblastoma have allowed a progression-free survival of approximately 80% at 5 years, patients that recur after combined chemotherapy and radiotherapy have incurable tumors with a median progression-free survival lower than 18 months. Among all strategies so far adopted, the Austrian/Boston Pediatric Neurooncology group has studied a 'metronomic plus antiangiogenic' strategy combining a previously used and published strategy of four drugs with other ones. The four-drug regimen (thalidomide, celecoxib, etoposide and cyclophosphamide) was implemented with fenofibrate, a peroxisome proliferator-activated receptor ligand (rosiglitazone) enhancing etoposide activity, bevacizumab and intrathecal therapy, alternating etoposide with liposomal cytarabine. The five oral agents and bevacizumab all inhibit angiogenesis via a number of different mechanisms, and the authors hoped to potentiate the therapeutic effect and escape the evolution of resistance mechanisms without increasing toxicity for the patients.

They report results on 16 patients (diagnoses: medulloblastoma, primitive neuroectodermal tumors and atypical-teratoid rhabdoid tumors), ten being alive at a median of 33 months. Among the seven

patients with medulloblastoma, five are alive with a range of 12–58 months from the treated recurrence, but three were also treated with other strategies (operation, reirradiation and systemic chemotherapy), only two have stopped treatment since 2 and 28 months, and one still presents macroscopic metastases. Moreover, side effects of intrathecal liposomal cytarabine were quite severe. Considering all these biases, even if results regarding overall survival are appreciable, a Phase II study has been launched to discriminate the true efficacy of this combination.

– Written by Maura Massimino

Blaney SM, Kocak M, Gajjar A et al. Pilot study of systemic and intrathecal mafosfamide followed by conformal radiation for infants with intracranial central nervous system tumors: a Pediatric Brain Tumor Consortium study (PBTC-001). *J. Neurooncol.* 109(3), 565–571 (2012).

With the aim of saving children with embryonal tumors under 3 years of age at diagnosis from craniospinal irradiation when deemed necessary for their histologic subtype, such as in medulloblastoma, the North America Pediatric Brain Tumor Consortium launched a pilot study using concomitant intrathecal mafosfamide (a pro-activated form of cyclophosphamide) and multiagent systemic chemotherapy, followed by conformal local irradiation. For the 71 patients without flow obstruction,

5-year progression-free survival and overall survival were $33 \pm 13\%$ and $51 \pm 11\%$, respectively. For the 20 medulloblastoma patients with no metastases, the 5-year progression-free survival was $65 \pm 19\%$, all receiving irradiation at the end of the systemic and intrathecal treatment. In the HIT (German Cooperative Group) experience, the corresponding progression-free survival rate in 31 patients without macroscopic metastases was $68 \pm 8\%$, 14 of which were progression- and radiation treatment-free. While the authors claim that their experience is not inferior for survival results from the one of the HIT group, it is to be underlined that the Pediatric Brain Tumor Consortium does not report neurocognitive and psychological outcome after this strategy, while the HIT group could detail the results after the intrathecal use of methotrexate. The functional outcome after intrathecal mafosfamide use could be of further interest.

– Written by Maura Massimino

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