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Review

Primary central nervous system lymphoma

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ABSTRACT

Primary CNS lymphomas (PCNSL) represent a subgroup of malignancies with specific characteristics, aggressive course, and unsatisfactory outcome in contrast with other lymphomas comparable for tumour burden and/or histological type. Despite a high chemo- and radiosensitivity, remissions are frequently shortlasting, mainly because the blood brain-barrier limits the access of many drugs to the CNS. Moreover, survivor patients are at high risk of developing severe treatment-related toxicity, mainly disabling neurotoxicity, raising the question of how to balance therapy intensification with side-effects control. Although the prognosis remains poor, it has significantly improved

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Cerebrospinal fluid
Methotrexate
Cytarabine
Thiotepa
Rituximab

over the past two decades as a result of better treatment strategies with a curative aim. Surgery has no impact on survival, and is reserved to diagnosis by stereotactic biopsy. Actual front-line therapy consists of high-dose methotrexate-based poly-chemotherapy. The optimal drugs combination has not yet been identified even if there is a suggestion for a synergistic role for the adjunction of cytarabine, thiotepa, and rituximab. Radiotherapy retains an important role as salvage therapy in refractory/relapsing patients, while its use is more debated in the setting of response consolidation in patients who achieve a complete remission after induction chemotherapy. High-dose chemotherapy supported by autologous stem-cell transplantation is increasingly used as an effective method aimed to control microscopic disease, and the pros and contras of this approach are outlined.

1. General information

Primary CNS lymphomas (PCNSL) are extranodal malignant lymphomas arising inside the central nervous system (including eyes) in the absence of systemic diffusion at the time of diagnosis. Currently, PCNSL are estimated to account for up to 1% of non-Hodgkin lymphomas (NHL) and about 3% of all primary brain tumours (Villano et al., 2011).

1.1. Epidemiology

1.1.1. Incidence

Very few population studies have been published about PCNSL. In general, incidence of lymphoma is given for all forms, without distinguishing between nodal and visceral ones. While lymphoma is a common tumour, PCNSL is a very uncommon cancer. Incidence data belong to the SEER database, Danish and Canadian registries (Olson et al., 2002; Krogh-Jensen et al., 1995; Hao et al., 1999). The first studies covered a similar period from 1973 to 1997. SEER data reported a rate of 1.6 per million a year and a statistical significant increase of incidence during the study period. Actually, SEER data estimated an annual percent change for PCNSL of three-fold higher during the period 1973–1985 compared with the period 1986–1997. In the Alberta Canadian province there was a non-significant increase of rates from 0.178 to 1.631 per million. Rates from the Danish registry showed no increasing trend for the non-AIDS related PCNSL. A more recent study based on the SEER data (period of diagnosis 1980–2008) showed a decline of incidence after the peak of 1995. However, a continuous increment for the oldest patients (>75 years) was reported (Villano et al., 2011).

1.1.2. Survival

Survival is poor for patients with primary CNS lymphoma. The Danish study (Krogh-Jensen et al., 1995) provided population-based survival figures. Overall survival was 53%, 38%, and 26% at 1, 2 and 5 years after diagnosis, respectively, for cases diagnosed during the period 1971–1990. For US patients diagnosed between 2000 and 2008, the corresponding survival estimates were 51.4%, 42.6%, and 31.2%. Survival was lower in the elderly and in blacks compared to white in the youngest group of patients (0–49 years) (Villano et al., 2011). A trend toward a survival's increase in more recent years was noted by Shiels et al. in immunocompetent US population (Shiels et al., 2016), while Zeremsky et al. pointed out that survival's advantage is more evident in patients enrolled in clinical trials than in "real life" patients (Zeremski et al., 2016).

1.2. Risk factors

PCNSL seems to occur with increasing frequency in immunologically impaired individuals and in the acquired immunodeficiency syndrome (AIDS). Risk factors are high in recipients of transplants receiving immunosuppressive therapy and in patients with congenital immunodeficiency disorders (Wiskott-Aldrich syndrome, X linked immunodeficiency, ataxia teleangectasia) (Krogh-Jensen et al., 1995). Several reports have been published on PCNSL as a secondary malignancy (DeAngelis,, 1991) due to the immunosuppressive therapy or an inherent immune impairment. O'Neill et al. (1995a) reported a 30-fold increase risk to develop a PCNSL in families with a history of malignancies.

PCNSL was one of the most common AIDS-defining malignancies. In the US, during 1981 and 1990, the HIV infection carried more than 3000-fold increased risk of developing the disease compared with the general population (Coté et al., 1996). The rise of incidence rates occurred since the beginning of the 1980s was an epiphenomenon of the AIDS epidemic and the increasing number of recipient of transplants (Krogh-Jensen et al., 1995). However, the influences of the widespread use of X-ray computer-assisted tomography (CT) scanning may have contribute to the rise of incidence for PCNSL in immunologically normal individuals. Therefore, it is not known to what extent radiodiagnostic tools may influence the incidence rise in immunological normal population.

Epstein-Barr virus and c-myc proto-oncogene translocation induce the proliferation of PCNSL in HIV patients by a known mechanism, while PCNSL in apparently immune-competent patients, who constitute the majority of cases, arises in an unknown way.

PCNSL are mostly present in individuals who are over 60 years, which is probably related to a reduction in immunological surveillance, particularly of T-lymphocytes. The proliferation of B-lymphocytes produced by chromosomal abnormalities or by viral stimulation might develop a monoclonal disease due to the lack of suppressive T-cells activity. This proliferation is particularly facilitated in the extranodal areas, which have unique immunological characteristics, such as the central nervous system.

2. Pathology and biology

It is well documented that lymphocytic migration inside the nervous tissue depends on a selective interaction of the lymphocytic molecules of adhesion with the vascular endothelium of the CNS (Constantin, 2008; Venetz et al., 2010). These interactions would at least partially explain the relationship of the neoplastic lymphocytes with the vessels and their successive localization in the perivascular spaces determining the characteristic vasocentric proliferation of the PCNSL. Additionally, the neoplastic cells tend to remain within the CNS with consequent extremely low incidence of systemic spread. Several diseases are associated with immunological impairment that has been widely described as a predisposing factor to lymphoproliferative malignancies. It is possible that either the disease itself or its treatment could induce the immunological suppression responsible for the occurrence of second malignancies (DeAngelis, 1991). PCNSL represent a histologically and immunohistochemically very homogeneous lymphoma type. Typical histological features include centroblastic cytology and perivascular tropism (Deckert and Paulus, 2007; Kluin et al., 2008).