


Systemic Approach to Recurrent Primary CNS Lymphoma: Perspective on Current and Emerging Treatment Strategies

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Abstract: There is no uniform standard of care for the treatment of refractory or recurrent primary central nervous lymphoma (r/r PCNSL). Many different systemic treatment regimens have been studied, but available data are based on small prospective or retrospective reports. There have been no randomized controlled trials in r/r PCNSL to date. Here, we provide an overview of published systemic regimens for the treatment of r/r PCNSL, as well as therapies that are under investigation. In addition, based on available data, we propose strategies of how to approach choice of therapy for different groups of patients in this disease setting. Patients can be mainly divided into three groups: 1) patients suitable for a re-challenge with high-dose methotrexate (HD-MTX)-based regimens and that may or may not be candidates for consolidation with high-dose chemotherapy with autologous stem cell transplant, 2) patients refractory to HD-MTX or that had early relapse, but suitable for an aggressive treatment strategy with re-induction with non-MTX-based therapy, possibly followed by high-dose chemotherapy with autologous transplant, and 3) patients not suitable for re-treatment with HD-MTX and that are not candidates for aggressive therapy. As PCNSL is a rare disease and as there is urgent need for better outcomes in r/r PCNSL, clinical trial participation is encouraged, especially in elderly or frail patients who are not candidates for high-dose chemotherapy and transplant.

Keywords: primary central nervous system lymphoma, PCNSL, recurrent PCNSL, B-cell lymphoma, ibrutinib, autologous stem cell transplant

Introduction

Diffuse large B-cell lymphomas (DLBCL) are aggressive B-cell lymphomas that may involve the central nervous system (CNS). Primary DLBCL of the CNS or primary central nervous system lymphoma (PCNSL) refers to a rare subtype of DLBCL involving the brain, eyes, leptomeninges, or spinal cord without evidence of extracranial systemic involvement. Primary intraocular lymphoma (PIOL) is a subtype of PCNSL that presents in the retina, vitreous chamber and/or the optic nerve and may have concurrent involvement at other sites within the CNS. PCNSL has an estimated annual incidence of 1500 cases in the United States accounting for 6% of all newly diagnosed malignant brain tumors.^{1,2} The incidence of PCNSL is highest among males and is currently rising in immunocompetent patients, particularly those with advanced age.³⁻⁵ Secondary DLBCL of the CNS or secondary CNS lymphoma (SCNSL) can be distinguished from PCNSL by either isolated relapse of DLBCL within the CNS or synchronous

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CNS and systemic involvement. Relapse of DLBCL within the CNS is a feared complication that may arise shortly after, or even during frontline therapy.^{6,7} As a result, prophylactic strategies focus on prevention of SCNSL during frontline therapy in high-risk subgroups of DLBCL. Patients with SCNSL and isolated CNS relapse are often treated as PCNSL, while patients with synchronous CNS and systemic disease pose a clinical dilemma.⁸

The molecular heterogeneity of DLBCL is divided by gene-expression profiling (GEP) into two major molecular subtypes based on their cell of origin: germinal center B-cell (GCB) and activated B-cell (ABC) subtypes.^{9–11} Studies in PCNSL have demonstrated that the majority of cases have gene expression profiles of ABC DLBCL.¹² Further, genomic characterization studies in PCNSL have demonstrated mutations in MYD88^{L265P} and CD79B, often seen in cases of ABC DLBCL.^{13–15} Historically, PCNSL has been considered a distinct entity from systemic DLBCL, but biologic links are evident. Comprehensive molecular characterization of DLBCL demonstrates genetic subtypes that frequently involve extranodal sites including the CNS and testis.^{16,17} Further, a number of targetable genetic features have been identified in DLBCL subsets that frequently invade the CNS.¹⁶ Improved understanding of the shared molecular biology between PCNSL and SCNSL along with novel agents that reliably penetrate CNS tumors has introduced a host of new therapeutic targets.^{18–20} In this review, we aim to discuss the current treatment landscape of these CNS lymphomas with an emphasis on treatment strategies for recurrent PCNSL.

High-dose methotrexate (HD-MTX) is the backbone for the treatment of newly-diagnosed PCNSL and also secondary CNS lymphomas. There are several treatment regimens with HD-MTX that have shown significant efficacy in newly diagnosed PCNSL that significantly vary regarding HD-MTX dose, paired drugs and treatment schedules.² Most of the different regimens have not been prospectively compared and it is not possible to conclusively state which of the regimens is the most effective. In addition, there has remained controversy about which type of consolidation regimen may be most beneficial after induction with MTX-based induction therapy. Trials that evaluated more aggressive upfront regimens typically select for patients with comparatively good performance status and these therapies may not be appropriate for many newly diagnosed patients, including the growing number

of elderly patients with PCNSL. The focus of this article is not on efficacy and comparison of upfront therapies, but on treatment options for patients with progressive or recurrent disease.

Despite significant efficacy of regimens for newly diagnosed PCNSL, most patients eventually relapse and require additional therapy. Relapses can be seen late, even over 10 years after initial therapy.^{21,22} There is a difference though between patients whose tumors do not respond to HD-MTX-based therapy (primary refractory patients) or patients who recur early (eg, within half a year from achieving a CR) and those whose tumors recur after having achieved a durable CR with MTX-based therapy. For the former, changing therapy to a non-MTX-based therapy is required, whereas for patients that had initially benefited from MTX-based therapy, a re-challenge with the same or a similar MTX-based treatment may be most reasonable. Over the past 15 years, there has been a growing body of evidence of treatment options for progressive or recurrent PCNSL.^{23,24} This includes data about repeat treatment with MTX-based therapy as well as new drugs. In addition, fit patients who achieve a CR or good response to re-induction therapy may be candidates for high-dose therapy with autologous stem cell transplant. For patients not suitable for autologous transplant, consolidation with low-dose radiation is another option for consolidation that can be considered.²⁵

Repeat Therapy with HD-MTX-Based Therapy

Repeat treatment with HD-MTX can be highly effective in patients with that had previously achieved a CR with HD-MTX-based regimens. Data of 22 patients, 19 of which had been treated with HD-MTX monotherapy at initial diagnosis and that had achieved a CR was re-challenged with HD-MTX monotherapy ($\geq 3 \text{ g/m}^2$). The overall response rate in this study was 91% to first salvage therapy with CR in 16 (73%) patients, 2 patients with a PR and one with a mixed response. Data showed that even a second salvage therapy may be effective in these patients.²⁶ Similarly, another retrospective study from Memorial Sloan Kettering Cancer Center on 39 patients with relapsed PCNSL after initial response to HD-MTX-based therapy with median time from initial diagnosis of 26 months (range, 8.7–178 months) with an objective response rate of 85% and CR rate of 74% and a 10% PR. Thirty-seven of the patients had received methotrexate, procarbazine and vincristine (MPV)

as their initial therapy. Different regimens were used at MTX re-challenge, the majority of which were MPV and rituximab (44%) and MPV (23%), but also single-agent MTX (15%) and MTX, BCNU and etoposide (10%). Median progression free survival was 16 months, median overall survival 41 months and 1-year overall survival 79%.²⁷ As different combination therapies that are used for initial induction appear to be effective for this patient population, this also provides a rationale for the development for additional combinations of therapy with MTX in the recurrent setting. A recently published combination regimen of MTX and ibrutinib showed promising activity.²⁸

There currently are no data that determine a minimum duration of CR to determine when patients would be candidates for repeat treatment with HD-MTX versus another treatment approach. The National Comprehensive Cancer Network (NCCN) guidelines are currently using a cut off of 12 months as a divider (<12 months defined as short duration, ≥12 months defined as long duration of previous response) (NCCN.org). Given the lack of clear evidence regarding a specific minimum time interval from initial CR, clinical judgement is still required to guide selection of patients who may be best suited for a re-challenge with HD-MTX-based therapy.

Non-HD-MTX-Based Therapies

For patients that are not suitable for a re-challenge with HD-MTX, there are data on a number of single agent and combination regimens that encompass a broad variety of mechanisms of action. The different regimens are summarized in Table 1.

Temozolomide

Temozolomide (TMZ) has been studied in recurrent PCNSL alone or in combination with rituximab.^{29–33} In a prospective Phase II study with 36 patients with recurrent PCNSL after HD-MTX-containing therapy and/or radiotherapy, monotherapy with TMZ showed an objective response rate (ORR) of 31%, with 9 complete and 2 partial responses.²⁹ A second study with 17 patients within part heavily pretreated recurrent PCNSL showed an ORR of 47%.³⁰ Two small retrospective series illustrated activity of a combination therapy of temozolomide and rituximab.^{32,31} The larger series of 15 patients used high-dose rituximab 750 mg/m² weekly in combination with a week-on/week-off schedule of TMZ 100–200 mg/m² (rituximab for up to 2 cycles) showed an overall response rate of 53%.³² This prompted an evaluation of this regimen in a prospective trial with

planned 40 patients. The study was closed early, after enrollment of 16 patients, due to slow accrual and preliminary analysis suggesting futility. The overall RR was 36%.³³ Overall, these results show modest activity of TMZ in recurrent PCNSL and this treatment is typically reserved for patients that are not suitable for more aggressive treatment strategies.

Pemetrexed

Pemetrexed has been an interesting drug to study in recurrent PCNSL as it is an antifolate, similar to MTX. The key difference to MTX is that pemetrexed targets several sites in folate metabolism, involving both purine and pyrimidine metabolism. A prospective trial of pemetrexate monotherapy, at 900 mg/m² every 3 weeks in 11 patients with relapsed or refractory PCNSL showed an overall response rate of 55% (OR and PR) and disease control rate, when including SD, of 91%.³⁴ A similarly designed prospective trial from China, on 17 patients, using the same regimen, showed a similar ORR of 59%, similar to that reported in the former trial. Survival data and toxicity profile were comparable as well.³⁵ A retrospective study of pemetrexed as salvage for not only relapsed PCNSL (n=17 evaluable PCNSL) but also secondary CNSL (SCNSL; n=12) illustrated an OR rate of 64.7% (all CR) and 59.3% (with 2 CR), respectively, further illustrating efficacy of this drug in the setting of relapsed CNS lymphoma.³⁶ Treatment of pemetrexed has also been studied in combination with rituximab in a prospective trial with 27 patients, showed an ORR of 62.9% with 22% of patients reaching a CR.³⁷ Of note, activity of pemetrexed was also confirmed in 12 elderly patients (age >65) with PCNSL that were felt to be unsuitable for HD-MTX-based induction.³⁸ Patient numbers are small, but the findings of an ORR of 83.3% (4 CR, 6 PR) and mOS of 19.5 months were encouraging. The dose of pemetrexed in this trial was lower, at 600 mg/m² every 3 weeks. These data suggest that pemetrexed may be a reasonable option for select frail or elderly patients who are not suitable to receive HD-MTX-based therapy for treatment of their PCNSL.³⁸

High-Dose Cytarabine Alone or in Combination

High-dose cytarabine (Ara-C) has been used as single agent and in combination with other agents.^{39–42} In a retrospective analysis on long-term survival of patients with PCNSL, 15 of 31 patients had relapsed after initial CR. Three patients were

Table 1 Prospective and Retrospective Studies of Systemic Therapies in Refractory or Recurrent PCNSL

First Author, Year	Drugs	Regimen (per Cycle)	Study Type	Number of Patients	Median Age (y)	CR (n, %)	PR (n, %)	mPFS (Months) Unless Specified	mOS (Months) Unless Specified
Plotkin 2004 ²⁶	HD-MTX	HD-MTX ≥ 3 g/m ²	Retrospective	22	58	16 (73)	2 (9)	NR	91.9
Pentsova 2014 ²⁷	HD-MTX-based therapy	Several regimens used; most common HD-MTX, procarbazine and vincristine \pm rituximab in 36 patients	Retrospective	39	66	29 (74)	4 (10)	16	41
Grommes 2019 ²⁸	HD-MTX, ibrutinib	HD-MTX 3.5 g/m ² ibrutinib 560 or 840 mg daily	Prospective	15 (9 PCNSL, 6 SCNSL)	62	8 (53)	4 (27)	9.2	Not reached
Reni 2007 ²⁹	Temozolomide	TMZ 150 mg/m ² x 5 days every 28 days	Prospective	36	60	9 (25)	2 (6)	2.8	3.9
Makino 2012 ³⁰	Temozolomide	TMZ 150–200 mg/m ² x 5 days every 28 days	Retrospective	17	68	5 (29)	3 (18)	1.9	6.7
Wong 2004 ³¹	Temozolomide, rituximab	TMZ 150 mg/m ² x 5 days every 28 days x 8, rituximab 375 mg/m ² IV every 28 days	Retrospective	7	64	5 (71)	2 (29)	6	8
Enting 2004 ³²	Temozolomide, rituximab	750 mg/m ² on days 1, 8, 15, 22 (max 2 cycles) plus TMZ 100–200 mg/m ² days 1–7 and 15–21	Retrospective	15	69	6 (40)	2 (13)	7.7	14
Nayak 2013 ³³	TMZ, rituximab	750 mg/m ² on days 1, 8, 15, 22 (cycle 1) plus TMZ 100–200 mg/m ² days 1–7 and 15–21	Prospective	16 (14 evaluable for response)	63	2 (14)	3 (21)	7 weeks	Not reached
Raizer 2012 ³⁴	Pemetrexed	Pemetrexed 900 mg/m ² every 21 days, low-dose dexamethasone	Prospective	11	70	4 (36)	2 (18)	5.7	10.1
Sun 2017 ³⁵	Pemetrexed	Pemetrexed 900 mg/m ² every 21 days	Prospective	17	66	5 (29)	5 (29)	NR	7.8
Zhang 2013 ³⁶	Pemetrexed	Pemetrexed 900 mg/m ² every 21 days	Retrospective	18 (17 evaluable PCNSL)	67	11 (65)	0 (0)	5.8	Not reached
Zhao 2015 ³⁷	Pemetrexed, rituximab	Pemetrexed 900 mg/m ² every 21 days, rituximab 375 mg/m ² on day 0	Prospective	27	53	6 (22)	11 (41)	6.9	11.2
Han 2016 ³⁸	Pemetrexed	600 mg/m ² every 3 weeks	Retrospective	12	74	4 (33)	6 (50)	9	19.5
Abrey 1998 ³⁹	Ara-C	Not specified in manuscript	Retrospective	3*	45	2 (67)	1 (33)	NR	5, 10, 82**
Chamberlain 2016 ⁴⁰	High-dose Ara-C	3 g/m ² for 4 doses	Retrospective	14	60	0 (0)	5 (36)	3	12 m OS = 41%
Arellano-Rodrigo 2003 ⁴¹	Etoposide, ifosfamide, Ara-C (VIA)	etoposide 100 mg/m ² /d, days 1–3, ifosfamide 1000 mg/m ² /d, days 1–5, cytarabine 2000 mg/m ² /12h day 1	Retrospective	16	54	6 (38)	0 (0)	NR	12 m OS = 41%

Del Rio 2011 ⁴²	ESHAP or DHAP plus rituximab	ESHAP = cisplatin 25 mg/m ² , days 1–4, cytarabine 2 g/m ² , day 5, etoposide 40 mg/m ² , day 5; methylprednisolone; DHAP = dexamethasone, cisplatin 100 mg/m ² , day 1; cytarabine 2 g/m ² x2 day 2; rituximab 375 mg/m ² for both regimens	Retrospective	22	59	6 (27)	7 (32)	9	Not reached
Mappa 2012 ⁴³	Rituximab, ifosfamide, etoposide (R-IE)	Rituximab 375 mg/m ² day 0, ifosfamide 2 mg/m ² /day, days 1–3, etoposide 250 mg/m ² day 1; for CR, PR, SD consolidation with WBRT or HDC/ASCT	Retrospective	22	60	6 (27)	3 (14)	2-year PFS = 21 ± 12%	2-year survival 25 ± 9%
Choquet 2015 ⁴⁴	Ifosfamide, carboplatin, etoposide (ICE)	Ifosfamide 5 g/m ² , day 2; carboplatin (AUC 5), day 2; etoposide 100 mg/m ² /d, days 1–3; ± rituximab day 1; ± HDC/ASCT consolidation	Retrospective	58	64	NR (48)	NR (22)	4.4 (not reached in patients receiving HDC/ASCT)	7.8 (not reached in patients receiving HDC/ASCT)
Herrlinger 2000 ⁴⁵	Procarbazine, lomustine, vincristine (PCV)	Procarbazine 60 mg/m ² d. 8–21, lomustine 110 mg/m ² day 1, vincristine 2 mg days 8 and 29	Retrospective	7	57	4 (57)	2 (29)	1, 4, 4, 12+, 14+, 29+, 39***	5, 11, 14+, 16+, 33+, 39, 55**
Fischer 2006 ⁴⁶	Topotecan	Topotecan 1.5 mg/m ² d. 1–5 every 3 weeks	Prospective	27	51	5 (19)	4 (15)	2	8.4
Voloschin 2007 ⁴⁷	Topotecan	Topotecan 1.5 mg/m ² d. 1–5 every 3 weeks	Prospective	15	56	3 (20)	3 (20)	2	32.2
Chamberlain 2014 ⁴⁸	Bendamustine	100 mg/m ² /day x 2 days	Retrospective	12	59	3 (25)	3 (25)	3.5	5.5
Collignon 2019 ⁴⁹	(Rituximab), gemcitabine, oxaliplatin ([R]-GEMOX)	Rituximab 375 mg/m ² , gemcitabine 1000 mg/m ² , oxaliplatin 100 mg/m ²	Retrospective	13	71	2 (15)	3 (23)	3.2	8.2
Korfei 2016 ⁵⁰	Temsirolimus	Temsirolimus 25 mg, 75 mg IV weekly	Prospective	37	70	CR 5 (14), CRu 3 (8)	12 (32)	2.1	3.7
Batchelor 2011 ⁵²	Rituximab	Rituximab 375 mg/m ² IV weekly x 8	Prospective	12	64	3 (25)	1 (8)	57 days	20.9
Grommes 2017 ⁶³	Ibrutinib	560 mg, 700 mg, 840 mg by mouth daily	Prospective	13	69	5 (39)	5 (39)	4.6	15
Soussain 2019 ⁶⁴	Ibrutinib	560 mg by mouth daily	Prospective	52	69	10 (19)	17 (33)	4.8	19.2
Ghesquieres 2019 ⁷²	Lenalidomide and rituximab	INDUCTION: Lenalidomide 20–25 mg every 21 out of 28 days; rituximab 375mg/m ² on day 1 up to 8 cycles MAINTENANCE: Lenalidomide 10mg by mouth daily 21 of 28 days up to 12 months	Prospective	50	69	13 (29%)	3 (7)	7.8	17.7

(Continued)

Table 1 (Continued).

First Author, Year	Drugs	Regimen (per Cycle)	Study Type	Number of Patients	Median Age (y)	CR (n, %)	PR (n, %)	mPFS (Months) Unless Specified	mOS (Months) Unless Specified
Tun 2018 ⁷³	Pomalidomide and dexamethasone	Pomalidomide 3 mg, 5 mg, or 7 mg every 21 of 28 days; Dexamethasone 40 mg every week x 8 weeks; then pomalidomide alone	Prospective	25	NR	8 (32); 6 CR, 2 CRu	3 (16)	5.3	NR
Nayak 2013 ⁸⁸	Nivolumab	Nivolumab 3 mg/kg IV every 2 weeks	Retrospective	5	64	4 (80)	1 (20)	13+, 14, 14+, 17, 17+ ^{**}	NR
Ambady 2019 ⁸⁹	Pembrolizumab or nivolumab, rituximab	Pembrolizumab: Treatment every 3 weeks; nivolumab: treatment every 4 weeks	Retrospective	6 (pembrolizumab, 5 patients; nivolumab, 1 patient)	65	3 (50)	0 (0)	NR	NR

Notes: Studies are listed in the order they are discussed in the manuscript. All percentages are rounded to the nearest full digit. ^{*}This study included 15 patients, but only the 3 patients that received Ara-C monotherapy are listed in this table. ^{**}Data for individual patients in months.

Abbreviations: Ara-C, cytarabine; AUC, area under the curve; CR, complete response, unconfirmed; HDC/ASCT, high-dose chemotherapy and autologous stem cell transplant; HD-MTX, high-dose methotrexate; mOS, median overall survival; mPFS, median progression free survival; NR, not reported; ORR, overall response rate; PCNSL, primary central nervous system lymphoma; PR, partial response; SCNSL, secondary central nervous system lymphoma; TMZ, temozolomide.

treated with cytarabine alone, yielding a CR in 2 and a PR in 3 patients. Of an additional 4 patients that received cytarabine plus other chemotherapy (the regimens were not further specified in the manuscript), there was 1 patient with a CR, 1 with SD and 2 with PD.³⁹ A single agent retrospective study on 14 patients showed a modest response rate of only 35%, all PR, with no CR reported.⁴⁰ A retrospective study on 16 patients with refractory (n=1) or relapsed (n=15) PCNSL that were treated with Etoposide, ifosfamide and cytarabine (VIA) at relapse, showed a CR in 6 (37%) of the patients with durable responses of over 15 months in at least 2 of the patients.⁴¹ In a French study of 22 patients who had relapsed after initial HD-MTX-based therapy, patients were treated with ESHAP plus rituximab or the DHAP regimen with or without rituximab. In total, 13 patients (59%) were chemosensitive to this approach with a CR rate of 27%. As the two latter regimens were combination therapies, it is not possible to assess the impact of cytarabine versus the other regimens studied.⁴²

Ifosfamide

Ifosfamide-based regimens have been studied in r/r PCNSL. A patient cohort of 22 consecutive patients with r/r PCNSL were treated with rituximab, ifosfamide and etoposide (R-IE). Prior regimens of 12 of these patients included WBRT and high-dose chemotherapy and autologous transplant. The overall response rate was 41%, with mostly durable responses, however 4 of the responders also underwent consolidation with high-dose chemotherapy and autologous transplant.⁴³ A retrospective study of 58 patients with r/r PCNSL or vitreoretinal lymphoma, treated at 4 different institutions in France, reported an impressive response rate of 70% to treatment with ifosfamide, carboplatin and etoposide (ICE).⁴⁴

PCV

The combination regimen of procarbazine, lomustine and vincristine (PCV) has been studied in a small series of 7 patients with progressive or recurrent PCNSL.⁴⁵ The regimen was of interest as procarbazine and lomustine can cross the BBB and as this is an established regimen in the treatment of gliomas. The study was published in 2000, prior to the introduction of temozolomide, which then replaced PCV as the main treatment for high-grade astrocytomas. The data show that PCV has evidence of efficacy in recurrent PCNSL. Four patients achieved a CR, 2 a PR and 1 patient progressed. One patient who was only treated with lomustine 110 mg/m² alone for 9 cycles

achieved a PR but lived for 39 months after start of second-line therapy.

Topotecan

Two prospective studies assessed the efficacy of single-agent topotecan in recurrent PCNSL.^{46,47} The first study reported on 27 patients of which 9 had a response (ORR = 33%).⁴⁶ A second trial with 15 patients showed similar results, with an ORR of 40%.⁴⁷ Significant myelotoxicity was reported in both regimens, as expected with this drug.

Bendamustine

Modest single-agent activity was observed in a retrospective study of 12 patients with relapsed PCNSL with half of the patients responding and short mPFS of 3.5 and mOS of 5.5 months.⁴⁸

Gemcitabine and Oxaliplatin

A retrospective French study on 13 patients, including older and frailer patients, showed modest activity in r/r PCNSL with a combination regimen of rituximab, gemcitabine and oxaliplatin (R-GEMOX). The overall response rate was 38%, with a median PFS of 3.2 months.⁴⁹

Temsirolimus

A study of 37 patients with refractory or recurrent PCNSL showed activity of single-agent temsirolimus, at 75 mg, with an ORR of 54%.⁵⁰ Responses, however, were short lived and the mPFS was only 2.1 months.

Rituximab

The CD20 targeted monoclonal antibody rituximab has been studied as single agent and in combination in patients with PCNSL. The drug is of interest as most PCNSL are expressing CD20 and as rituximab has led to improved survival in virtually all systemic CD20 positive lymphomas, with overall minimal added toxicity. There has remained controversy regarding the efficacy and the role of rituximab in the treatment of PCNSL. The molecule is too large to cross an intact BBB and there is concern for lack of its ability to reach tumor cells after closure of the BBB in patients that are responding to treatment. However, a study of the ⁹⁰Y-labeled anti-CD20 antibody ibritumomab tiuxetan showed intratumoral uptake of the drug in 4 of 6 patients that underwent SPECT imaging, with increasing uptake of up to 5 days after administration.⁵¹ There were 4 responses reported with this drug, including one durable response of 30+ months after administration of only one dose of treatment. A small prospective study with single

agent rituximab 375 mg/m² in 12 patients with recurrent PCNSL showed an ORR of 36% (3 CR, 1 PR), illustrating single agent activity of rituximab in this disease.⁵² Several retrospective studies also report improved outcome from the addition of rituximab to the respective standard regimens in newly diagnosed PCNSL,^{53–57} while another study did not identify benefit from the addition of rituximab.⁵⁸ It is of note though that patients in the latter study only received a total of 4 doses of rituximab. The to-date only prospective study randomizing patient to standard therapy with or without rituximab did not find added benefit from rituximab.⁵⁹ This was an intergroup trial of 200 patients with newly diagnosed PCNSL, treated patients with either methotrexate, carmustine, teniposide and prednisone (BMVP) with or without rituximab. However, the number of cycles of rituximab given in this study was limited to 6, raising the question of whether the amount of rituximab given was sufficient to show a clear benefit between the treatment arms.

Ibrutinib

Both PCNSL and subsets of DLBCL with a predilection for the CNS are often reliant on chronic active B-cell receptor (BCR) signaling. Ibrutinib is an oral small-molecule that irreversibly inhibits Bruton's tyrosine kinase (BTK) and has selective activity in subsets of DLBCL with a molecular profile resembling PCNSL.^{60,61} Clinical studies in both PCNSL and SCNSL have demonstrated high response rates after ibrutinib monotherapy.^{28,62,63} In a Phase 1 study, ibrutinib monotherapy was given to patients with relapsed or refractory PCNSL and SCNSL.⁶³ In this study, 10 (77%) patients with PCNSL responded, including 5 (38%) who achieved a complete response. The durability of response was only 4.6 months. In SCNSL, 5 (71%) patients responded including 4 (57%) complete responses. Overall, the median PFS for SCNSL was 7.4 months, but two patients received ASCT consolidation. A multicenter Phase 2 study of ibrutinib monotherapy in 52 patients with relapsed PCNSL showed that 27 (52%) patients responded including 10 (19%) complete responses. However, the median PFS was only 3.3 months (95% CI, 2–6.4).⁶⁴ Ibrutinib has excellent clinical activity in both PCNSL, and SCNSL, but monotherapy is unlikely to be curative. In another phase 1 study, 18 patients with PCNSL were treated with escalating doses of ibrutinib monotherapy for 14 days as part of a window study design prior to combination of ibrutinib with temozolomide, etoposide, liposomal doxorubicin, dexamethasone, and rituximab (TEDDi-R).⁶² All the chemotherapy agents had demonstrated *in vitro* synergy with

ibrutinib in models of ABC DLBCL.⁶⁵ Of 16 patients evaluable for response, 14 (86%) achieved a complete response, including patients refractory to HD-MTX-based regimens. Notably, the 2-year durable CR rate was 66.7% (95% CI: 28.2–87.8).⁶⁶ A number of patients on this study developed serious aspergillosis infections when no antifungal prophylaxis was given, however. Since durable remissions were observed on this study, the regimen is undergoing further study with concomitant antifungal prophylaxis in both PCNSL and SCNSL. In a phase 1B study, ibrutinib has also been added to HD-MTX and rituximab in 15 patients with PCNSL and SCNSL.²⁸ In PCNSL, 8 (89%) patients responded, including 6 (67%) complete responses. In SCNSL, 4 (67%) patients responded and 2 (33%) achieved a complete response. The durability of response to the regimen is unknown since responding patients were allowed treatment with ASCT consolidation.

Immunomodulatory Agents

Another class of targeted agents for PCNSL and SCNSL are the oral immunomodulatory agents, lenalidomide and pomalidomide.⁶⁷ These agents use multiple mechanisms, including direct cytotoxic effects and effects on the tumor microenvironment. Lenalidomide binds cereblon and downregulates IRF4 through degradation of Ikaros transcription factors.⁶⁸ IRF4 is a direct target of NF-κB transcription factors induced by B-cell receptor (BCR) signaling and is overexpressed in most cases of PCNSL.⁶⁹ Lenalidomide has single-agent activity in both PCNSL^{70,71} and SCNSL.⁷⁰ In a phase 1 study of lenalidomide in PCNSL and SCNSL, 6 (86%) patients with PCNSL responded including 1 (14%) complete response. In SCNSL, 4 (57%) responses were observed, including 2 (29%) complete responses. Immunomodulatory agents have also been tested as combination therapy for relapsed or refractory PCNSL.^{72,73} In a multicenter phase 2 study, 50 patients with relapsed or refractory PCNSL received lenalidomide and rituximab followed by lenalidomide monotherapy.⁷² The overall response rate was 32.0% (95% CI, 21.9–51.2) including 13 (29%) complete responses. However, the median PFS was only 7.8 months (95% CI, 3.9–11.3). In a multicenter phase 1 study, pomalidomide was tested in combination with dexamethasone followed by pomalidomide monotherapy.⁷³ In 25 evaluable patients, the overall response rate was 48% (95% CI, 28–69) including 8 (32%) patients who achieved a complete response. The median PFS was 5.3 months (95% CI, 3.7–16.6). Immunomodulatory agents are

rational-targeted agents for CNS lymphomas, but will be most effective as combination therapy.

Hematopoietic Stem Cell Transplantation

High dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is a standard approach for younger fit patients with relapsed DLBCL that is sensitive to salvage chemotherapy. ASCT is associated with long-term disease control in about half of patients and the treatment-related mortality is low at 1–3%.^{74,75} Durable disease-free control is described with ASCT in patients with SCNSL, though its role in PCNSL is less well-defined.⁷⁶ In one of the earliest retrospective reports describing ASCT in 20 patients with relapsed or refractory PCNSL, the 3-year probability of event-free (EFS) and overall survival (OS) were 53% and 64%, respectively.⁷⁷ These promising findings led to a multicenter phase II study evaluating HDC with thiotepa, busulfan, and cyclophosphamide (TBC) with ASCT in 27 patients, including 15 who were chemosensitive (12 CR, 3 PR) to salvage high-dose cytarabine and etoposide and 12 who were chemorefractory.⁷⁸ Post-ASCT, 26 patients were in CR and one had progressive disease. At a median follow-up of 36 months, the median OS was not reached for the chemosensitive patients compared with 18.3 months for the chemorefractory group. A retrospective study from Memorial Sloan Kettering Cancer Center evaluating the same TBC conditioning regimen in 17 patients with CNS lymphoma (8 PCNSL, 9 SCNSL) had equally remarkable findings with estimated 3-year PFS and OS of 93%.⁷⁹ Notably all patients achieved CR with salvage therapy; chemorefractory patients were not transplanted. A more recent German Cooperative Group Study studied salvage induction with rituximab, high-dose cytarabine and thiotepa followed by conditioning with rituximab, carmustine, and thiotepa in 39 patients with relapsed PCNSL.⁸⁰ While the results were less encouraging with a 2-year PFS of 46% at a median follow-up of 45 months, only 4 patients were in CR pre-ASCT. Twenty-two (56%) achieved CR post-ASCT. These findings underscore the importance of chemosensitive disease. Thiotepa seems to be an essential component of conditioning regimens for PCNSL. Data from a Japanese Transplant Registry revealed that HDC containing thiotepa was a significant factor for PFS on multivariate analysis.⁸¹ Ongoing shortages of thiotepa may negatively impact outcomes.

HDC with ASCT is a reasonable approach for young, fit patients with chemosensitive disease and may be

associated with superior outcomes compared with other available salvage options. Indeed age may be less relevant than fitness, with a recent retrospective study demonstrating similar promising outcomes in elderly patients.⁸² Among 37 patients with a median age of 67 (range 65–77) who underwent ASCT in the second (or greater) line setting, the two year PFS and OS were 54% and 65.6%, respectively. The treatment-related mortality was low at 3.8%. With several efforts underway to determine if frontline consolidation with ASCT will become standard, the future relevance of ASCT in the relapsed setting remains to be seen. We anxiously await the results of the randomized multicenter trial comparing ASCT to an intensive polychemotherapy approach (CALGB 51,101; NCT01511562). Patients who relapse following upfront ASCT may be candidates for allogeneic transplant.⁸³ Small case reports demonstrating successful outcomes with allogeneic transplant suggest a graft versus lymphoma benefit despite the previously assumed immune privileged environment of the CNS.^{84,85}

Novel Immunotherapy Approaches

A gained understanding of CNS immune trafficking^{86,87} has opened avenues for immunotherapy in CNS lymphoma. PCNSL has a unique genetic landscape that is characterized by frequent PD-L1-L2 copy gains along with rare translocations involving the PD-1 ligand loci.¹⁶ A small series studying PD-1 blockade with nivolumab was encouraging with 100% overall response rate (3 CR) among 4 patients with relapsed/refractory PCNSL.⁸⁸ A patient series of 6 patients who received PD-1 inhibitor therapy in combination with rituximab showed an ORR of 50% (3 CR).⁸⁹ Results from multicenter trials with nivolumab and pembrolizumab will be forthcoming (NCT02857426, NCT03255018). Anti-CD19 CAR-T cells are proving effective in SCNSL.^{90,91} Administration of a fourth-generation dual CD19/CD70 CAR-T to a patient with relapsed PCNSL led to disease-free survival which has been maintained with more than 17 months follow-up.⁹² Given that increased neurotoxicity has not been described in this single patient with CNS disease, expansion of CAR-T to patients with PCNSL is likely to be studied further.

Discussion

There is an increasing number of treatment options for patients with refractory or recurrent PCNSL, many of which did not exist just 20 years ago. However, there is currently no uniform standard of care, and the relatively

large number of treatment options, which are all based on relatively small trials, makes the choice of treatment challenging. In addition, there are significant differences in institutional preferences.

There are, however, several unifying conclusions that we feel can be derived from the currently available data on systemic treatments in refractory or recurrent PCNSL:

- Patients should be considered for enrollment in clinical trials as there is a need for better treatment options for patients with recurrent PCNSL and as there is no clear standard of care.
- If no clinical trial is available, then patients who had a durable remission after initial induction with HD-MTX-based therapy, should be considered for a re-challenge with HD-MTX-based therapy. For patients suitable for consolidation with autologous stem cell transplant, this option should be considered based on high rates of durable responses that have been reported. Non-MTX-based combination regimens, including TEDDi-R, are also being studied in this patient population, but should not be given off trial until further safety data are available.
- In patients not suitable for HD-MTX-based therapy, other single agent or combination regimens with reasonable response rates (Table 1) should be considered. These include patients with severely reduced renal function and patients that have progressed on or shortly after HD-MTX-based treatment. Favorable response rates have been reported with ibrutinib, lenalidomide, pomalidomide, pemetrexed and TMZ. The duration of remissions to these agents, however, is often short. The role of rituximab has not yet been conclusively answered in this setting.

Clinical research in PCNSL is challenging. While response rates and survival in this disease compare favorably to other high-grade malignancies of the CNS, they compare unfavorably to outcomes in patients with many systemic high-grade B-cell lymphomas. PCNSL is a rare disease. Enrollment in prospective clinical trials is therefore strongly encouraged. However, many patients, especially the growing number of older and frail patients with PCNSL, may not be candidates for aggressive treatment regimens or autologous transplant. This also includes patients unsuitable for treatment with HD-MTX. There may be a window of opportunity to study non-MTX-based regimens and more indolent treatments in this patient group. As PCNSL is rare, there should also be an

emphasis on the collection of real-life data through institutional and collaborative databases to capture important outcome data related to the different treatment approaches for this disease. Only few centers have large enough PCNSL clinical volumes to conclusively evaluate efficacy of certain treatments as a single institution and collaboration between institutions should be encouraged.

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