Primary Central Nervous System Lymphoma

Subjects: Oncology

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Primary central nervous system lymphoma (PCNSL) is a highly aggressive non-Hodgkin lymphoma confined to the central nervous system (CNS) and mainly affects elderly patients.

Keywords: primary CNS lymphoma ; elderly ; chemotherapy ; immunotherapy

1. Introduction

Studies carried out with different nationwide population cohorts have revealed an increased incidence among elderly patients over time, both overall and in the immunocompetent subgroup [1][2][3][4][5]. Large population studies in the United States have shown an increase in the PCNSL rate of 1.7% per year in people older than 65 years (with stable rates in other age groups) during the period 1992–2011 [1] and an increase in the incidence, from 0.2 in 1973 to 2.1 per 100,000 in 2013, in people older than 70 years [3]. In addition, a population-based study in Sweden revealed an increased incidence, from 0.43 to 1.66 per 100,000 habitants among patients aged 70 and older between 2000–2002 and 2012–2013 [2]. A nationwide population-based study reported an overall increase among PCNSL patients diagnosed in the Netherlands between 1989 and 2015 as a result of the increasing incidence in the group older than 60 years, exhibiting a twofold increase in PCNSL incidence during this period [4]. This increase remains largely unexplained even though it may be partially due to the global aging of the population, longer life expectancy and advances in diagnostic techniques and approaches.

PCNSL overall survival (OS) has steadily improved for the youngest patients. In contrast, despite advances in the management of the older population, the prognosis of elderly patients remains poor [2][3][4][6]. An American nationwide report showed that PCNSL survival has not improved for patients older than 70 years since the 1970s, remaining at approximately 6–7 months, even though the median OS of all patients doubled in the same period [3]. However, the results from nationwide reports include patients treated only with palliative care, a common situation for elderly individuals, which is not always reported. A Dutch nationwide population-based study revealed that, while the use of chemotherapy has progressively increased in elderly patients up to age 70 years, with a consequent improvement in OS, approximately 40% of patients older than 70 years did not receive antineoplastic therapy, exhibiting poor prognosis [4]. A systematic review and meta-analysis by Kasenda et al. of 783 elderly patients diagnosed with and treated for PCNSL from 1977 to 2014 revealed a progressive OS improvement over time [6].

Regarding 1st line treatment, elderly patients are more often untreated or less vigorously treated than younger patients [4][7][8][9][10]. Altogether, physiological status related to age, higher rate of comorbidities and differences in therapeutic management may contribute to the poorer prognosis in elderly patients with PCNSL and warrant to be better investigated and taken into account, in order to optimize management strategies and tolerance and improve outcomes.

2. Clinical Aspects

Functional status at the time of diagnosis, an independent prognostic factor in PCNSL [11][12][13], is usually lower in elderly patients than it is in younger patients [7][9]. Clinical manifestations in elderly patients are similar to those in younger patients, including focal neurological deficits, neurocognitive and/or behavior changes, symptoms of increased intracranial pressure and, less frequently, epilepsy. However, elderly patients display a higher proportion of cognitive impairments at diagnosis than those in other age groups [7][9][14]. Unpublished data from the French LOC network study show a higher proportion of cognitive impairments at the time of diagnosis in patients older than 60 years (65% versus 48%, $p < 0.001$). In elderly patients, cognitive symptoms could be inaccurately attributed or associated with other prevalent pathologies in this age group (such as vascular or degenerative diseases), increasing the delay in diagnosis [14] and affecting the prognosis [9][15][16]. In addition, neurocognitive dysfunction at diagnosis was recently reported as an independent prognostic factor [17][18].

Older age is also associated with a higher frequency of comorbidities, which may increase the risk of therapy-induced toxicity that alters the pharmacokinetics and pharmacodynamics of therapy and may increase the risk of toxicities. However, as discussed below, elderly patients with PCNSL can achieve a response even to more intense treatments, so they should not be excluded from these therapies only on the basis of age criteria, but rather on the basis of a global assessment for fitness. Nevertheless, this approach is still very scarce. In a pilot study, Schorb et al. have utilized the Cumulative Illness Rating Scale–Geriatric score as an inclusion criterion in addition to age [19]. Such approaches should be developed.

3. Diagnosis

The PCNSL diagnostic approach in the elderly population is similar to that of other age groups. Histopathological confirmation by cerebral stereotactic biopsy or positive cytology in the CSF or vitreous biopsy sample is required to establish the diagnosis before starting treatment and should be obtained without delay [20][21]. Because steroids may induce rapid tumor shrinkage [22][23][24][25][26][27], their use before brain biopsy should be delayed as much as possible as it may prevent pathological confirmation [20][21].

Stereotactic biopsy is considered a safe high-yield diagnostic procedure in PCNSL [28], even in elderly patients and in cases of deep lesions that are quite common [29][30][31]. However, elderly patients present more frequently with deteriorated functional status and/or the presence of multiple comorbidities, preventing the use of biopsy to obtain samples. In these situations, a noninvasive diagnostic tool with high sensitivity and specificity would be useful.

In the past decade, several biomarkers measured in the CSF and the vitreous (in the case of vitreoretinal involvement) were investigated as potentially useful for the diagnosis of PCNSL, such as IL-10, IL-6, CXCL13, miRNA 19-21-92a , neopterin, CD19, and MYD88 hotspot mutations [32][33][34][35][36][37][38][39][40][41][42][43][44][45]. Although biopsy remains the gold standard for diagnosis, the increase in the CSF IL-10 level and CSF IL-10/IL-6 ratio, with sensitivities ranging from 60 to 97% and specificities ranging from 90 to 100% [38][39][40][41][42], are helpful tools for diagnostic guidance, especially in atypical radiological presentations and when performing a biopsy is not feasible. Preliminary results also suggest their potential predictive role in posttreatment evaluation for monitoring treatment responses [40]. A combined analysis of MYD88 mutation and IL-10 level in the CSF was reported with a sensitivity and specificity of 94% and 98%, respectively, in newly diagnosed PCNSL [45].

4. Treatment

A retrospective study devoted to elderly patients failed to show a clear benefit of extending cytarabine consolidation treatment after methotrexate-based chemotherapy (R-MPV regimen consolidated with three cycles of high-dose cytarabine instead of one) but was associated with increased toxicity in elderly patients [46].

Recent advances in DLBCL have been used to evaluate the activity of innovative agents in PCNSL, mainly in refractory/relapsing (R/R) tumors, with notably targeted therapies and immunotherapy, such as imids [47][48][49][50][51][52], ibrutinib [53][54][55][56] and anti-PD-1 [57][58][59]. As these novel agents demonstrate promising efficacy in term of objective response rate and good safety profiles in clinical trials or retrospective studies without limitation of age they are excellent candidates to be incorporated in 1st line induction and/or maintenance treatment in the near future and could benefit elderly patients.

These reports show that HD-MTX is also a feasible and active treatment in the oldest patients but requires adapted doses according to urinary clearance and comorbidities. For patients unfit for HD-MTX treatment, due to impaired renal function or other comorbidities, temozolomide chemotherapy may be a treatment option. In a series of 17 elderly patients (6 in the oldest group) treated with temozolomide monotherapy as 1st line therapy, 29.4% had prolonged responses for at least 12 months and survived for more than 24 months with good tolerance [60].

WBRT alone can also be considered as a therapeutic option in the first-line for unfit patients and induces a high response rate. However, responses are most often of short duration [61] and given the high risk of neurotoxicity in elderly patients, we rather recommend chemotherapy options in this setting.

References

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