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Invited abstracts

Extranodal lymphomas

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Primary CNS lymphomas

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The use of high-dose methotrexate (HD-MTX)-based chemotherapy, followed or not by whole-brain radiotherapy, is the commonest therapeutic approach for primary central nervous system lymphomas (PCNSL) [1]. The current therapeutic knowledge in this field comes from non-randomized phase-II trials, meta-analyses of published series, large retrospective, multicentre series, and a single phase III trial, which was prematurely terminated due to inadequate accrual. Numerous methodological pitfalls were highlighted in both prospective and retrospective series, further hampering interpretation of results. Importantly, the first worldwide randomized trial with completed accrual was recently reported [2]. This trial demonstrated that, in patients $\leqslant$75 years old with PCNSL, the addition of HD-cytarabine to HD-MTX results in consistently better outcome and acceptable toxicity over HD-MTX alone. MTX+cytarabine is an active combination that may be considered as the control arm for future randomized trials since it is supported by the best level of evidence available in the field of PCNSL. Despite this benefit, current results in PCNSL patients remain unsatisfactory. Accordingly to the worldwide used therapeutic strategies for aggressive lymphomas, it is unthinkable to treat PCNSL exclusively with antimetabolites and the assessment of other drugs active against other phases of the tumour cell cycle should be considered for future trials. Some alkylating agents (i.e., temozolomide, ifosfamide, thiotepa, nitrosoureas) are interesting candidates since they are able to cross the blood-brain barrier, exhibit anti-lymphoma activity, are active against phase-G0 cells, and increase cytotoxicity of antimetabolites. Rituximab could be another candidate, especially considering its safe profile. Its combination with HD-MTX-based chemotherapy is feasible [3], but several doubts on its capability to cross the blood-brain barrier exist. High-dose chemotherapy supported by ASCT has produced encouraging results in PCNSL [4]. However, this strategy seems feasible in young and fit patients, which excludes one third of PCNSL patients. Interestingly, some authors recently suggested that this strategy could replace consolidation radiotherapy [5], which deserves to be assessed in a future randomized trial. It is clear that a more effective international multidisciplinary collaboration is needed in the fight against PCNSL. Evaluation of single agents in phase II trials on patients with failed PCNSL, and definition and assessment of treatment-related neurotoxicity in prospective trials should be strongly encouraged.

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Secondary CNS involvement: Who needs, and which type of, CNS prophylaxis?

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Secondary central nervous system (CNS) involvement occurs with a variable frequency in adult patients affected by non-Hodgkin lymphoma (NHL). This complication can be detected as isolated site of relapse from a systemic lymphoma or in association with systemic disease. In any form, secondary CNS involvement represents a devastating and usually fatal complication of NHL, with a median survival of 4–5 months. Lymphoma cells can reach the CNS by haematogeneous route, spreading directly from adjacent bones or by centripetal growth along neurovacular structures, which is more common in lymphomas of the regions near of the base of skull [1]. Various risk factors and models for CNS recurrence have been described. Aggressive lymphomas like diffuse large B cell lymphomas (DLBCL) [2] are more likely to involve the CNS, and there is an increased risk of CNS dissemination when patients present with advanced disease, an involvement of certain extranodal organs (testes, breast, ovary, paranasal sinuses, skin, soft tissue and bone marrow) [3–6] and localisations in the anatomical regions near to the base of the skull, an high age-adjusted International Prognostic Index (aaIPI), an elevated serum lactate dehydrogenase (LDH). In general, secondary CNS involvement occurs within the first 14 months from

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lymphoma diagnosis (median 8 months; range 1–39) [4]. This early occurrence of CNS relapse suggest strongly that patients have subclinical disease at initial diagnosis.

The incidence of CNS relapse in DLBCL has been reported in a number of series [7–9,10]. A retrospective study of the GELA reported an incidence of CNS relapse of 2.2% in DLBCL patients, mostly as isolated site of recurrence [8]. One hundred and six (4.2%) among the 2514 patients admitted to the Norvegian Radium Hospital with lymphoma from 1980 to 1996 developed CNS involvement: 70 (66%) patients had a CNS relapse after treatment conclusion and 36 (34%) patients experience CNS progression during primary treatment [9]. Histology subtypes were DLBCL, anaplastic lymphoma, centroblasitic and immunoblastic and PTCL) [9]. The RICOVER-60 trial documented CNS events in the 1217 included patients (age range 61–80 years) with DLBCL randomized between CHOP and R-CHOP [7]. Fifty-eight (4.8%) cases with CNS lymphoma dissemination were reported [11]. Multivariate analysis identified extranodal involvement at more than one site, the presence of B symptoms (fever, night sweats, loss of weight) and raised serum LDH levels as predictors of CNS recurrence in DLBCL. Patients with all these three characteristics (n = 77) had a 25% risk of CNS relapse at 2 years, compared with a risk of 5% in all other patients. Moreover the authors stated that if patients received the combined treatment R-CHOP compared to CHOP, intrathecal methotrexate had no role in preventing CNS disease. Finally the Southwest oncology group (SWOG) recently reported their experience with the same conclusions [10]. Cumulative incidence of CNS relapse was observed in 2.8% of the 899 patients with aggressive lymphoma (intermediate or high grade – working formulation), without benefice of CNS prophylaxis in those patients with bone marrow involvement at diagnosis.

Given the dismal outlook once CNS relapse has occurred, attempts have been directed to the prevention of this complication. Standard practices for patients with DLBCL with high risk of CNS dissemination usually include a systematic CSF analysis at diagnosis including cell counts, protein and glucose levels, cytology, flow cytometry [12], and a CNS prophylaxis in the selected high-risk patients. The most used CNS prophylaxis regimen is intrathecal administration of methotrexate, realized in 10–15% of DLBCL patients. However there is no uniformity of practice [1,13]. Whether CNS prophylaxis should include both systemic CNS-active and intrathecal chemtotherapy is unclear and should be re-evaluated in the context of the actual standard rituximab combined-chemotherapy that appears to give no advantage in terms of prevention of CNS relapse. However intrathecal injections impair the quality of life of patients during treatment and, most importantly, may be associated with rare but major complications such as myelopathy, arachnoiditis or leucoencephalopathies [14,15]. Because of these side effects, it is important to identify patients who will really have benefit of CNS prophylaxis, i.e. patients who present at the time of diagnosis the highest risk of CNS relapse. Such approach will allow us to avoid therapeutic complications in patients without CNS recurrence risk. However, to date, no suitable biomarker is available to stratify patients in need of CNS prophylaxis.

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