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Improving outcomes in primary CNS lymphoma

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is an aggressive disease with previously poor prognosis. The advent of high-dose methotrexate-based induction regimens as well as use of consolidation therapy has greatly improved this prognosis in recent decades, but durable remission still eludes half of patients. In this review, we summarize the progress made in the treatment of PCNSL as well as the challenges that remain, with a focus on defining optimal induction and consolidation regimens, including the promise of developing biotherapies. Future studies will help delineate the best combination of existing and novel treatment strategies, with the goal of expanding the cohort of patients achieving a cure.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare aggressive non-Hodgkin lymphoma confined to the brain, spine, eyes and leptomeninges. It represents only 4% of intracranial neoplasms, and 4–6% of extranodal lymphomas [1]. Phenotypically, PCNSL is almost always a diffuse large B-cell lymphoma (DLBCL), and histological analysis has demonstrated an overwhelming majority fit an activated B cell or non-germinal center B cell subtype, which has been hypothesized to contribute to its relatively poor prognosis [2]. The incidence of PCNSL has increased in recent years, particularly in patients over the age of 60 years [3], and is now at an overall rate of 0.5 per 100,000 [4,5]. There have been improvements in treatment outcomes over the past several decades, reflecting advances in therapeutic strategies during this time, and the disease is now considered curable in some patients. However, survival is still inferior to extranodal lymphomas outside the CNS. This is in part due to persistently poor outcomes in certain subpopulations, such as the elderly [6] and patients with refractory disease [7], coupled with a relapse rate of up to 50%. In this review, we hope to highlight the challenges that remain in the treatment of PCNSL, with the goal of elucidating promising means of increasing the cure rate without debilitating neurotoxicity.

2. Increasing complete response: induction strategies

Historically, the initial treatment of PCNSL focused on whole brain radiotherapy (WBRT) alone, and while responses were common, durable responses were rare [8]. Induction chemotherapy regimens that have proven highly effective in systemic non-Hodgkin lymphoma, such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), failed to improve survival in PCNSL over radiation alone [9]. The introduction of high-dose intravenous methotrexate (optimally doses $> 3\,g/m^2$ in 2 week intervals, but even doses of $1\,g/m^2$ afford blood-brain barrier penetration) robustly increased response rates and median overall survival (OS) [10], but use of methotrexate alone was not sufficient [11]. Current consensus is that a multimodal regimen with high-dose methotrexate as the backbone is essential [12]. Considerable controversy remains, however, regarding the optimal

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chemotherapies to be used in combination with methotrexate, as well as whether different combinations are required for special patient populations, such as the elderly or those with primary refractory disease.

2.1. Optimum induction regimen

Most trials evaluating combination chemotherapy regimens in PCNSL have been single arm studies. In a rare randomized Phase II trial directly comparing methotrexate alone to methotrexate plus cytarabine, the addition of cytarabine increased the overall response rate (ORR) from 40% to 69%, an effect attributable entirely to a significant increase in complete response (CR) rate, from 18% to 46% [13]. However, there was a substantial increase in high grade hematologic toxicity as well (15% versus 96%), including three deaths. Furthermore, the methotrexate or methotrexate plus cytarabine were combined with WBRT and the OS was not better than WBRT alone, unlike any other Phase II trial combining methotrexate with WBRT [14]. Combining methotrexate with vincristine and procarbazine (MVP) demonstrated even more impressive response rates (CR 58%, ORR 94%) with diminished hematologic toxicity [14]. However, this regimen included intrathecal methotrexate as well as subsequent WBRT. The addition of rituximab, a monoclonal antibody targeting the B cell marker CD20, is also a seminal development in the treatment of PCNSL. A retrospective single institution study of high-dose methotrexate with or without rituximab revealed an impressive increase in both CR rate (36% versus 73%) and median progression-free survival (PFS, 4.5 months versus 26.7 months) [15]. This improved outcome is seen even though rituximab has low penetration in the CSF [16,17], possibly due to focal blood-brain barrier disruption or slow penetration into the brain parenchyma [18]. Multiple alternate chemotherapy regimens including rituximab have been investigated, including rituximab, methotrexate, vincristine and procarbazine (R-MVP) [19]; rituximab, methotrexate, cytarabine and thiotepa (MATRix) [20]; rituximab, methotrexate and temozolomide (MR-T) [21,22]; and rituximab, methotrexate, etoposide, carmustine and prednisone (R-MBVP) [23]. To date, only one prospective randomized comparison trial has been performed in the general population, demonstrating the superiority of MATRix over a 2 or 3 drug combination of the same agents [20]. None of these regimens is clearly superior, and thus the choice of induction regimen is largely determined by geographic tendencies and physician preferences at present (Table 1).

2.2. Special population: elderly

Elderly patients comprise half of those with PCNSL. They are also the population most likely to suffer consequences from standard treatments, such as renal insufficiency requiring methotrexate dose reduction [24]. Given concerns that elderly patients may be poor candidates for consolidative treatments such as myeloablative chemotherapy or WBRT, the choice of induction regimen in the elderly is of paramount importance. Unfortunately, many PCNSL trials exclude elderly patients, due to age or performance status restrictions. Several studies have investigated the feasibility and efficacy of different high-dose methotrexate-based regimens specifically in this population. Rituximab, methotrexate and procarbazine with lomustine yielded a median PFS of 10 months and an overall survival (OS) of 20 months [25]. Similarly, R-MVP followed by cytarabine produced a median PFS of 10 months and OS of 28 months [26]. Subgroup analysis in this study demonstrated an increase in CR rate in patients receiving rituximab. Neither of these studies included WBRT as consolidation. Only one study directly compared different methotrexate-based regimens in the elderly, R-MVP and methotrexate/temozolomide. While the outcomes did not show a statistically significant difference, there was a trend towards improved PFS (9.5 months versus 6.1 months) and OS (31 months versus 14 months) in the R-MVP group [27]. Overall, these studies suggest that induction chemotherapy with a regimen combining rituximab and high-dose methotrexate is recommended even in elderly patients, a proposal supported by meta-analysis data [28]. Even patients greater than 80 years of age can tolerate and benefit from high-dose methotrexate-based regimens [29]. In elderly patients whose comorbidities may preclude upfront treatment with methotrexate, monotherapy with other agents such as pemetrexed [30] and temozolomide [31] has been explored in small trials, suggesting these may be viable alternatives, though larger scale prospective studies are warranted.

Table 1
Upfront induction regimens for PCNSL.

	Regimen	Reference	Consolidation	ORR	Median PFS	Median OS
R-MVP	Rituximab, methotrexate, vincristine, procarbazine	Morris [18]	rdWBRT + HDC-ASCR	95%	3.3 years	6.6 years
		Omuro [45]	HDC-ASCR	97%	NR	NR
		Omuro[a] [26]	Cytarabine	82%	9.5 months	31 months
MR-T	Methotrexate, rituximab, temozolomide	Rubenstein [20]	Etoposide + cytarabine	77%	2.4 years	NR
		Glass [21]	WBRT + mTMZ	85%	5.4 years	7.5 years
		Omuro[a] [26]	N/A	71%	6.1 months	14 months
MATRix	Methotrexate, cytarabine (ara-C), thiotepa, rituximab	Ferreri [19,41]	WBRT or HDC-ASCR	87%	4.2 years	NR

Abbreviations: HDC-ASCR = high dose chemotherapy with autologous stem cell rescue; mTMZ = maintenance temozolomide; N/A = not applicable; NR = not reached; rdWBRT = reduced dose whole brain radiotherapy; WBRT = whole brain radiotherapy.

[a] Patients > 60 years old, no rituximab.