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Review

The possible role of maintenance treatment for primary central nervous system lymphoma

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is a rare and aggressive brain tumor. The prognosis is poor, with high rates of relapse and disease progression after treatment. In addition, PCNSL affects a largely older population, so that a significant proportion of patients are ineligible for intensive therapies and high-dose chemotherapy. The elderly patients are also susceptible to the accelerated and detrimental cognitive side effects of whole-brain irradiation which is an alternative consolidation to high-dose chemotherapy. Maintenance therapy has been shown to be a promising strategy to prolong remission time in other hematopoietic malignancies. Herein, we discuss the place of maintenance treatment in PCNSL in view of perspective obtained from hematological malignancies and non-Hodgkin's lymphoma.

1. Introduction

Primary central nervous system (CNS) lymphoma (PCNSL) is an extranodal, malignant non-Hodgkin lymphoma (NHL) confined to the brain, eyes, leptomeninges, or spinal cord, in the absence of systemic lymphoma. Pathologically, it is almost exclusively a diffuse large B-cell lymphoma (DLBCL). PCNSL is an aggressive life-threatening lymphoma, with a median survival time without treatment of 3 months [1]. Although PCNSL is rare, accounting for only 1% of all cases of lymphoma and up to 4% of primary brain tumors [2,3], its incidence in immunocompetent patients has been steadily rising over the last 30 years. Recent studies report a prominent increase in elderly adults, but not in younger individuals [4]. Indeed, up to 70% of immunocompetent patients with PCNSL are elderly. Those elderly patients cannot tolerate aggressive chemotherapy and are at high risk of acquiring severe treatment related-neurotoxicity [5]. A recent survey of data bases identified 25,792 patients with PCNSL. Analysis of these cases showed that even though the median overall survival of all patients doubled from 12.5 months in the 1970s to 26 in the 2010s, this survival benefit was limited to patients age < 70. Survival in the elderly population did not change in the last 40 years (6 months in the 1970s vs 7 in the 2010s, p-value = .1) [6]. The poor outcome seen in the vulnerable and particularly elderly patient population highlights the need for an alternative approach aiming to maintain treatment response without hampering quality of life.

The vast majority of PCNSLs (> 95%) express B-cell markers such as CD20, CD19, and CD79a as well as monotypic surface immunoglobulin light chains and correspond to non-germinal center B-cell-like (non-GCB) DLBCL (CD10-BCL6 + IRF4/MUM1 +). Mutations analysis of PCNSL identified mutations in key signaling pathways of nuclear factor-kappa B (NF-κB), most frequently affecting *CD79B* and *MYD88* [7], a pattern similar to systemic DLBCL, particularly the activated B-cell (ABC) subtype [8,9]. However, no specific molecular/genetic feature has as yet been proven to be clearly specific to PCNSL, suggesting that the microenvironment plays an important role in the peculiar behavior of PCNSL.

The treatment of PCNSL is challenging. Despite its high chemosensitivity and radiosensitivity and the high initial overall response rate (ORR; ~70–80%), remissions are frequently short-lasting. Even among patients who achieve complete remission (CR) with induction chemotherapy, about half relapse, and those who are older do so sooner [10–12]. To prolong survival and delay relapses, consolidation therapy is often recommended following the induction phase of treatment. The induction phase rests on high dose methotrexate (HD-MTX)-based polychemotherapy whereas consolidation, which originally included whole-brain radiotherapy (WBRT), is now often replaced by intensive chemotherapy or high-dose chemotherapy with autologous stem cell support [10]. Although the overall prognosis of PCNSL remains poor, it has

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significantly improved over the past two decades as a result of better treatment strategies with a curative aim. However, survivors are at high risk of acquiring severe treatment-related toxicity, mainly disabling neurotoxicity in elderly survivors. This poses a dilemma: Should therapy be intensified to improve the cure rate or downgraded to reduce side effects?

In the elderly who cannot tolerate consolidation therapy, maintenance treatment may serve as a feasible alternative approach after an initial response in PCNSL. The aim of this review is to discuss the rational and place of maintenance treatment in PCNSL in view of perspective obtained from maintenance treatment in hematological malignancies and NHL.

2. Definition of maintenance treatment

Maintenance treatment is defined as therapy that is designed to prolong the response achieved through induction and prevent relapse. It differs from consolidation which is given after induction in order to eliminate as much minimal residual disease as possible. It is probably most needed in incurable disease with a high relapse rate and short expected progression-free survival (PFS) but is also used in disease with long PFS such as follicular lymphoma or multiple myeloma. Maintenance treatment may include chemotherapy or other drug classes, vaccines, antibodies, or small-molecule targeted therapy. It may be given for an extended period of time by administration of regular daily doses or as pulse treatment given every several weeks or months [13].

3. Principles of maintenance treatment and how it might work

Two main approaches to maintenance therapy are used, with different biologic effects. Continuation-maintenance is based on the concept that extending therapy beyond a prescribed number of cycles improves outcome. A component of the first-line treatment is administered past its standard duration [13,14], with the purpose of reducing the dose-intensity of treatment or eliminating some agents from poly-drug therapy to continue treatment with the less toxic agent(s). Switch-maintenance approach is supported by the Norton-Simon hypothesis that sensitive cancer cells grow rapidly whereas resistance cells grow slowly [15]. Thus, after first-line therapy which kills sensitive cells, patients are immediately switched to a different agent administered in a separate phase to eliminate the slower-growing resistant cancer clones. It is sometimes referred to as “early second-line therapy” and may be continued until disease progression. Maintenance strategies are considered effective if they yield better outcome in terms of survival or quality of life (QoL) or both than the same therapeutic agent used for disease progression [16]. Close observation with initiation of second-line therapy at the earliest sign of progression may be an alternative approach in selected patients.

Maintenance therapy may also be used as metronomic chemotherapy. Metronomic chemotherapy, a term coined by Hanahan et al. [17], is the administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks [18]. The concept is based on pioneer work done by Browder et al. [19] and Klement et al. [20] showing that mice bearing subcutaneous tumors responded to frequent repeated low doses of chemotherapy, even when they displayed acquired drug resistance when the same agents were given in a conventional way. These findings suggested that metronomic chemotherapy could serve as an alternative to standard maximal tolerated dose therapy. But, if aggressive induction and consolidation chemotherapy at the maximal tolerated dose failed to eliminate the disease, how would milder treatment do so? It has been demonstrated that metronomic chemotherapy has multitarget properties. One target is the endothelial cells of tumor vasculature that produce an anti-angiogenic effect and other mechanisms that affect tumor microenvironment have been identified as well [21]. Metronomic therapy promotes anti-tumor immunity by depleting T-reg cells and activating natural killer cells, T-cells, and dendritic cells while inhibiting tumor-initiating cells which are intrinsically resistant to anticancer drugs [21–23]. These composite mechanisms of action may eventually lead to re-induction of tumor dormancy. Thus, in face of the growing appreciation of the pathogenic roles played by tumor angiogenesis and the microenvironment in various hematological malignancies [24,25], metronomic chemotherapy may be a novel promising means to target these factors [26], and it may be best utilized in the maintenance setting when the disease burden is low. The PEP-C metronomic regimen (low doses of prednisone, etoposide, procarbazine, and cyclophosphamide) is one example that has been found effective in the treatment of patients with refractory relapsed lymphoma [27]. The availability of various immune-modulatory drugs (such as lenalidomide) and microenvironment-targeted therapies opens new horizons for metronomic therapy but clinical trials are needed to select the best regimen for each disease and to prove efficacy. It should be noted that trials which include a maintenance phase regimen have an intrinsic bias in them due to selection of best responding patients. By definition, only patients that responded to earlier treatment can proceed to the maintenance phase. Therefore, there is an intrinsic survival issue that can only be solved by performing phase III trials comparing directly patients with and without maintenance treatment.

4. Considerations in drug selection for maintenance treatment

Because maintenance therapy is non-curative, its impact on QoL is of utmost importance. The ideal maintenance treatment should be effective in prolonging PFS and also OS, and be convenient, easy to administer, nontoxic, and cost-effective. Therefore, when selecting an agent for maintenance therapy, many patient-specific and disease-related factors need to be considered. Patient-related factors include age, pharmacogenetics, pharmacokinetics, performance status, concomitant comorbidities and organ dysfunctions, previous treatments and their toxicities, route and frequency of administration, and short- and long-term toxicities. Disease-related factors include chemosensitivity or chemoresistance to prior therapies, disease burden after consolidation, multi-clonal disease, driver mutations, genetic subtype, active escape pathways, receptor surface expression or binding with targeted agent, and tumor microenvironment. The risks must be weighed against the benefits for each individual patient. Tolerance of chronic treatment and patient compliance are major concerns. To date, no clinical trial has demonstrated a significant improvement in QoL with maintenance treatment compared to observation. It should be noted that chronic drug exposure as used in maintenance treatment can enhance or induce drug resistance [28] and may enhance clonal evolution of the cancer [29].

5. Maintenance treatment in hematological malignancies

Maintenance therapy has been classically used for hematological malignancies such as acute lymphoblastic leukemia [30,31] and low-grade NHL (Table 1) [32,33]. Various guidelines, such as the National Comprehensive Clinical Network (NCCN), recommend its use. However, the FDA has so far approved only 4 drugs, 3 of them CD-20 targeted agents (Table 1), for maintenance therapy for specific indications: rituximab, for patients with previously untreated follicular CD-20-positive NHL who achieved a response to rituximab in combination with chemotherapy [34]; ofatumumab (Arzerra), the monoclonal antibody, for patients with recurrent or progressive chronic lymphocytic leukemia (CLL) who have been in CR or partial response (PR) after two or more lines of prior therapy for up to 2 years [35]; and obinutuzumab (Gazyva) was recently approved for patients with follicular lymphoma after obinutuzumab-bendamustine treatment who relapsed on or were found refractory to a rituximab-containing regimen [36].

Rituximab maintenance is also recommended for mantle cell

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