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The effect of adding rituximab to high dose chemotherapy

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High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has been proved to be an effective salvage treatment in chemo-sensitive relapsed patients for both aggressive and indolent lymphomas.[1,2] Since that, many investigators have extended this approach as part of the initial therapy of patients with aggressive lymphomas, especially those considered at poor prognosis, with conflicting results in randomized studies.[3-4] Indeed a recent meta-analyses of up to 11 randomized trials in aggressive lymphomas, showed a similar OS in patients receiving first-line HDC + ASCT or standard chemotherapy.[5] Most treatment failure can be ascribed to disease relapse after ASCT, which usually occurs within 1 to 2 years of transplantation or to rapid disease progression during HDC because of failure of induction therapy to control the disease. New strategies aimed to improve the effectiveness of HDC with ASCT for both aggressive and indolent lymphomas are needed. The chimeric anti-CD20 monoclonal antibody Rituximab has been shown to be an effective therapeutic option and improves efficacy when used in combination with chemotherapy for both indolent and aggressive lymphomas.[6-7] It seems reasonable to explore the use of Rituximab along with HDC and ASCT

Aggressive Lymphomas

There is evidence that Rituximab can be added to combination chemotherapy CHOP21 or dose-dense CHOP14 without significant increase in haematologic toxicity and this resulted in significantly longer overall and event-free survival compared with CHOP alone in elderly patients with DLCL.[7-8] On this basis, we initiated a prospective trial in 2001 in patients with DLBCL at diagnosis on the hypothesis that Rituximab would be tolerated safely during HDC improving its efficacy. We compared two groups of 118 previously untreated patients <61 years with Diffuse Large B-Cell Lymphoma (DLBCL), stage III-IV at aaIPI Intermediate-high or high risk enrolled into two non-randomized phase II clinical trials with up-front HDC and ASCT with or without Rituximab. Seventy-seven were enrolled into R-HDC trial (study group) that consisted in an induction treatment lasting two months with four courses of R-MegaCEOP chemotherapy; then two courses of intensified chemoimmunotherapy R-MAD (Mitoxantrone, High-dose Ara-C and dexamethasone) followed by ASCT with BEAM as conditioning regimen. Forty-one patients were enrolled into HDC trial (control group) that consisted in an induction treatment lasting two months with MACOPB chemotherapy for 8 weekly infusions followed by the same intensified and HDC regimens without Rituximab. Three-year failure-free survival (FFS) and 3-yr overall survival (OS) rates were improved in R-HDC group compared to HDC group: FFS 64% vs 46% (p=0.016); OS 80% vs 54% (p=0.004). (Figure 1).

A better outcome for patients treated with R-HDC was confirmed in both IPI groups (Figure 2).

The risk of failure and death was confirmed as significantly reduced in R-HDC group by Cox's model.[9] Our results suggest that Rituximab administered to patients with DLBCL during high dose chemotherapy before ASCT can significantly increase the outcome compared with traditional HDC without Rituximab. Hoerr et al10, reported the effects of preautografting treatment with Rituximab in relapsed chemosensitive non-Hodgkin's lymphoma patients. In contrast to patients with low-grade non-Hodgkin's lymphoma, both disease-free and overall survival rates were significantly increased when Rituximab was included in the pretransplantation salvage therapy (ESHAP, DHAP, MINE or ICE) for patients with intermediate-grade non-Hodgkin's lymphoma (3-yr OS 75% vs 52%). High-dose Rituximab (1000 mg/m^2) was administered concurrently before and after ASCT with BEAM as conditioning regimen in 67 patients with relapsed B-cell

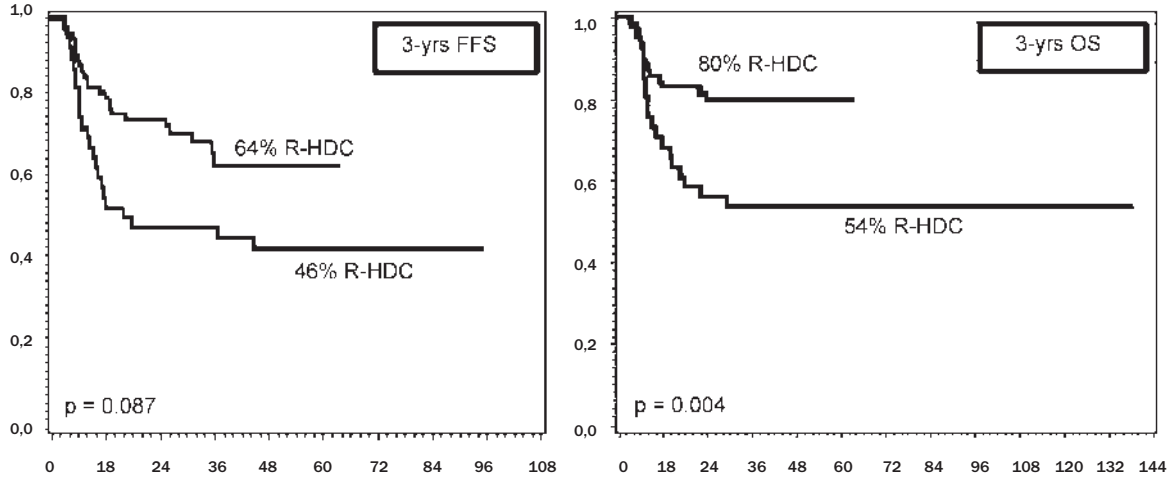

Figure 1.

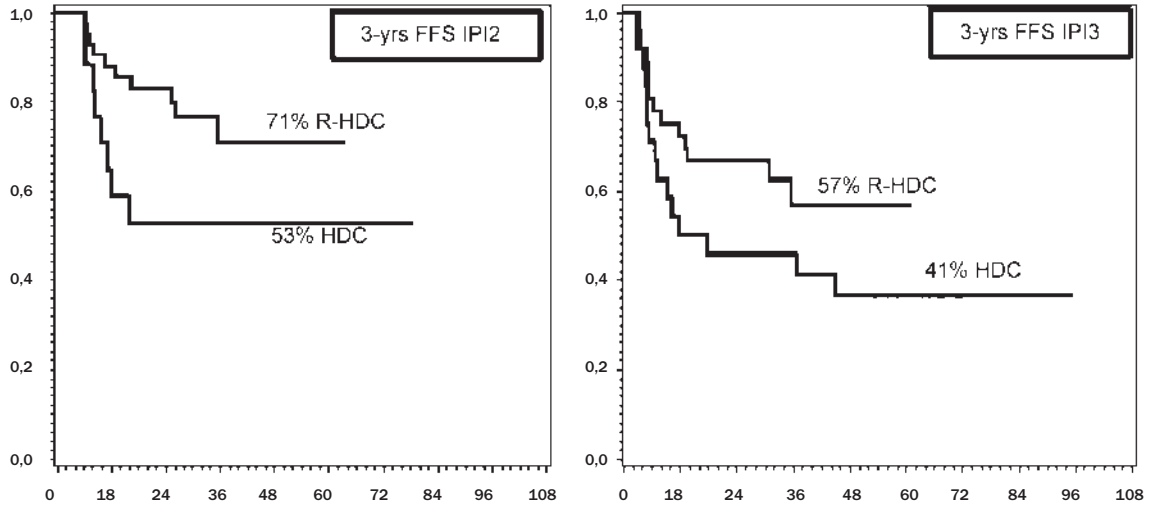

Figure 2.

aggressive lymphoma. The 2-yr OS rate was 80% compared to 53% of a control group treated without Rituximab with no increased rate of infections.11 Concerns have been raised on increased infection rate, later immune reconstitution and longer time to engraftment in patients undergoing ASCT after having received rituximab. Benekly *et al.*[12] reported a significantly higher bacterial infection rate in rituximab-treated patients than in patients who did not receive rituximab. Other researchers have demonstrated that the immunosuppressive effects of Rituximab slightly delay immune recovery, however these delays do not result in an increased incidence of post-transplantation infection.[13] A delay in platelet or neutrophil engraftment were reported in patients treated with Rituximab prior to ASCT.[10-11]

Indeed, in our study median times to neutrophil (> 0.5×10^9/L) and platelet (> 50×10^9/L) engraftment was not different for patients treated with or without Rituximab with no delay in stem cell harvest (R-HDC vs HDC group: 9 vs 9.5 days for neutrophils and 13 vs 11 days for platelets). Also the rate of acute severe infection was comparable in both groups. However in the Rituximab-HDC group two patients developed late infections (disseminated Herpes Zoster virus and bacterial meningitis) one year after ASCT underlying the need of careful monitoring these patients. These encouraging results provide the rationale for conducting prospective, randomised trials that test the potential benefit of adding Rituximab to HDC compared to

standard chemoimmunotherapy. Such a trial is currently ongoing, conducted by Intergruppo Italiano Linfomi comparing Rituximab-HDC (R-CHOP14/R-MegaCHOP14 + R-MAD + ASCT vs R-CHOP14/R-MegaCHOP14) in young patients with DLBCL at poor prognosis (aaIPI intermediate-high or high risk). The future results will provide new perspectives on the use of Rituximab in addition to HDC in aggressive B-cell lymphomas.

Follicular lymphomas

HDC and ASCT has been shown to be effective in the long-term control of relapsed follicular lymphoma.14 Lymphoma however can progress after ASCT. Lymphoma cells often contaminate bone marrow and peripheral blood stem cell collections and may contribute to relapse after ASCT.[15] The presence of bcl2+ cells in peripheral blood and/or bone marrow decreases with ASCT and patients with a molecular response after ASCT have a significant lower risk of relapse, the chance of relapse being proportional to the quantity of PCR positive cells found in peripheral blood or bone marrow.[16-17] Attempts to reduce the amount of neoplastic cell in the harvest has been made with in-vitro purging with cytotoxic agents, anti-B-cell monoclonal antibodies and complement or immunomagnetic beads. A recent retrospective large cohort study reported the outcomes of *in vitro* purging with anti B-cell monoclonal antibodies with a significant 26% and 32% reduction in 5-year relapse and OS rate, respectively, in patients receiving an in-vitro purged harvest. However these techniques are usually expensive, not reliable and produce loss of cells.[18] More recently, *in vivo* purging was achieved by administering rituximab prior to ASCT. Magni *et al.*[19] used rituximab for *in vivo* purging of autologous stem-cell collection before ASCT for follicular and mantle cell lymphoma. Ninety-three per cent of the PBSC harvested were PCR negative after two courses of HDC (Cyclophosphamide and Ara-C) with Rituximab compared with 40% of cells in the control group treated without Rituximab. Preliminary results suggest that 3-year relapse-free survival rate may exceed 80%. The addition of Rituximab after ASCT may achieve additional clinical and molecular response for several months after the discontinuation of Rituximab itself. In 31 patients with follicular and mantle cell lymphoma, Rituximab was given 8 weeks after ASCT weekly for 4 weeks. 4-year EFS was 81%. No detectable PCR positive cells were found in 22% of patients before ASCT, in 53% after ASCT, in 72% after Rituximab and in 100% 6 months post transplant.20 Various conventional chemotherapy schedules in combination with Rituximab have been employed in Follicular Lymphoma at diagnosis, including R-CVP, R-CHOP and R-FM. All these schemes have shown high therapeutic efficacy along with good tolerability. However young patients with poor prognosis (ie FLIPI high risk) might benefit from an early intensification treatment with HDC and ASCT. A recent Italian trial conducted by GITMO/IIL randomized 136 poor-prognosis follicular lymphoma patients < 60 years between Rituximab-HDS and CHOP-Rituximab. Preliminary results showed a better CR and 2-year EFS rates in favor of patients treated with R-HDS, however no difference in survival have been observed so far.[21] More studies with longer follow-up are needed to better define the role of R-HDC in follicular lymphoma at diagnosis.

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