

# The role of whole brain radiation in primary CNS lymphoma

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## Case presentation

*A 63-year-old woman presented with progressive dizziness and headaches. A brain magnetic resonance imaging (MRI) revealed a 3 × 4 cm contrast enhancing single mass in the right parietal lobe; stereotactic biopsy of the mass revealed a CD 20-positive diffuse large B-cell lymphoma (DLBCL). Body fluorodeoxyglucose-positron emission tomography scan and bone marrow biopsy were negative. The patient had no other health issues. She had good performance status when starting treatment with the combination of rituximab, high-dose methotrexate (HD-MTX) (3.5 g/m<sup>2</sup>), and high-dose cytarabine (HD-Ara-C) (2 × 2 g/m<sup>2</sup>). After 4 courses, she achieved a partial radiographic response. After 2 more courses, she achieved a complete radiographic response. After achieving complete response (CR), myeloablative, nonmyeloablative chemotherapy, or whole brain radiotherapy (WBRT) were considered as consolidative treatments to reduce the risk of relapse.*

## Introduction

Primary central nervous system lymphoma (PCNSL) is a malignant DLBCL confined to the central nervous system (CNS). HD-MTX-based chemotherapy followed by consolidative WBRT has, historically, been the standard of care. One randomized trial compared consolidative WBRT with observation in patients who achieved complete remission after induction chemotherapy. Although containing methodological flaws, it suggested that WBRT might prolong the duration of response but not overall survival (OS). Herein, we review the optimal role of WBRT in the management of PCNSL.

## Background

PCNSL is a malignant DLBCL confined to the CNS.<sup>1</sup> PCNSL is rare with an estimated incidence of 2/10<sup>6</sup> persons per year in Western countries.<sup>2</sup> Historically, WBRT and steroids have been the mainstay of treatment of PCNSL, however, although leading to good remission rates, the relapse rate was very high resulting in a 5-year OS <20%.<sup>3</sup> With HD-MTX-based chemotherapy, the outcome of PCNSL patients has improved.<sup>3</sup> The combination of HD-MTX-based chemotherapy followed by consolidative WBRT is still a commonly used approach.<sup>4</sup> Alternatives to WBRT for consolidation treatment

include conventional-dose chemotherapy or high-dose chemotherapy supported by autologous stem cell transplantation (ASCT). The objectives of this focused review are to summarize the data investigating the role and optimal place of WBRT in patients with PCNSL.

## Methodology

Based on the findings of a Cochrane review (search from 1950 to February 2014),<sup>5</sup> we additionally searched MEDLINE from March 2014 onwards to identify randomized trials investigating the role of WBRT in PCNSL. Keywords used included: “primary CNS lymphoma,” “PCNSL,” “radiotherapy,” and “WBRT.” Besides the trial identified by the Cochrane review (Thiel et al<sup>6</sup>), no further completed randomized trials were identified. However, 3 ongoing randomized trials investigating WBRT in PCNSL were found on trial registries (Table 1). We also considered selected, prospective, nonrandomized studies reporting on treatment with or without WBRT. Some retrospective data are considered complementary.

## Radiotherapy without chemotherapy as first-line treatment

PCNSL is often multifocal with diffuse brain infiltration; therefore, WBRT rather than focal radiotherapy is used. One of the earliest prospective clinical trials included 41 patients with newly diagnosed PCNSL recruited in a multicenter study using 40 Gy plus a 20 Gy boost (RTOG 83-15).<sup>7</sup> Only 63% of patients had evaluable posttreatment scans, which showed CR in 16 patients (39%) and unconfirmed CR (“almost CR”) in 5 patients (12%). The median OS was 11.6 months, with 1- and 2-year OS of 45% and 25%, respectively. This prospective study demonstrated that radiotherapy was active, but remissions were not durable and OS was still poor with WBRT alone.<sup>7</sup> Another finding was that patients >60 years of age had a significantly worse prognosis. Another prospective trial (North Central Cancer Treatment Group 96-73-51) investigated the combination of WBRT with high-dose steroids in elderly patients (≥70 years of age) with newly diagnosed PCNSL.<sup>8</sup> Nineteen patients (mean age, 76 years) were recruited and treated with 41.1 Gy plus 9 Gy boost followed by high-dose steroids. The response rate was 42%, but the OS rate was only 33% after 6 months and the trial was terminated early.<sup>8</sup> In summary, WBRT alone or in combination with steroids is of limited effectiveness.

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**Table 1. Completed and ongoing randomized clinical trials investigating the role of WBRT in newly diagnosed primary CNS lymphoma**

Investigator/trial	Year	Patients	Eligibility criteria	Control arm	Intervention arm	Outcome	Comment
Thiel et al (G-PCNSL-SG-1) <sup>6</sup>	2010	N = 551	Newly diagnosed PCNSL, ≥18 y, KPS ECOG ≤3	HD-MTX (ifosfamide) + WBRT	HD-MTX (ifosfamide)	Median OS 32.4 (WBRT) vs 37.1 mo; median PFS 18.3 (WBRT) vs 11.9 mo	Trial had several methodological flaws, non-inferiority margin not met
IELSG 32 (#NCT01011920)	Ongoing	N = 219 (1st randomization), N = 118 (2nd randomization)	Newly diagnosed PCNSL, 18 to 65 y (ECOG 0 to 3), up to 70 y if ECOG ≤2	Induction treatment followed by WBRT 36 ± 9 Gy	Induction treatment followed by HDT-ASCT with carmustine and thiotepa	Primary end point is 2 y event-free survival	First randomization proofed efficacy of rituximab. Results from 2nd randomization are pending
RTOG 1114 (#NCT01399372)	Ongoing	N = 89	Newly diagnosed PCNSL, ≥18 y, KPS ECOG ≤3	Sequential R-MPV and HD-AraC	Sequential R-MPV, lower-dose WBRT (23.4 Gy), and HD-AraC	Primary end point is PFS	Recruitment complete, results pending
PRECIS (#NCT00863460)	Ongoing	N = 140	Newly diagnosed PCNSL, ≥18 to 60 y	Sequential R-MBVP and R-HD-AraC followed by 40 Gy WBRT	Sequential R-MBVP and R-HD-AraC, followed by HDT-ASCT with thiotepa, busulfan, and cyclophosphamide	Primary end point is 2 y PFS	Estimated completion of recruitment, February 2017

ECOG, Eastern Cooperative Oncology Group; Gy, Gray; HDT-ASCT, high-dose therapy with ASCT; IELSG, International Extranodal Lymphoma Study Group; KPS, Karnofsky performance status; R-MBVP, rituximab/HD-MTX/carmustine/etoposide/HD-AraC; R-MPV, rituximab/HD-MTX/procarbazine/vincristine; RTOG, Radiation Therapy Oncology Group.

## Radiotherapy in combination with chemotherapy

To improve the disappointing outcomes in PCNSL patients with WBRT alone, chemotherapy was added to WBRT. The RTOG 88-06 trial enrolled 52 patients who were treated with 2 to 3 cycles of cyclophosphamide, doxorubicin, vincristine, and dexamethasone (CHOD), together with intrathecal MTX followed by WBRT at a total dose of 59.4 Gy (41.4 Gy plus 18 Gy tumor boost). Ten patients (19%) achieved a CR after CHOD and this rate was further increased after WBRT to 38%, with a median OS of only 16.1 months and a 2-year OS rate of 42%.<sup>9</sup> By indirect trial comparison, results from RTOG 88-06 were disappointingly very similar compared with RTOG 83-15.<sup>7</sup> The first randomized trial in PCNSL was launched by the United Kingdom Medical Research Council to investigate whether the addition cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) after WBRT would prolong OS. However, this trial was terminated after 53 enrolled patients (target, 90 patients), due to poor accrual. There was no evidence that the addition of CHOP to WBRT improved OS (hazard ratio, 1.19; 95% confidence interval, 0.51-2.76; median OS, 14 months for WBRT plus CHOP vs 26 months for WBRT only),<sup>10</sup> that is likely explained by the poor CNS penetration of the drugs in the CHOP regimen.

The addition of HD-MTX to the treatment of PCNSL has improved outcomes. Studies included single-agent HD-MTX followed by WBRT,<sup>11</sup> HD-MTX in combination with other CNS penetrating drugs followed by WBRT,<sup>12,13</sup> or HD-MTX alone or in combination, deferring WBRT.<sup>14</sup> This cumulative evidence has established HD-MTX as a standard component of PCNSL treatment. Although several different combinations with HD-MTX exist, there is only randomized evidence for the addition of HD-MTX plus HD-Ara-C. In this randomized study of 89 newly diagnosed PCNSL patients, WBRT at a 36 Gy dose with or without a 9 Gy boost was considered in the protocol, but it was up to the local investigators whether or not to defer WBRT in patients >60 years of age who achieved CR.<sup>15</sup> More recently, the IELSG 32 randomized trial demonstrated that the addition of rituximab significantly improved radiographic response, progression-free survival (PFS), and OS compared with HD-MTX/HD-Ara-C. The addition of thiotepa to rituximab/HD-MTX/HD-Ara-C further increased response rates in this trial, and there was a trend toward better PFS and OS after a median follow-up of 30 months.<sup>16</sup>

Based on a systematic review<sup>5</sup> and our updated MEDLINE search, there is only 1 randomized trial that investigated whether consolidative WBRT (45 Gy) can safely be omitted from HD-MTX without compromising OS (primary end point) in patients with newly diagnosed PCNSL who achieved a CR after induction chemotherapy (Table 1).<sup>6</sup> This non-inferiority trial (N = 551) had several methodological limitations, including a large number of dropouts or patients lost to follow-up, inconsistencies between per-protocol and intention-to-treat analyses, and an underpowered design. However, results from this trial suggested that disease control may be improved with WBRT (median PFS, 18.3 vs 11.9 months; *P* = .14), but omitting WBRT may not be associated with inferior OS (median OS, 32.4 vs 37.1 months; hazard ratio, 1.06; 95% confidence interval, 0.80-1.40); however, the prespecified margin for non-inferiority was not met, therefore uncertainty remains regarding the interpretation of these trial results.<sup>6</sup>

In summary, the progress achieved in the treatment of newly diagnosed PCNSL over the last few decades is mainly attributable to optimization of effective systemic chemotherapy. However, randomized

data are limited, and conclusions from inter-trial comparisons are subject to selection bias.

## Adverse effects of WBRT

The detrimental effect of radiation on neural progenitor cells has been well documented in preclinical animal models, which provide some explanations for the clinical neurotoxicity observed in humans treated with brain radiation.<sup>17-19</sup> With the overall improvement of prognosis of PCNSL patients, the issue of neurotoxicity has become increasingly apparent. Clinical symptoms of neurotoxicity can range from mild short-term memory difficulties to more significant sequelae such as gait disturbances, incontinence, and disabling dementia, which can negatively impact survivors' quality of life.<sup>20-22</sup>

In the RTOG 93-10 phase 2 trial, 102 patients with newly diagnosed PCNSL were treated with MPV, intrathecal MTX followed by WBRT, and then HD-AraC. The initial WBRT dose was 45 Gy and later reduced to 36 Gy for patients who achieved CR to induction chemotherapy. This treatment was associated with a median PFS of 24 months and OS of 36.9 months. Lymphoma control was encouraging, but delayed neurotoxicity including memory deterioration, personality change, gait disturbance, or urinary incontinence emerged as severe complications in ~15% of patients. Patients >60 years old were most vulnerable to the neurotoxic side effects of this regimen.<sup>13</sup> Similar findings were reported in another prospective phase 2 study (N = 31) investigating the sequential treatment of CHOD and carmustine, vincristine, cytarabine, and MTX, followed by WBRT (45 Gy plus a 10 Gy boost for single lesions).<sup>23</sup> The 5-year OS was 31%, with clinical dementia occurring in 5 of the 8 patients ≥60 years alive. This complication developed early, 16 months after treatment in the first patient, and was correlated with brain atrophy and leukoencephalopathy on serial computed tomography or MRI scans.<sup>23</sup> Although the onset of neurotoxicity in patients ≥60 years appears early, younger patients may be affected later. Based on a retrospective series of 185 patients, the overall 5-year incidence of developing neurotoxicity was estimated to be 30%; interestingly, long-term survivors <60 years of age still had a risk of ~20% even over 5-years after treatment<sup>24</sup> and similar results have been reported in a large pooled data set of elderly patients.<sup>25</sup> In the above-mentioned randomized trial,<sup>6</sup> neurotoxicity was only evaluated in those patients with CR. In this subpopulation, 49% of patients who received WBRT had clinically apparent, treatment-related neurotoxicity vs 26% in the group without WBRT. Although planned, mental status examinations were not conducted in most patients; therefore, the incidence of neurotoxicity was mainly based on clinical judgment and probably under-estimated,<sup>6</sup> but this is a general issue in measuring neurotoxicity in PCNSL trials. These results demonstrate that iatrogenic neurotoxicity is not only associated with WBRT but also with chemotherapy.<sup>26</sup> However, systematic, comprehensive neurocognitive testing in PCNSL survivors (N = 80) strongly suggests that WBRT is the driving factor negatively impacting cognitive function and also quality of life.<sup>27,28</sup>

## Alternative consolidative approaches

### Reduced-dose WBRT

In 1 multicenter phase 2 trial, 52 patients with newly diagnosed PCNSL were treated with induction R-MPV and, in those patients who

achieved a CR after 5 to 7 cycles of chemoimmunotherapy, a lower dose of WBRT (23.4 Gy) was administered. Patients who did not achieve a CR received WBRT at a dose of 45 Gy.<sup>29</sup> After WBRT, all patients received 2 cycles of HD-Ara-C for further consolidation. Thirty-four patients (65%) achieved a CR, with 31 patients receiving lower-dose WBRT. After a median follow-up of 5.6 years, the median PFS and OS were 3.3 and 6.6 years, respectively.<sup>29</sup> Neurocognitive testing was conducted only in the lead center of the trial and the analysis included those patients who remained progression-free and underwent evaluations for up to 48 months after treatment (N = 12; median age, 58 years; 3 patients ≥60 years). In this selected population, there was no evidence of cognitive decline during the follow-up period, except for motor speed. However, a few long-term survivors still developed new white matter changes on MRI (5 with grade 2; 2 with grade 3), suggesting some long-term effects, but it is unclear whether these are of clinical significance and whether HD-MTX or lower-dose WBRT are the underlying causes in these cases. Together with the above-mentioned preclinical studies,<sup>17-19</sup> it remains questionable whether there is any "safe," while effective dose, of WBRT. In fact, of those 12 patients comprehensively tested, only 3 were >60 years of age and data from other series demonstrated that long-term neurotoxicity in younger patients can occur very late with incidence rates increasing even after 5 years.<sup>24</sup>

In summary, the achieved long-term outcome with R-MPV, lower-dose WBRT, and consolidative HD-Ara-C compared with the historical MPV protocol is encouraging; however, it remains questionable whether the low-dose WBRT is the key element of this success and whether the incidence of neurotoxicity will remain low with longer term follow up.

### Consolidation with myeloablative chemotherapy supported with ASCT

A multicenter phase 2 study (N = 79) investigated thiotepa-based high-dose chemotherapy supported by ASCT (HDT-ASCT) after induction with 4 courses of rituximab/HD-MTX and 2 courses of HD-Ara-C/thiotepa in newly diagnosed PCNSL patients.<sup>30</sup> After a median follow-up of 29 months, 2-year OS was 82% and only 10 patients (13%) required WBRT after HDT-ASCT due to failure to achieve CR.<sup>30</sup> Similar results were observed in the preceding pilot trial.<sup>31</sup> A single-center phase 2 study (N = 32) investigated R-MPV induction followed by HDT-ASCT with thiotepa, cyclophosphamide, and busulfan in patients younger than 67 years with newly diagnosed PCNSL, leading to a 2-year PFS and OS of 79% and 81%, respectively.<sup>32</sup> Only 3 patients (9%), who would have been eligible for HDT-ASCT, received WBRT. These 2 studies demonstrated that HDT-ASCT is associated with encouraging long-term survival in selected patients without any detrimental neurotoxicity reported so far and that only a minority of patients require WBRT after successful HDT-ASCT. However, patients participating in these HDT-ASCT trials may be favorably selected, therefore inter-trial comparisons to studies, including WBRT, are difficult. One needs to consider that many PCNSL patients may not be eligible for HDT-ASCT. A comprehensive review on HDT-ASCT in PCNSL has recently been published.<sup>33</sup>

### Consolidation with nonmyeloablative chemotherapy

Besides HDT-ASCT, non-cross-resistant drugs at high, nonmyeloablative doses can also be used as consolidation after successful induction chemoimmunotherapy. In a multicenter, single-arm, phase 2 study, 44 PCNSL patients were treated with a combination of HD-MTX, temozolomide, and rituximab; patients who achieved CR were consolidated with a combination of HD-Ara-C and etoposide.<sup>34</sup>

After a median follow-up of 4.9 years, the 2-year PFS was 57% and the 4-year OS was 65%. Interestingly, 2-year PFS (57%) in the intent-to-treat population is similar to that reported in another study that used lower-dose WBRT for consolidation in a comparable cohort of patients.<sup>29</sup>

## Radiotherapy for residual and relapsed disease

In the case of residual disease after chemotherapy, WBRT is often used to achieve CR.<sup>29-31</sup> This approach seems reasonable and is comparable to strategies in systemic non-Hodgkin lymphoma or Hodgkin lymphoma. However, the decision on whether to use WBRT in cases of residual disease is typically based on contrast-enhanced MRI. This imaging modality may identify lesions, which do not represent active lymphoma.<sup>35</sup> And, in contrast to the situation in extra-CNS non-Hodgkin lymphoma, the role of positron-emission tomography remains to be established in PCNSL.

There is no prospective trial on WBRT in relapsed/refractory PCNSL, but 2 retrospective series have been reported. In 1 study, 27 patients who received HD-MTX monotherapy were treated with WBRT at first or later relapse. After treatment with a median WBRT dose of 36 Gy, the overall response rate was 74% (37% CR and partial response, respectively), resulting in a median PFS of 9.7 and median OS of 10.9 months after initiation of WBRT; 4 patients (14.8%) developed late clinical neurotoxicity.<sup>36</sup> In another retrospective study, 48 patients (50% with refractory disease) were treated with WBRT following HD-MTX-based chemotherapy and 79% of patients achieved response (58% CR and 21% partial response), resulting in a median PFS and OS of 10 and 16 months, respectively. Treatment-related clinical neurotoxicity was observed in 22% of patients.<sup>37</sup> In summary, WBRT may be effective in refractory/relapsed PCNSL, but the duration of response is short and clinical neurotoxicity is significant. WBRT for refractory/relapsed PCNSL should be reserved for patients in whom systemic treatment is not a viable option.

## Ongoing randomized trials

Three randomized trials are investigating the role of WBRT for consolidation in newly diagnosed PCNSL (Table 1). The IELSG32 trial (n = 219) included 2 randomizations. The first randomization investigated the optimal induction treatment<sup>16</sup> and in the second randomization, patients with at least stable disease were randomly allocated between HDT-ASCT and WBRT (N = 118); final results are pending.<sup>16</sup> A similar trial in the Association des Neuro-Oncologues d'Expression Française/Groupe Ouest-Est d'Étude des Leucémies et Autres Maladies du Sang (ANOCEF/GOELAMS) group (recruitment target, N = 140) randomized patients after R-MBVP induction to

either WBRT with 40 Gy or HDT-ASCT, with results also pending. These 2 studies will provide evidence for the comparison of HDT-ASCT vs WBRT for consolidation in newly diagnosed PCNSL. In another study, investigators are examining the role of lower dose WBRT vs consolidation with HD-Ara-C. Patients receive R-MPV induction followed by either WBRT (23.4 Gy) and HD-Ara-C or HD-Ara-C without WBRT. This trial is to recruit 89 patients with PFS as the primary end point (Table 1).

## Conclusion

Based on the first randomized trial in PCNSL, although it was terminated early, the addition of CHOP after WBRT did not provide any apparent benefit. Only 1 non-inferiority randomized trial has compared WBRT to observation in patients achieving CR suggesting that disease control may be improved with WBRT, but omitting WBRT may not be associated with impaired OS; however, the non-inferiority margin was not met, therefore uncertainty remains as to whether WBRT can safely be omitted in patients achieving CR. Three ongoing, randomized trials are investigating WBRT compared with consolidation with conventional dose chemotherapy or HDT-ASCT. These results will provide better evidence for future clinical decision-making. Based on the currently available evidence, which mainly stems from informal inter-trial comparisons, alternative options to WBRT such as myeloablative or nonmyeloablative chemotherapy consolidation are associated with similar outcomes and less neurotoxicity. The pros and cons of these options should be discussed with the patient. For elderly patients (eg, 60 years and older), we recommend omitting WBRT except as a palliative salvage therapy. The patient from the case report above underwent HDT-ASCT for consolidation and is in ongoing remission after 2 years.

## Authorship

Contribution: B.K. and T.T.B. conceived the review; B.K. performed the literature research, collected data, and performed data analysis; B.K., T.T.B., J.L., G.I., A.J.M.F., and J.R. interpreted the data, wrote the manuscript, and approved the final version before submission.

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