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Supplement Article

XVI. CNS prophylaxis in aggressive lymphomas: for whom and how

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Introduction

Dissemination in the central nervous system (CNS) in patients with aggressive lymphoma is a relatively rare but a frequently deadly complication that occurs between 5 (diffuse large B-cell lymphoma, DLBCL) and 30% (Burk itt lymphoma, BL and B-cell lymphoblastic lymphoma, B-LL) [1] in different subtypes of non-Hodgkin lymphoma (NHL). However, although a CNS prophylaxis is normally included into treatment regimens for BL and B-LL, in other NHL a prophylactic treatment is not systematically warranted because it may increase the toxicity of systemic chemotherapy.

For whom?

Diffuse large B-cell lymphoma

Central nervous system relapse occurs in about 5% of DLBCL patients. Median time from diagnosis to detection of CNS disease is less than 1 year, suggesting that seeding of the CNS occurs early in the course of the disease. The outcome of patients with CNS relapse is poor, with median survival times of 2–5 months [2,3]. Prophylactic treatment likely reduces the incidence of CNS relapse but may increase the toxicity of systemic chemotherapy, and the incidence of CNS dissemination is not high enough to suggest the use of prophylaxis treatment in all patients affected by DLBCL. In addition, the best strategy to prevent CNS dissemination remains to be defined, and most of commonly used strategies are inadequate to prevent intraparenchymal and/or meningeal relapses.

The major issue remains to identify the patients at high risk of CNS relapse.

Clinical risk factors

Central nervous system dissemination is more common in DLBCL patients with high international prognostic index score (IPI), which increased lactate dehydrogenase serum level and the involvement of more than one extranodal site. Moreover, DLBCL arising in some extranodal organs, such as the testis, paranasal sinuses, the hard palate, the orbit, paravertebral masses, and the bone marrow seems to have a high risk of CNS relapse [4]. A retrospective review of nearly 800 patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) suggested that initial implication of bone marrow in DLBCL raises the likelihood of CNS relapse [5]. A large retrospective series of primary lymphoma of the testis (373 patients) conducted by the International Extranodal Lymphoma Study Group, reported 5-year and 10-year risks of CNS relapse of 20 and 35%, respectively [6]. More recently, in a multicenter phase II prospective study (International Extranodal Lymphoma Study Group 10, IELSG-10) [7] addressing the role of R-CHOP21 plus CNS prophylaxis with intrathecal methotrexate (IT-MTX), 12 mg total dose, weekly for four times, during the first two R-CHOP21 courses plus irradiation to the contralateral testis at 25 to 30 Gy, Vitolo *et al*. showed a cumulative incidence of CNS relapse at 5 years only about 6%. However, in the absence of a comparison group without CNS prophylaxis, authors cannot ascribe these results to the introduction of CNS prophylaxis only.

Role of rituximab

The addition of rituximab (R) to CHOP chemotherapy has been shown to improve the clinical outcomes of DLBCL. A cohort of 399 elderly patients treated with CHOP with or without systemic rituximab was analyzed in a French study showing that age-adjusted IPI of at least 2 was the only independent predictive factor of CNS recurrence [8]. In a German study, the estimated 2-year incidence of CNS disease was 6.9% (CI 4.5; 9.3) after CHOP-14 and 4.1% (CI 2.3; 5.9) after R-CHOP-14. R-CHOP was able to reduce the relative risk for CNS disease to 0.58 (95% CI 0.3; 1.0, $p = 0.046$) [9]. More recently, Guirguis *et al*.

showed that addition of rituximab to CHOP may decrease the incidence of CNS relapse in patients with DLBCL compared with historical data. Relapses appear to be more parenchymal and occur after one year from diagnosis with median time to CNS relapse of 17 months (6–35 months) and most of them were isolated CNS events. However, the outcomes following CNS relapse remain poor. This may again reflect the superior effect of rituximab in controlling systemic disease. Authors suggested that R-CHOP may overcome the need for CNS prophylaxis in patients with DLBCL, with the exception of testicular lymphoma [10].

Biological risk factors

A small subset of patients with DLBCL harbouring *MYC* gene rearrangements or a combination of MYC and BCL-2 translocations was associated with CNS involvement of about a rate of 30% [11].

Flow cytometry analysis

The diagnosis of CNS dissemination is frequently suspected on the presence of related signs or symptoms, and it is confirmed by standard conventional cytology (CC) examination of cerebrospinal fluid (CSF) and neuroimaging techniques. Recent studies demonstrated that flow cytometry (FCM) assessment of CSF is more sensitive than CC to detect occult leptomeningeal disease in patients with aggressive lymphoma at risk of CNS dissemination. FCM-positive CSF is an adverse prognostic value on survival and is associated with a significantly high risk of CNS progression [12].

Mantle cell lymphoma

Data concerning the risk of CNS involvement in patients with mantle cell lymphoma (MCL) are controversial and based mainly on the results of small retrospective single-centre case series. Although it is very rare at diagnosis, at the time of relapse the incidence of CNS involvement in MCL patients is 4–22%. In two retrospective studies, the median time of CNS relapse from diagnosis was 12–51 months, and the median survival from the time of CNS involvement was 2–9 months. Although CNS relapse in MCL has not been investigated extensively, its frequency appears to be higher than that observed in indolent lymphoma subtypes and may vary widely from 4 to 26% in different case series, being comparable with that of DLBCL. CNS relapse is often a feature of relapsed/refractory MCL and is mainly associated with systemic relapse. [13] In a recent trial, Conconi *et al*. analyzed 142 MCL patients: disease relapse at the CNS was observed in 11 of 142 patients (7.8%; 95% CI, 3.9–13.4%). CNS involvement occurred after a median of 13.8 months (range: 3.7–95 months). The cumulative risk of CNS relapse steadily increased until 10 years: 7.2% (95% CI, 3.6–13.9%) at 2 years, 10.6% (95% CI, 5.6–19.4%) at 5 years and 13.6% (95% CI, 7–25%) at 10 years. CNS relapse had a dismal impact on outcome: median survival after CNS relapse was 6.3 months (range: 1.5–78 months). Blastoid variant, high Mantle Cell Lymphoma International Prognostic Index score, high ki67 and high LDH serum level are predictors of CNS involvement.[14]

Clinical risk factors

Among several clinical variables at diagnosis, only blastoid variant, high Mantle Cell Lymphoma International Prognostic Index score, high ki67 and high LDH serum level are predictors of CNS. Results were similar also when limiting the analysis to the risk of CNS involvement at first relapse: blastoid variant and elevated serum LDH levels retained their prognostic impact.

It is controversial whether prophylaxis can really prevent CNS relapse. According to European Mantle Cell Lymphoma Network recommendations [15], pre-treatment work-up in patients with MCL does not include routine assessment of the CSF.

How?

Diffuse large B-cell lymphoma

Intrathecal chemotherapy (usually including methotrexate, cytarabine and steroids) has been largely used in high-risk patients as a strategy for CNS prophylaxis [4], but recently, the RICOVER-60 trial showed that IT-MTX failed to reduce the risk of CNS relapse progression in a series of elderly patients with DLBCL treated with R-CHOP14 [9]. Following the large experience in acute lymphoblastic leukaemia and Burkitt lymphoma, another therapeutic option regards the use of drugs with good CNS bioavailability when administered at high doses, like cytarabine, methotrexate and ifosfamide. The GELA randomized trial, which compared CHOP without rituximab to a combination containing high doses of methotrexate and ifosfamide plus IT-MTX delivery (ACVBP regimen), has demonstrated that ACVBP has been associated with a significantly lower CNS relapse rate (8.3% for CHOP vs 2.7% for ACVBP; $p = 0.002$). These results prompted the French group to treat with these prophylaxis patients with DLBCL except those with an age-adjusted IPI equal to 0 who do not currently receive IT-MTX, also in rituximab era.

In a recent study, the Nordic Lymphoma Group treated 156 high-risk DLBCL patients with six courses of R-CHOEP-14 (R-CHOP plus etoposide) followed by a course of high-dose cytarabine and a course of high-dose methotrexate. Authors

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observed a 3-year FFS of 65%, an OS of 81% and a CNS relapse rate of 4.5%.

In the International Extranodal Lymphoma Study Group 10 study [7], addressing the role of R-CHOP21 plus CNS prophylaxis with IT-MTX plus irradiation to the contralateral testis in patients with primary testicular lymphoma, the 5-year overall outcome was good with a PFS and OS of 74 and 85% and the 5-year cumulative incidence of CNS relapse was reduced but still present at 6%. To further reduce of CNS relapse, the new International Extranodal Lymphoma Study Group 30 study intensified CNS prophylaxis with the addition of an intermediate dose of MTX at the end of R-CHOP and substitution of liposomal cytarabine for IT-MTX.

Mantle cell lymphoma

The aggressive clinical course observed in most cases has led to the design of intensive treatment protocols, including high-dose chemotherapy followed by autologous stem cell transplant. It is controversial whether prophylaxis can really prevent CNS relapse. In a series of MCL patients, the incidence of CNS infiltration observed in patients receiving high dose MTX-containing regimens was the same as that detected in the remaining patients. Because of the lack of comparative data, it is even more difficult to evaluate the CNS-prophylactic effect of HD-Ara-C and high dose MTX-containing regimens given to young and fit MCL patients, as in the HyperCVAD/MA regimen.

Conclusions

Despite the relatively low frequency of CNS relapse in aggressive lymphoma, the devastating effects of this condition and the potential toxicity of CNS-directed therapy justify efforts to better define the target population and to optimize CNS prophylaxis. Risk models developed so far showed a low sensitivity in predicting CNS involvement implying a potential overtreatment in up to 70% of patients deemed at high risk. New updated risk models in rituximab treated patients should be implemented along with a better identification of patients at risk who really should receive CNS prophylaxis can be focused on detection of occult CNS disease at diagnosis by using more sensitive methods for CSF evaluation such as FCM [12]. The optimal regimen for CNS prophylaxis in aggressive lymphoma patients has not been established, thus far and should be modulated among different level of 'intensity' such as standard intrathecal chemotherapy, 'active' intrathecal chemotherapy with liposomal cytarabine or more aggressive systemic treatment with high doses of drugs with a good CNS bioavailability reserved to patients at true high risk of CNS dissemination.

Conflict of interest

Umberto Vitolo is a member of a Roche global advisory board. Giulia Benevolo and Annalisa Chiappella have no conflicts of interest to declare.

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