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Review

Primary central nervous system lymphoma: Current state of anti-CD20 therapy and appraisal of reported response criteria

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is an aggressive non-Hodgkin's lymphoma which is confined to the central nervous system and may also affect intraocular structures. Despite high initial rates of response to methotrexate-based chemotherapy, more than 50% of patients will experience relapse and about 10% have disease that is refractory to chemotherapy. Outcome in patients who fail treatment is very poor, and therefore new therapeutic approaches that may increase the rate of complete response and the proportion of durable remission are sought. Based on the pivotal role that anti-CD20 therapy now plays in the treatment outcome of aggressive systemic B-cell lymphomas, a similar approach is commonly being adapted for PCNSL despite the lack of evidence for its effectiveness. This review examines the current status and level of evidence for the use of monoclonal antibodies against the CD20 surface antigen, which is present on normal and malignant B-cells in PCNSL. The review covers both systemic and local (intracerebrospinal fluid or intravitreal) administration of CD20 monoclonal antibodies in PCNSL. In addition, it scrutinizes the response criteria commonly reported for evaluation of treatment outcome. The importance of differentiating unconfirmed complete response from partial response is outlined and the lack of consensus on response criteria for atypical imaging presentations of PCNSL is delineated.

1. Introduction

The vast majority of primary central nervous system lymphomas (PCNSL) are diffuse large B-cell lymphomas (DLBCL), with T-cell lymphomas comprising only about 4–5% of all cases [1]. Upfront high-dose methotrexate (MTX)-based chemotherapy, followed or not by whole brain radiotherapy, is associated with a high overall response rate in immunocompetent patients [2]. However, about 50% of responsive patients experience relapses, and an additional 10–15% are refractory to chemotherapy. The outcome in failed patients is remarkably poor, with a median survival ranging between 2–6 months; therefore, novel therapeutic approaches that may maximize both the proportion of initial complete response and the rate of durable disease control are being explored [2]. Some of these novel therapeutic strategies add anti-CD20 therapy to MTX-based chemotherapy or combine initial high-dose chemotherapy with subsequent autologous stem cell transplantation. This review examines the current status of anti-CD20 therapy in PCNSL as well as the commonly used criteria for evaluation of response that should determine whether a complete response has been achieved.

2. Methods

A comprehensive literature search was performed to identify relevant studies published from January 2000 to December 2013, using Medline and Google Scholar. Search terms included: CNS lymphoma, primary CNS lymphoma, malignant lymphoma, diffuse large B-cell lymphoma, CNS aggressive lymphoma, leptomeningeal lymphoma, CD20 monoclonal antibodies, immunotherapy, cerebrospinal fluid, intra-ocular lymphoma, vitreous, rituximab, response criteria, imaging, MRI, PET, contrast enhancement, and International primary CNS lymphoma collaborative group. The evidence classification of the reviewed publications was categorized according to the recommendation and guidelines of the European Federation of Neurological Societies scientific task force [3]. This classification includes four classes. Class I: prospective randomized, well controlled clinical trials; class II: prospective studies (observational, matched-group cohort and case-control studies); class III: retrospective studies; and class IV: uncontrolled case series, case reports and expert opinions.

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3. Anti-CD20 therapy for PCNSL

DLBCL, the most common type of PCNSL, express B-cell antigens such as CD79a, CD19, and CD20, as well as monotypic surface immunoglobulin light chains [1]. CD20 was the first B-cell specific antigen to be defined by monoclonal antibody (mAb) research [4]. The CD20 molecule is a 297 amino acid phosphoprotein with four transmembrane domains, and it plays a critical role in B-cell development. It is found on normal and malignant B-cells, but not on progenitor B-cells, plasma cells, hematopoietic stem cells, or other normal tissues. CD20 is known to function through binding to Src family tyrosine kinases and consequently it is involved in the phosphorylation cascade of intracellular proteins. CD20 is an optimal surface antigen target since the tetratransmembrane protein essentially remains on the membrane of B-cells without dissociation or internalization upon antibody binding. In addition, it is not shed and not found unbound in the circulation.

Rituximab is a first generation chimeric murine mAb against the CD20 antigen. Its mechanisms of action include complement-mediated cytotoxicity, antibody-mediated phagocytosis, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent growth inhibition and apoptosis [4]. The use of rituximab has led to significant improvements in treatment outcomes for both aggressive and indolent systemic non-Hodgkin's lymphomas (class I level of evidence) [5], and regimens that combine rituximab with chemotherapy are now considered standard therapy for systemic aggressive B-cell malignancies.

3.1. Systemic administration of rituximab in PCNSL

Standard therapy for PCNSL consists of MTX-based polychemotherapy, a treatment that is associated with a high initial response rate [2,6–10]. The use of rituximab in PCNSL is advocated because of its positive effect in systemic DLBCL, leading to the hope that it will improve the rate of sustained response in PCNSL. Moreover, rituximab might contribute to better control of subclinical manifestations of systemic lymphoma, which can be detected in PCNSL [11,12]. However, the antibody rituximab is an immunoglobulin (Ig) G_1 kappa containing 1328 amino acids, with an approximate molecular weight of 144 kD. As a large protein, its penetration into the central nervous system (CNS) is poor, with 0.1% of systemic concentration reaching the leptomeningeal compartment [13]. It should be noted that these measurements provide only an indirect measure of parenchymal concentration. Based on its poor penetration into the CNS, the maximal concentration and efficacy of rituximab in the CNS might be assumed to occur in the early treatment phase, during blood–brain barrier (BBB) breakdown within the tumors (Fig. 1A), as has been suggested by a study using an animal model of CNS lymphoma [14]. In a clinical study, cerebrospinal fluid (CSF) levels of rituximab were assessed after its systemic administration in four patients with active leptomeningeal disease. CSF levels ranged between 3–4% of the corresponding serum levels, pointing to the critical effect of BBB breakdown on CNS drug penetration [9].

Despite the fact that rituximab is frequently added to the initial treatment regimen of PCNSL, the level of evidence supporting its use is still very low. The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly intravenous dose of 375 mg/m^2 rituximab infusion for up to eight doses (class IV) [15]. An MRI response was observed in 36% of patients, suggesting that the antibody may be effective even if the BBB is not readily permeable. An animal model supported this clinical observation by demonstrating extended animal survival with rituximab single agent therapy [16]. It has been postulated that there is a slow leak of the long half-life mAb into the main tumor mass, with mAb trapped by binding to CD20 antigen on tumor cells, thus attaining sufficient concentration for antitumor activity.

Other studies used intravenous rituximab in combination with a high-dose MTX-based chemotherapy regimen as initial treatment for newly diagnosed PCNSL, [6,9,17–20] or as salvage treatment for recurrent parenchymal CNS lymphomas [21–25]. The level of evidence in these studies is low, with two reports categorized as class III [17,19] and all others as class IV [6,9,18,20–25]. Two studies suggested that the addition of rituximab to high-dose MTX-based chemotherapy improves the rate of complete response and overall survival [17,19] in patients with newly diagnosed PCNSL based on retrospective analysis of historical controls (class III). Overall, the addition of rituximab to systemic polychemotherapy was well tolerated except for a higher rate of neutropenia observed in one study [9].

Targeting CD20 tumor cells for selective radioimmunotherapy is another approach that has a proven efficacy in systemic non-Hodgkin's lymphomas, even in patients previously treated with rituximab (class I) [26,27]. The radioactive source in this class of drugs is conjugated to the mAb that binds to CD20 antigen. The addition of radiation to the CD20 specific mAb most likely contributes to added efficacy against B-cell lymphomas. The assumption is that low-dose rate radiation emitted from the conjugated mAb radioactive source may induce less CNS toxicity compared with the high-dose radiation of conventional external-beam cranial irradiation. This approach was shown to be feasible in pilot studies treating patients with relapsed or refractory CNS lymphomas using intravenous radiolabeled indium-111 and yttrium-90 monoclonal antibodies (class IV) [28–30]. Myelosuppression is a major toxicity issue because the radioactive mAb also accumulates in bone marrow; thus, patients with low bone marrow reserves are at risk of neutropenia, thrombocytopenia, or both [31]. Although capable of targeting brain lymphoma when the BBB is disrupted, these radioimmunoconjugates cannot adequately treat microscopic lesions located behind an intact BBB, suggesting that high relapse rates can be expected [30].

3.2. Local administration of rituximab

Circumvention of physiological blood-barriers, namely the BBB and the blood–vitreous barrier, is an approach that uses direct introduction of drugs into the CSF or vitreous compartments. The aim is to augment extracellular drug concentration and to achieve high local or interstitial drug levels with low systemic exposure.

Injection of rituximab into the CSF via either lumbar puncture or intraventricular administration was evaluated in two phase I studies that determined the median tolerated dose (25 mg/injection), cytologic responses, and pharmacokinetic parameters in both the CSF and serum of refractory or recurrent CNS lymphoma patients [32,33]. In these studies, objective responses were documented with conversion of positive CSF cytology to negative, and regression of parenchymal and leptomeningeal lesions documented on MRI studies in some patients (class IV). Other reports of intra-CSF rituximab describe experience with single patients or small case series of PCNSL patients (class IV) [34–36]. A few additional studies have demonstrated a sustained response in Epstein-Barr virus-associated post-transplant lymphoproliferative disease that was confined to the CNS (class IV) [37,38].

In general, intra-CSF rituximab therapy was well tolerated, with the most common adverse events being grade I self-limited paresthesias, chills, and rigors. Of note is the observation that serum rituximab concentrations after intraventricular injection exhibited a slow and steady increase over the course of treatment, indicating a slow transfer from CSF to serum [33]. This may induce immune