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The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma

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To estimate the value of whole brain radiotherapy (WBRT) in the treatment of primary CNS lymphoma (PCNSL), it is important to recall the goals of treatment when confronted with this disease. Presumably, our goals of PCNSL treatment are to improve neurological deficits, improve or maintain quality of life, delay neurological progression, prolong progression-free survival, prolong overall survival, and eventually achieve a cure.

Very few of these goals are achieved with WBRT in the current landscape of improved systemic therapy options for PCNSL. Historically, it had been recognized that PCNSL is less sensitive to irradiation than lymphomas elsewhere in the body and might therefore potentially require higher doses to achieve local control. Accordingly, Radiation Therapy Oncology Group (RTOG) study 8315 explored whether treating the whole brain at 40 Gy and increasing the tumor dose to 60 Gy would result in improved outcome. In fact, median overall survival was only 11.6 months from the start of radiotherapy; 16 of 26 patients with posttreatment CT scans were considered to have had a complete response, a finding commonly cited to demonstrate the efficacy of RT in that disease. Importantly, however, these 16 patients represent a highly selected population because patients who progressed during radiotherapy were not included in that analysis.[1]

With the introduction of high-dose methotrexate into the first-line treatment of PCNSL, the survival outcome was greatly improved. This established initial chemotherapy containing high-dose methotrexate as a new standard of care, although its superiority over RT alone was never formally demonstrated in a randomized clinical trial. It soon also became apparent, however, that the encouraging activity of combined modality treatment came at a high price. There was a major risk of severe neurotoxicity in surviving patients, with a dramatic increase of risk in the elderly.[2] The association of the administration of WBRT and delayed neurotoxicity, defined by cognitive decline and characteristic changes on neuroimaging, has been confirmed repeatedly ever since.[3,4] Accordingly, the increasing awareness that the administration of WBRT was probably incompatible with long-term survival with adequate quality of life resulted in numerous approaches to treating PCNSL with systemic chemotherapy or combined systemic and intraventricular chemotherapy alone.[5–9] Although retrospective analysis had failed to support a role for WBRT in prolonging overall survival many years ago,[10] clinical practice did not respond accordingly; WBRT continued to be used at many sites globally, even in the first-line setting. Thus, it was stated that a randomized clinical trial would be necessary to formally demonstrate that WBRT could be omitted from the first-line treatment of PCNSL without compromising overall survival. This major endeavor was eventually agreed upon with the formation of the German PCNSL Study Group in the late 1990's and took until 2009 to complete enrollment. Patients with histologically confirmed PCNSL received high-dose methotrexate chemotherapy as monotherapy until 2005 and in combination with ifosfamide thereafter as initial treatment. Patients who achieved complete response were then treated with consolidating WBRT or observation alone, based on a randomization done prior to induction chemotherapy. Patients without complete response were treated per initial randomization with WBRT or high-dose cytarabine. The latter was considered the best alternative systemic treatment at the time the trial was designed. The initial report of the primary outcome measures,[11] as well as the final report,[12] indicated that omitting WBRT from initial treatment did not compromise survival regardless of the way the data were interpreted, including by various subgroup analyses.

Given the current dichotomy of PCNSL treatment of aiming for a cure in young (fit) patients versus maintaining remission in older (frail) patients,[13] it becomes apparent that there is no longer a role for WBRT in the initial treatment of the disease. If we want to cure young patients, we cannot take the risk of inducing cognitive impairment for their remaining lifetime. In the elderly, where we aim for maintaining the remissions we achieve, we should not use WBRT because of the greatly increased sensitivity of elderly patients to treatment-associated neurotoxicity. In light of the absence of a survival benefit for standard-dose radiotherapy (30×1.5 Gy) in the G-PCNSL-SG-1 trial,[11,12] the rationale for using a lower dose of WBRT (eg, 13×1.8 Gy)[14] in this setting remains doubtful.

This leaves us with the consideration of whether PCNSL should be treated with WBRT at recurrence. A retrospective study of 48 patients treated with salvage WBRT reported a complete response rate of 58% and a partial response rate of 21%; median survival from initiation of WBRT was 16 months.[15] While these data may be cited to support the role of WBRT in recurrent PCNSL, randomized data are again more compelling and are in fact available from the G-PCNSL-SG1 trial. The efficacy of WBRT as a salvage treatment was demonstrated for progression-free survival but not for overall survival.[11] The quality of postprogression survival in patients who received WBRT, when compared with those without WBRT, remains to be explored.

Table 1. Key conclusions

- There is no safe dose of WBRT for the brain.
- Reduced-dose WBRT will not be more effective than standard-dose WBRT.
- Intensifying chemotherapy up-front will not make WBRT for consolidation more effective.
- Intensifying chemotherapy up-front will not make WBRT for consolidation safer.
- PCNSL needs to be "cured" at initial diagnosis, not at recurrence: WBRT at recurrence remains an option, but probably does not prolong survival.

Overall, these published data allow one to reach some conclusions on the treatment of PCNSL as summarized in Table 1. I would be hesitant to randomize either young or fit patients, or elderly or unfit patients, for a trial containing WBRT at any dose. Is there any role for RT in this disease at all? Only prospective trials can support the claim that WBRT with hippocampal sparing is safer than standard WBRT, and this would only address the safety concern and not the efficacy. Could there be a role for focused RT, for example, in partial responders or for consolidating remission? Traditional views say "no", but traditional views also said that there was no role for surgery until it was examined in a reasonably sized patient population for the first time.[16]

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