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High dose chemotherapy and autologous transplantation in anti-CD20 antibodies era: still a place?

High dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) is recommended in young (<65 years) patients with diffuse large B-cell lymphoma (DLBCL) without a complete response (CR) after first line chemotherapy or in patients with chemosensitive DLBCL at relapse. According to Italian Society of Haematology guidelines and others, this approach, as first line treatment should be considered in young patients with an intermediate/high or high-risk according to the age-adjusted International Prognostic Index (aa-IPI) only in approved study protocols.[1,2] So far, in the pre-rituximab era, no clear benefits were shown in such patients, and conflicting results were generated in randomized studies, with similar survival rates in patients receiving either first-line HDC and ASCT, or standard chemotherapy without rituximab.[3-7]

The addition of rituximab to CHOP21 or dose-dense CHOP14 significantly improves the overall and event-free survival compared with CHOP alone either in elderly or in young low-risk patients with DLBCL,[8-10] however, less data are available in young DLBCL patients with a poor prognosis.[11-12]

Recently, on the basis that risk assessment is a moving target, a Revised International Prognostic Index (R-IPI) was retrospectively applied to patients with DLBCL treated with R-CHOP distinguishing three separate prognostic groups with different 4-year OS rates: very good risk 94%, good risk 79% and poor risk 55%.[13] However, patients with poor prognosis had still a chance of cure of no more than 45-55% and they should be considered for investigational approaches in the context of clinical trials designed to ensure that potentially curative therapy is not compromised. The addition of rituximab to HDC and ASCT was tested in relapsed aggressive and follicular lymphoma patients. The results indicate that this approach is safe and possibly effective.[14-16] Thus far, few data have been reported that describe the results of HDC and ASCT supplemented with rituximab as first line treatment in high-risk DLBCL and mainly as abstract forms.[15,17-19]

On this basis, the Gruppo Italiano Multiregionale Linfomi e Leucemie from June 2002 to December 2005 conducted a phase II trial (registered at http://www.clinicaltrials.gov, NCT00556127) aimed to explore the combination of rituximab with dose-dense chemotherapy and HDC with ASCT in untreated DLBCL patients with a poor prognosis. Ninety-seven consecutive patients with age-adjusted IPI score 2-3 DLBCL were enrolled

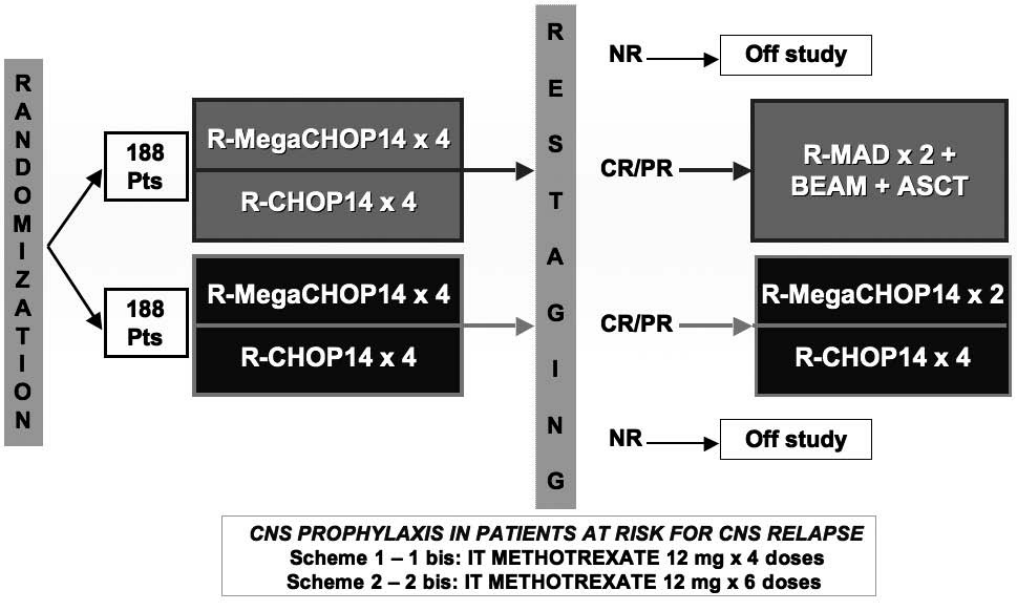

Figure 1. Italian Lymphoma Intergroup trial: IIL-DLCL04. R-MegaCHOP14: rituximab (375 mg/m^2), doxorubicine (70 mg/m^2), cyclophosphamide (1200 mg/m^2), vincristine (1.4 mg/m^2, maximum 2 mg) day 1, prednisone (40 mg/m^2) orally days 1 to 5, peg-filgrastim subcutaneously 24 hours after chemotherapy; R-CHOP14: rituximab (375 mg/m^2), doxorubicine (50 mg/m^2), cyclophosphamide (750 mg/m^2), vincristine (1.4 mg/m^2, maximum 2 mg) day 1, prednisone (40 mg/m^2) orally days 1 to 5, G-CSF (5 μg/Kg/day) days 3 to 10; MAD: mitoxantrone (8 mg/m^2/day), high-dose cytarabine (2 g/m^2/12 hours for six doses in three hour infusions), dexamethasone (4 mg/m^2/12 hours) days 1 to 3, G-CSF (5 μg/Kg/day) 24 hours after the last dose of high-dose cytarabine until peripheral blood stem cell (PBSC) harvest or recovery from neutropenia, Rituximab (375 mg/m^2) day 4 and day before harvest (day 10); BEAM: carmustine (300 mg/m^2) day -7, etoposide (100 mg/m^2/12 hours), cytarabine (200 mg/m^2/12 hours) days -6 to -3, melphalan (140 mg/m^2) day -2, Autologous Stem Cell Tranplantation (ASCT) day 0, peg-filgrastim day 1.

into the study. The results demonstrate that rituximab-HDC is effective as a first line treatment in a large cohort of patients with a poor prognosis with a prolonged and adequate follow-up: the CR rate was high (82%) and the long-term outcome was also highly favourable with four-year FFS and OS rates of 73% and 80%, respectively.[20]

Actually the standard therapy for advanced stage DLBCL is rituximab-CHOP chemotherapy as shown by randomized trials conducted either in elderly or in young low-risk patients and by a historical comparison of population-based study,[8,9,21] but the appropriate therapy for young patients with IH and H risk DLBCL is still an unanswered issue. Several phase II non-randomized studies incorporating rituximab into dose-dense or dose-intense schemes, R-CHOP14-like, but without ASCT showed that such approaches are feasible and effective in high-risk young DLBCL patients. The estimation of the outcome of young patients with poor prognosis from these studies is difficult; the reported two or five-year PFS for patients with aa-IPI intermediate-high or high risk score did not exceeded 45-61% indicating that there is a place for new approaches in these patients that are unlikely to be cured by standard R-CHOP.[11,12,19] Intensified chemoimmunotherapy with HDC and ASCT is one possible strategy to treat DLBCL with poor prognosis. A second option may be to evaluate predictors at diagnosis, other than IPI and R-IPI, that would be potentially able to identify

patients at poor prognosis that may be candidated to intensified therapies. In patients treated without rituximab two distinct gene expression profiles (Germinal Center Cell and Activated B Cell) or tissue microarrays predict different prognosis in DLBCL.[22-23] Conversely, in patients treated with R-CHOP-like regimens these models were not always predictive and different biological markers or models such as, microvascular density and others may preliminary identify patients that are likely to fail R-CHOP alone.[24-26] Alternatively, the interim evaluation of response with early positron emission tomography (PET) scanning has shown promise as a prognostic factor in retrospective series of DLBCL, but requires further investigation in prospective series because contradictory results have been reported.[27,28]

Another therapeutic option that should be investigated to increase outcome in poor prognosis DLBCL patients is the addition of radioimmunotherapy. Preliminary data from phase II studies in aggressive lymphomas (DLBCL and mantle cell lymphoma) suggest that ^{90}Y-ibritumomab tiuxetan is effective also in this setting, namely as consolidation treatment after chemoimmunotherapy or as a part of conditioning regimen before ASCT.[29-36] Recently, the addition of ^{90}Y-ibritumomab tiuxetan to high dose chemotherapy conditioned with BEAM regimen, was tested in 41 aggressive relapsed/refractory lymphoma patients, including DLBCL, MCL or transformed lymphoma, that were considered at poor prognosis with standard autologous stem cell transplantation.[30] The outcome was promising with a 2-year OS and PFS of 88.9% and 69.8% respectively. Data were encouraging, but larger phase III randomized trials are needed to clarify this issue.

In conclusion, results suggest that HDC supplemented with anti-CD20 antibodies and ASCT approach may be effective in young DLBCL patients with a poor prognosis. However, the issue if rituximab-HDC may be more effective compared with Rituximab-dose-dense chemotherapy in these patients will be addressed only by randomized phase III trials that are currently ongoing into the major cooperative groups. The Italian Lymphoma Intergroup is currently conducting a randomized trial (IIL-DLCL04 registered at http://www.clinicaltrials.gov, 00499018) comparing full course of rituximab-dose dense chemotherapy (RCHOP14 or R-Mega CHOP14) alone with a brief rituximab dose dense chemotherapy followed by rituximab-HDC with ASCT in young patients with DLBCL at intermediate-high and high risk (Figure 1). The results of this and other ongoing trials will provide new perspectives in the treatment of DLBCL with poor prognosis.

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