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A selected review of abstracts from the 10th Congress of the European Association of Neuro-Oncology

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The European Association of Neuro-Oncology (EANO) is the largest neuro-oncology meeting in Europe. It meets biannually and reproducibly provides an exciting forum to present new brain cancer clinical trials and research data. The EANO 2012 meeting comprised 3 days of presentations; nearly 80 oral presentations and over 350 abstracts, providing a contemporary overview of neuro-oncology that includes both metastatic diseases of the CNS as well as primary brain tumors. This article attempts to highlight select abstracts presented at this year's meeting in a short review that provides a portrait of a large and multifaceted meeting.

Metastatic disease to the CNS

■ Parenchymal brain metastases

Several abstracts were presented regarding brain metastasis. Most notable was a large retrospective series of patients ($n = 777$) treated with surgery followed by whole-brain irradiation (WBI) or WBI alone [1]. Outcome was determined to be dependent upon recursive partitioning analysis class, graded prognostic assessment class, performance status and tumor histology. The best outcome was seen in breast cancer brain metastases. From the same institution, 329 patients with one or two brain metastases were retrospectively evaluated for outcome, comparing surgery followed by WBI and a stereotactic radiotherapy boost (SRB) versus WBI and, in responding patients, a SRB [2]. The group treated by surgery followed by WBI and SRB resulted in the best outcome and breast

cancer-derived metastases benefited most from WBI and SRB.

■ Leptomeningeal disease

A study from Spain demonstrated the safety of intra-cerebrospinal fluid (CSF) chemotherapy as determined by the incidence of treatment-related side effects. Furthermore, the study noted that side effects were disproportionately higher in patients treated by a ventricular access device or in those patients receiving intra-CSF liposomal cytarabine [3]. Another study from Spain utilized CSF flow cytometry and a monoclonal antibody directed against epithelial cell adhesion molecule in patients with carcinomatous meningitis and determined a 75% detection rate of malignant cells in the CSF [4]. The authors postulate tumor burden, as determined by the proportion of positive cells, has survival implications.

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However, no comparison with CSF cytology was provided. A retrospective study of 240 patients with leptomeningeal disease (165 with solid tumors, 50 with lymphoma and 25 with leukemia) demonstrated that, following pretreatment neuraxis imaging (including brain and complete spine MRI) and radioisotope CSF flow study, approximately a third of patients had radiographic abnormalities that altered leptomeningeal disease-directed treatment [5].

Primary brain tumors

■ Primary CNS lymphoma

The Bonn group treated 89 elderly patients with primary CNS lymphoma (PCNSL) in a prospective Phase II trial using a systemic polychemotherapy (which included high-dose methotrexate and cytarabine) and an intra-CSF liposomal cytarabine regimen [6]. Although treatment-related mortality and morbidity were high (nearly 25%), a third of patients survived for over 5 years. The International PCNSL Collaborative Group presented retrospective data on 48 patients with primary leptomeningeal CNS lymphoma [7]. The outcome did not appear to differ according to the treatment administered and median overall survival was 18 months. In a large study (n = 249) of genomic alterations in patients with PCNSL, the five most frequent abnormalities were 6p loss (corresponding to HLA loss), 6q loss, *CDKN2A* homozygous deletions, 12q loss and 7q gains [8]. *CDKN2A* homozygous deletions and 6q loss were associated with shorter survival.

■ Meningiomas

A study from Germany assessed the methylation status of the *TIMP-3* gene, which localizes to chromosome 22 and is frequently lost in meningioma. The study demonstrated that the *TIMP-3* gene is often methylated, thereby silencing *TIMP-3* expression and, presumably, facilitating tumor invasion. *TIMP-3* promoter methylation was more frequently seen in high-grade meningiomas [9]. In a prospective two-step Phase II trial of patients with recurrent high-grade meningioma (n = 7) using a long-acting somatostatin analog, the primary end point (radiographic response) was not met (no objective responses were seen). However,

the median and 6-month progression-free survival were 4.2 months and 43%, respectively, similar to a prior retrospective study of a long-acting somatostatin analog in recurrent meningioma [10].

■ Gliomas

Low-grade gliomas

A provocative study from France suggested that neoadjuvant temozolomide (TMZ) chemotherapy can, in selected patients, reduce tumor volume, thereby permitting an extensive resection [11]. This was not considered feasible prior to TMZ. Two studies emphasized the importance of PET imaging (using differing radioligands, ¹⁸F-fluoroethyl-tyrosine and ¹¹C-methionine) in determining tumor grade and outcome in tumors that, by anatomic MRI, appear to be low-grade gliomas [12,13]. Both studies suggested that increased uptake by the amino acid radioligand predicted higher tumor grade and decreased survival. An Italian prospective Phase II trial of dose-dense TMZ in patients with progressive or recurrent oligodendroglioma demonstrated a partial response rate of 35%, a significant reduction (defined as a >50% reduction of pretreatment frequency of seizures) in seizures (seen in 85% of patients) and a median progression-free survival of over 33 months [14]. Whether these results differ significantly from standard-dose TMZ is uncertain and perhaps warrants a prospective randomized trial, as suggested by the authors.

Anaplastic gliomas

Upfront trials

The long-term follow-up study to the European Organization for the Research and Treatment of Cancer (EORTC) trial for newly diagnosed anaplastic oligodendroglioma (AOT) was presented again and demonstrated a significant survival advantage for the codeleted 1p19q cohort of AOT treated with adjuvant radiotherapy plus procarbazine, lomustine and vincristine (PCV) chemotherapy [15]. This study, along with the companion Radiation Treatment Oncology Group (RTOG) study, is clinically relevant as both demonstrate a twofold increase in median overall survival in patients with codeleted 1p19q AOT treated initially with

radiotherapy plus PCV compared with radiotherapy alone followed at recurrence with an alkylator-based chemotherapy (12–14 vs 7 years). Furthermore, there was no survival advantage seen in the larger group of patients with AOT who are uni- or non-deleted when comparing radiotherapy plus PCV with radiotherapy, suggesting a limited (if any) effect of adjuvant PCV on survival in patients with nondeleted anaplastic glioma. The potential benefit of adjuvant chemotherapy is being addressed in another prospective Phase III EORTC trial (CATNON), which is comparing radiotherapy with radiotherapy plus TMZ, and is open and actively accruing. In an analysis of data from the German NOA-04 trial (radiotherapy vs TMZ or PCV chemotherapy), methylation of the tumor *MGMT* gene promoter was prognostic and associated with improved median overall survival in patients with an *IDH1* mutation whether patients received radiotherapy or TMZ/PCV [16]. However, in patients with wild-type *IDH1* and methylated *MGMT*, a survival advantage was only seen in patients who were administered TMZ/PCV.

Glioblastoma

Upfront trials

Two presentations outlined novel adjuvant immunotherapy approaches [17,18]. One discussed a Phase I trial that used a peptide vaccine derived from 11 HLA-binding tumor-specific antigens combined with standard-of-care radiotherapy plus TMZ. The preliminary work suggests that the vaccine was safe when combined with standard-of-care radiotherapy plus TMZ [17]. The other presentation discussed a preclinical study in which the immune response in mice to an *IDH1* peptide vaccine derived from the common R132H mutation was assessed and found to be immunogenic [18]. Both of these studies add to the increasing literature available regarding the applicability of immunotherapy in the management of glioblastoma (GBM). The German NOA-08 trial (elderly patients with GBM or anaplastic astrocytoma treated with standard-dose radiotherapy, 60 Gy or dose-dense TMZ) was again presented, demonstrating a survival advantage with dose-dense TMZ treatment in elderly patients with tumors showing promoter

methylation of the *MGMT* gene [19]. This, and a similar Nordic trial (elderly GBM patients treated with standard or hypofractionated radiotherapy vs standard-dose TMZ), suggests that elderly patients with GBM show a similar survival benefit when treated with TMZ only and deferred radiotherapy when compared with radiotherapy only. In addition, survival is improved in the small cohort (~30%) of elderly patients with GBM and *MGMT*-methylated tumors when treated with TMZ, a practice-changing treatment strategy. Two imaging studies assessed apparent progression following completion of radiotherapy plus TMZ in an attempt to differentiate between pseudoprogression and early disease progression [20,21]. In a French retrospective cohort of 58 patients, very early disease progression (progression while receiving radiotherapy plus TMZ) was seen in 20%, pseudoprogression in 17% and early disease progression in 33% of patients [20]. Using a novel blood pool agent, ferumoxytol, which, unlike gadolinium, does not extravasate into the tumor interstitium, relative cerebral blood volume (rCBV) was determined with perfusion MRI using both contrast agents [21]. Ferumoxytol-determined rCBV was superior in differentiating pseudoprogression (defined as low rCBV) from early disease progression (high rCBV).

Salvage trials

Two studies correlated response to bevacizumab with advanced imaging [22,23]. A small French study suggested serial fluorodeoxyglucose-PET imaging, when performed at baseline and repeated while patients were receiving bevacizumab, predicts survival [22]. This study, however, conflicts with the National Cancer Institute (NCI) trial of bevacizumab for recurrent GBM and suggests, at present, that there is not a radiologic biomarker predictive of response to angiogenic inhibition. In a German retrospective study of 30 patients on bevacizumab, advanced MRI using susceptibility-weighted sequences demonstrated that hypodense susceptibility signals predicted for failure on bevacizumab [23]. The source of the susceptibility signal is not fully understood,

although they hypothesized it to result from tumor invasion, co-option of cerebral vasculature and microbleeds.

Quality of life

Two studies evaluated quality of life (QoL) in caregivers of patients with gliomas [24,25]. Both studies demonstrate that caregivers of patients with brain tumors have a compromised QoL when compared with caregivers with non-CNS cancers. In part, these differences reflect the unique care situation in patients with brain tumors as disease progression, mobility and cognition are negatively affected. Another study in patients with gliomas suggests a marked discordance between patients and their caregivers when reporting QoL; patients appear to consistently rank QoL higher than their caregivers throughout the disease course [26]. This finding emphasizes the importance of including the caregiver assessment of patient QoL. The EORTC trial of AOT alluded to above assessed cognition and QoL in a small cohort of patients

(n = 35) compared with controls 2.5 years after treatment [27]. Outcome was variable, wherein 41% of patients did not show significant cognitive impairment, 25% were mildly to moderately impaired, 31% were severely impaired and 78% were independent in activities of daily living. Both recurrent seizures and disease progression negatively affected cognitive performance; however, there appeared to be no difference in outcome with regard to primary therapy (radiotherapy or radiotherapy plus PCV).

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