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Role of targeted therapy in central nervous system lymphoma

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Abstract

Longer life expectancy, better diagnostic measures and advances in neuro-imaging account for the increasing numbers of diagnosed cases of primary central nervous system (CNS) lymphoma (PCNSL). Unfortunately, PCNSL is usually diagnosed late and that leads to poor performance status of patients, reducing their chances of accurate and timely therapy. This accounts for significant differences between real-life treatment outcomes and clinical trials. Although PCNSL had long been considered incurable, rapidly evolving therapeutic paradigms have shown significant progress with an absolute necessity for efficient diagnosis, staging and initiation of therapy conducted at experienced centers. High-dose methotrexate combined with rituximab and high-dose cytarabine in younger patients, or alkylating agents and rituximab in older patients, still remains the standard of care as induction therapy, while relapsed/refractory disease is a challenge necessitating the search for new, safe and effective therapeutic approaches.

Thanks to the discovery of the crucial molecular pathways leading to lymphomagenesis, it is now possible to target points of deregulation of specific pathways and stop the cancerous process. The very recent developments of efficient therapies, including high-dose methotrexate-based chemotherapy and targeted therapies comprising the monoclonal antibody rituximab and the immune checkpoint inhibitors lenalidomide and ibrutinib, have brought about improved outcomes.

Such novel agents bring hope for better results and seem to hold great promise for the treatment of patients with relapsed/refractory PCNSL. The key to future approaches is to target different molecular pathways in order to overcome mechanisms of resistance.

Key words: diffuse large B-cell lymphoma, primary central nervous system lymphoma, targeted therapy

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Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is a rare type of aggressive non-Hodgkin lymphoma (NHL). It comprises about 1% of all NHL cases and 4–5% of all primary brain tumors [1]. PCNSL is defined as a malignancy confined exclusively to the central nervous system (CNS), i.e. the brain parenchyma, spinal cord, eyes, cranial nerves and/or meninges [2]. The incidence rate of PCNSL is significantly higher in immunocompromised patients such as people with human immunodeficiency virus (HIV) infection or solid organ transplant recipients [3]. Longer life expectancy, better diagnostic measures, and advances in neuroimaging account for the increasing numbers of diagnosed cases of PCNSL [4]. The latest developments of efficient therapies including high-dose methotrexate-based chemotherapy (MTX) and targeted therapies comprising rituximab and the immune checkpoint inhibitors lenalidomide and ibrutinib, have brought about outcome improvement. Unfortunately, PCNSL is usually diagnosed

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late, leading to poor performance status of patients, preventing them from getting accurate and timely therapy. This accounts for the significant differences between real-life treatment outcomes and clinical trials [5–7].

The etiology of PCNSL is still poorly understood. It is mainly associated with immunosuppression (chronic use of immunosuppressive agents, HIV/AIDS patients, organ transplant recipients), but it can also be found in immunocompetent patients.

PCNSL is a rare type of lymphoma. It accounts for 1% of all non-Hodgkin lymphoma cases and 4–5% of all primary brain tumors. Each year, 1,500 patients in the USA are diagnosed, mostly people aged 40–60. It is rare in the pediatric population, but there has been a significant increase in the incidence ratio in elderly people in recent years [1, 4].

PCNSLs share some common features with systemic diffused large B-cell lymphomas (DLBCLs). However, there are a few key characteristics that distinguish them. Histologically, mature non-Hodgkin B-cell lymphomas constitute c.95% of PCNSLs and are almost identical with DLBCLs of other organs. The most common markers of PCNSLs are B-cell markers such as CD20, CD19, CD22 and CD79a. Other prevalent markers of PCNSLs are BCL6 (60–80%), a marker of germinal-center (GC) B cells, and IRF4/MUM1 (90%), a marker of late GCB cells and plasma cells, with approximately 10% being CD10+ [2, 6, 8–10].

Although this is a disease long considered incurable, rapidly evolving therapeutic paradigms have shown significant progress in PCNSL, with an absolute necessity for efficient diagnosis, staging, and initiation of therapy conducted at experienced centers. High-dose methotrexate (HD-MTX) combined with rituximab and high-dose cytarabine in younger patients as alkylating agent, and rituximab in older patients, remains the standard of care as induction therapy [11–13]. Relapsed/refractory disease still remains a challenge, necessitating the search for new, safe and effective therapeutic approaches.

This review aims to highlight recent advances in PCNSL treatment options, placing the emphasis on targeted therapy.

Novel agents as treatment options

Establishing the crucial molecular pathways leading to lymphomagenesis has been a milestone in the development of new agents that can target points of deregulation of specific pathways and stop the cancerous process.

One of the first agents used in targeted therapies was rituximab. Rituximab is a monoclonal antibody targeting the CD20 cell surface protein. This protein is present on PCNSL cell surface. The antibody connects with the CD20 marker, leading to immune system activation and destroying marked cells. It has been established that the CHOP regimen incorporating rituximab has significantly improved the outcomes of patients suffering from systemic DLBCL. In PCNSL, the challenge comes with the blood–brain barrier (BBB). Rituximab is a significantly large particle (145 kD) and it is not clear whether it can pass the BBB. There is a suggestion that the BBB is generally disrupted by neoplastic process. This theory is partially backed by neuroimaging that shows homogenous enhancement with gadolinium contrast agent where the cancerous infiltration occurs. A study has shown that when active leptomeningeal involvement was present, the CSF concentration of rituximab was 3–4% of the serum concentration. This finding may suggest that there is a slight possibility of penetration through the BBB [14, 15]. There is a promising way of enhancing the permeability of the BBB with tumor necrosis factor alpha coupled with NGR (NGR-hTNF). NGR-hTNF is a particle that targets CD131 vessels that leads to better penetration through the endothelium, and that in turn improves tumor access of cytostatics. This method has been used to boost the uptake of rituximab combined with CHOP regimen (R-CHOP) and proved to be effective [16].

Despite several meta-analyses of studies on regimens containing rituximab, it is unclear whether this agent actually improves overall survival (OS) in PCNSL patients. There are discrepancies between age groups. It has been suggested that younger patients (under 60) may benefit more from regimens containing rituximab, whereas in older patients a higher risk of neurotoxicity has been shown. Moreover, it has been pointed out that an induction regimen comprising MTX with or without cytarabine with alkylating agent and rituximab in patients under the age of 70, followed by consolidation in the form of WBRT, autologous stem-cell transplant (ASCT), or non-myeloablative chemotherapy, has been associated with high response rates, long-term disease control, and minimal neurotoxicity in a few single-arm, phase II trials.

Unfortunately, it is difficult to draw conclusions regarding the effect of each drug individually in these trials. Although the overall evidence of benefits resulting from adding rituximab to chemotherapy schemes is slight, the low toxicity of this kind of treatment has resulted in the widespread use of such regimens in PCNSL [3, 12, 14, 15, 17].

Nuclear factor-κB (NF-κB) is a major pathway generally active in PCNSLs. Its increased activity shows in NF-κB-regulating genes, genes of the NF-κB complex, NF-κB target genes and the nuclear location of the p50 protein in tumor cells. Amplification of the *MALT1* gene (37%) and activating mutations of the *CARD11* gene (16%) in a part of PCNSL leads to this overactivity of NF-κB.

In spite of nodal DLBCLs showing inactivating mutations of TNFAIP 3, in PCNSLs this inactivation is not significant in activating the NF-κB pathway. This pathway can be targeted with ibrutinib, a Bruton's tyrosine kinase

(BTK) inhibitor, that, thanks to its small size (MW 5,440), provides promising CNS distribution, thus representing a potential treatment for PCNSL. It stops cell growth and induces apoptosis in DLBCL driven by active, chronic BCR signaling. Ibrutinib, a first class oral BTK inhibitor, has been investigated as a single agent and in combination with chemotherapy in CNS lymphoma. A large, multicenter, phase II French study investigated ibrutinib at a dose of 560 mg in 52 patients with relapsed/refractory PCNSL. This reported an overall response rate (ORR) of 50% after two months of treatment; 25% of patients experienced disease progression at two months, and 62% discontinued treatment at a median follow-up of nine months [18]. Ibrutinib showed a good tolerability at 560 mg and 840 mg a day doses, and its activity in the brain clinically, biologically and radiologically in PCNSL in a phase I study conducted by the National Cancer Institute (NCI) with 18 patients treated with single-agent ibrutinib for two weeks before the addition of chemotherapy (dose-adjusted temozolomide, etoposide, doxorubicin, dexamethasone, intrathecal cytarabine and rituximab); PR was noted in 83% of patients treated with single agent ibrutinib, and CR was assessed in 86% of patients treated with combination chemotherapy. This study included patients with newly diagnosed and relapsed/refractory PCNSL, with median progression-free survival (PFS) in patients with relapsed/refractory disease of 15.3 months [19].

The next disruption occurring in DLBCL and PCNSL is mutation in the gene *MUM1* which is responsible for pathogenesis of B-cell lymphomas through upregulating the transcription of *MYC* and other genes. Immunomodulatory drugs such as lenalidomide and pomalidomide can downregulate this path. There is evidence that lenalidomide can be used with good outcomes in treating relapsed systemic DLBCL and mantle cell lymphoma (MCL). Its role in managing PCNSL is yet to be tested, but there are ongoing clinical trials [5, 6, 18, 20]. In 2018, a phase I study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma concluded that remission with this regimen is achievable, with good therapeutic activity [21].

A third-generation immunomodulatory drug, pomalidomide has shown promising efficacy in combination with dexamethasone in a phase I study at a dosage of 5 mg/day for 21 days of a 28-day cycle that was assessed to be the maximum tolerable dose; ORR was 40% and median PFS was 5.3 months [22]. Additionally, another clinical trial suggested that immunomodulatory therapy may be a good choice for people older than 60 and for those who do not qualify for WBRT as consolidation and maintenance process. Preliminary results of this study are promising. It is possible to achieve improved PFS and OS with low doses of MTX as induction treatment followed by low dose lenalidomide maintenance, and at the same time provide therapy that is well tolerated by older patients [23]. A phase II, multicenter, French LOC network study of rituximab and lenalidomide conducted in relapsed/refractory PCNSL and intraocular lymphoma demonstrated an ORR of 63% with a median PFS of 8.1 months; lenalidomide was administered at a dosage of 20–25 mg/d on days 1–21 of 28 in combination with rituximab per month as induction therapy for eight cycles followed by maintenance lenalidomide 10 mg/day [24]. Thanks to these findings, there is a need to further investigate the effect that immunomodulatory drugs have on PCNSL.

Another interesting target in treating PCNSL is PD-1. The cancerous process occurring in PCNSL leads to a high inflammation response mediated by T-cells and macrophages. Mutations in 9p24.1 *loci* are often seen in PCNSL. They lead to excessive expression of PD-1 ligands. This process can be stopped by targeting this path with the anti-PD-1 antibody nivolumab. Nivolumab has been used to treat other lymphomas (e.g. testicular lymphoma or Hodgkin lymphoma) with this genomic alteration with good effect, and thus there have been attempts to administer it in relapsed PCNSL. Data so far suggests that nivolumab is an excellent active agent in PCNSL and can lead to satisfactory responses [5, 22, 25].

Novel agents seem to hold promise for the treatment of patients with relapsed/refractory PCNSL. Most trials have comprised patients with refractory or relapsed disease, making it difficult to assess their prospects in treating newly diagnosed PCNSL. A major challenge remains the short durability of responses and mechanisms of resistance with worsening prognosis and limited therapeutic options. The key to future approaches is to target different molecular pathways to overcome these mechanisms of resistance.

Author's contributions

RK 50%, MD-D 50%.

Conflict of interest

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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