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Neuro-oncology: a selected review of ASCO 2012 abstracts

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The American Society of Clinical Oncology (ASCO), the largest clinical oncology meeting in the USA, meets annually and reproducibly provides an exciting forum to present new cancer clinical trials and research data. The ASCO 2012 CNS tumors section comprised 3 days of presentations and over 130 abstracts, providing an overview of neuro-oncology, including both metastatic diseases of the CNS and primary brain tumors. This brief review attempts to highlight select abstracts presented at this year's meeting in an organized manner that will provide a portrait of a large and multifaceted meeting.

Metastatic disease of the CNS

■ Parenchymal brain metastases

Several abstracts were presented, the most notable utilizing an oral poly(ADP-ribose) polymerase inhibitor, veliparib, in conjunction with whole brain irradiation (WBI) for patients with polymetastatic brain metastases [1]. Based upon the results of this Phase I study, a larger Phase II study is being initiated to determine if the laboratory-documented radiosensitization of poly(ADP-ribose) polymerase inhibitors augments WBI for the treatment of patients with brain metastases.

■ Leptomeningeal disease

Several abstracts were presented, and of particular note was a retrospective study of 240 patients with leptomeningeal disease (LMD; 165 with solid tumors, 50 lymphoma and 25 leukemia). This demonstrated that, following pretreatment complete neuraxis imaging (brain and complete spine MRI and radioisotope cerebrospinal fluid flow study), approximately one-third

of patients manifested radiographic abnormalities that impacted LMD-directed treatment [2]. Radiographic abnormalities were more common in patients with solid tumor-related LMD compared with hematological tumors (40 vs 15%), suggesting the utility and need of complete neuraxis imaging in both cohorts of patients with LMD.

Primary brain tumors

■ Primary CNS lymphoma

A single abstract concerning an elderly cohort (defined as age >60 years) was derived from the large (n = 411) German primary CNS lymphoma (PCNSL) randomized trial of high-dose methotrexate (HD-MTX) with or without ifosfamide followed in patients with a complete response to observation or WBI [3]. In comparison with younger patients, older patients with PCNSL in the German trial had half of the progression-free and overall survival, nearly two-times the treatment-related toxicity and approximately half the radiographic response. In a small study

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of patients with recurrent PCNSL, following successful re-induction (i.e., achievement of a second complete response) with standard-dose chemotherapy, patients were treated with high-dose chemotherapy (using busulfan, thiotepa and cyclophosphamide [BTC]) followed by autologous peripheral stem cell transplantation (PSCT) [4]. The 3-year follow-up suggests this retreatment paradigm should be considered in otherwise eligible patients with recurrent PCNSL. The issue of the appropriate high-dose conditioning chemotherapy regimen (BTC vs busulfan, etoposide, cytarabine and melphalan [BEAM]) is unresolved, although the authors suggest improved outcome with BTC. From the same group, another small prospective study suggested the feasibility of treating newly diagnosed PCNSL patients at high risk for recurrence with a standard HD-MTX regimen and, following achievement of a complete response, consolidation with high-dose chemotherapy and autologous PSCT [5]. Based on this and similar studies, a Southwest Oncology Group randomized trial has recently opened to evaluate whether PSCT is of value in newly diagnosed patients with PCNSL achieving a complete response to HD-MTX. Another report from the Memorial Sloan-Kettering Cancer Center (NY, USA) neuro-oncology group described outcome in the trial utilizing rituximab, HD-MTX, procarbazine, vincristine and high-dose cytarabine (R-MPV-A) followed by reduced-dose WBI (23.4 Gy) in newly diagnosed PCNSL that is being evaluated in a randomized Phase II Radiation Treatment Oncology Group (RTOG) trial comparing R-MPV-A with or without reduced-dose WBI [6].

■ Gliomas

Anaplastic gliomas

Upfront trials

The most significant presentations at the 2012 American Society of Clinical Oncology Annual Meeting with respect to CNS tumors concerned long-term follow-up from the RTOG and European Organization for the Research and Treatment of Cancer (EORTC) trials for newly diagnosed anaplastic oligodendroglial tumors (AOT), a subset of WHO grade 3 anaplastic gliomas [7]. Both studies previously reported no difference in overall survival in patients treated either with radiotherapy (RT) alone or RT and procarbazine, lomustine and vincristine (PCV), regardless of genotype (i.e., the presence or absence of the 1p19q codeletion characteristic

of a fraction of oligodendroglial tumors). In what is clearly a practice-changing result, both EORTC and RTOG trials in longer follow-up demonstrate a twofold increase in median overall survival in patients with 1p19q codeleted AOT treated initially with RT plus PCV compared with RT alone followed at recurrence with an alkylator-based chemotherapy (12–14 vs 7 years). What remains uncertain is why survival increases so dramatically with initial combined therapy (RT plus PCV) versus sequential therapy, and further whether temozolomide (TMZ) may be substituted for PCV and result in a similar outcome. As a consequence of these studies not yet published, the recently opened CODEL trial for codeleted AOT was temporarily closed and will reopen later this year as a trial comparing RT plus PCV to RT plus TMZ following maximal safe resection to determine if, in fact, these two chemotherapy regimens are equi-efficacious.

Salvage trials

Four abstracts were presented with respect to recurrent anaplastic gliomas; three described salvage therapy with bevacizumab as either a single agent [8] or in combination with fotomustine, a nitrosourea, or rilotumumab, a monoclonal antibody directed at HGF [9,10]. In a large retrospective study of 163 patients with recurrent anaplastic gliomas, outcome following salvage therapy not otherwise specified was as follows: median progression-free survival (PFS) 7.1 months; 6-month PFS 58%; median overall survival 18.3 months; and 12-month overall survival 63% [11].

Glioblastoma

Upfront trials

Seven abstracts were notable regarding the treatment of newly diagnosed glioblastoma (GBM). In a randomized Phase III trial of TMZ-based chemoradiotherapy with or without the monoclonal antibody directed against the EGF receptor nimotuzumab (n = 142), no significant difference in survival was demonstrated [12]. In a single-institution Phase II trial, TMZ-based chemoradiotherapy that included bevacizumab as well as erlotinib showed an improvement in PFS, but no change in overall survival replicating prior published data from two similarly designed single-arm Phase II studies from UCLA (CA, USA) and Duke (NC, USA) [13]. No data were presented from the two recently completed large randomized Phase III trials (RTOG 0825 and

AVAglio) that compared TMZ-based therapy with or without the addition of bevacizumab. Both trials were designed to determine if there is a survival advantage to the addition of bevacizumab to TMZ-based chemoradiation. The North Central Cancer Treatment Group presented two single-arm Phase II trials that used a similar treatment paradigm adding a novel agent (everolimus [Rad001], a mTOR inhibitor, in one trial and dasatinib, a Src inhibitor, in the second trial) to standard-of-care TMZ chemoradiation [14,15]. Neither trial demonstrated an improvement in survival relative to standard of care. In a novel factorial design, an eight-arm trial compared couplets and triplets of novel agents (*cis*-retinoic acid, thalidomide, celecoxib and dose-dense TMZ) to standard of care, demonstrating the feasibility of this approach in GBM and suggesting that the trial design may be applicable to assessing multiple agents simultaneously in either the newly diagnosed or recurrent setting [16]. One of four vaccine studies was presented as a work in progress using the dendritic cell vaccine ICT-107 [17]. The study is designed as a Phase IIb trial using a vaccine prepared with six tumor-specific antigens in patients with HLA-A1- or A2-positive complete, or near complete, tumor resections. This trial and the other three vaccine-based trials currently enrolling represent a promising new immunotherapy approach to GBM.

In what is a practice-changing trial, the German NOA-08 study compared standard-dose 60 Gy RT with dose-dense TMZ in elderly patients with GBM [18]. The trial demonstrated similar outcome in both treatment arms; however, outcome was dependent upon MGMT promoter methylation status, wherein MGMT tumors had improved outcome when treated with TMZ, whereas unmethylated tumors had improved outcome with radiotherapy. This trial is one of three for elderly patients, and of the two published trials (NOA-08 and the Nordic trial), both suggest TMZ-only therapy to be equi-efficacious when compared with radiotherapy. The combined Canadian and European elderly GBM trial in progress compares hypofractionated RT

with or without TMZ and will determine if any benefit is observed with combination therapy in this large patient population [19]. There are, in addition, two other trials for elderly GBM using bevacizumab in conjunction with RT: the ARTE trial and bevacizumab plus TMZ in a single-institution trial at UCLA [20].

Salvage trials

Two trials, both works in progress, were presented. The Phase II REACT vaccine trial using the EGF receptor variant 3 vaccine, rindopepimut, is enrolling patients. Rindopepimut will be used in conjunction with bevacizumab in bevacizumab-naïve patients and as add-on therapy in patients progressing on bevacizumab [21]. TOCA 511 is a novel Phase I/II trial using a retroviral replicating vector that delivers cytosine deaminase to the tumor (administered by intratumoral injection at time of reoperation) followed by oral 5-fluorocytosine that, in tumor, is converted by cytosine deaminase to 5-fluorouracil, a cytotoxic chemotherapy [22]. In the first prospective trial of re-radiation for recurrent GBM, the German group assessed outcome comparing the anti-CD95 ligand-binding fusion protein, APG101, in conjunction with re-radiation versus re-radiation only [23]. Median PFS was 4 months and 6-month PFS favored RT plus APG101. A difference in response to salvage therapy was suggested in patients with recurrent GBM that had discontinued bevacizumab (best outcome) versus patients progressing on bevacizumab (worst outcome) [24]. This observation is relevant for the large cohort of patients treated with upfront bevacizumab as per the RTOG0825 and AVAglio trials.

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