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Salvage therapy for relapsed or refractory diffuse large B-cell lymphoma: impact of prior rituximab

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma in the developed world.[1] Anthracycline based combination chemotherapy regimens became standard of care in the 1970s after a series of studies showed long-term disease free survival with this approach. It was the pivotal study by the Group d'Etude des Lymphomas de l'Adulte (GELA), comparing CHOP versus the same regimen plus rituximab that changed practice. The use of rituximab, a monoclonal antibody targeting CD20 along with combination chemotherapy, CHOP or equivalent regimens led to complete remission (CR) rates of 75-80% and 3-5 year progression free survival (PFS) of 50-60%.[2] Retrospective analysis of this strategy demonstrated that in adult DLBCL patients of all ages, 2-year OS increased from 52% with anthracycline based chemotherapy to 78% in the post-rituximab era.[3]

Despite this major advance, a significant proportion of patients will either experience early treatment failure, partial response or relapse after the initial chemotherapy. The initial approach to relapsed DLBCL management is to determine if the patient is a candidate for high-dose chemotherapy and autologous stem cell transplant (ASCT). In the PARMA trial, chemotherapy-sensitive relapsed DLBCL patients were randomized to salvage chemotherapy with platinum and cytarabine based regimen alone or in combination with ASCT. Both EFS and OS were significantly superior in the transplant group versus the chemotherapy alone group (46% and 53% *vs.* 12% and 32% respectively). Chemotherapy sensitive patients did significantly better than those who were chemotherapy-resistant (5-year PFS 43% *vs.* 1-year survival of 22%).[4] Based on these results, HDT/ASCT has become the standard of care in younger patients with chemosensitive relapsed or primary refractory aggressive lymphoma.

Role of rituximab in salvage therapy

In this issue of the journal, Martin and colleagues report the GEL/TAMO study, which evaluated the influence of prior rituximab use in response rates of R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma.[5] The efficacy of rituximab-containing salvage after induction treatment with rituximab containing chemotherapy has not been well established. In this retrospective analysis, 163 patients with relapsed or refractory DLBCL, who received R-ESHAP with curative intent, were analyzed. Patients were stratified according to whether rituximab

(R) had been administered previously, during induction therapy (n=94, R+ group) or not (n=69, R- group). Significantly higher response rates were seen in the R- group in univariate analysis but not in multivariate analysis (PFS 57% *vs.* 17% at four years and OS 64% *vs.* 38% at four years). Prior exposure to rituximab was an independent adverse prognostic factor of both PFS and OS. This trial addresses several important issues and raises key questions. First, Martin and colleagues question the efficacy of rituximab use in salvage therapy in an era when R-CHOP is accepted as standard of care for induction therapy. Second, the incidence of rituximab resistance in diffuse large B-cell lymphoma and its implications in the post-rituximab era are also not known. Third, this study highlights the importance of CR and validates the known risk factors such as second line age-adjusted IPI (s-aaIPI) in relapsed disease. Finally, the role of ASCT in relapsed lymphoma treated with rituximab is questioned, given the refractoriness of disease observed in patients who received rituximab during induction therapy.

Several investigators, including the HOVON group and the MKSCC group have shown improved response rates by adding rituximab to salvage regimens such as DHAP and ICE (Table 1), but the majority of the patients in earlier studies had not been previously exposed to rituximab. The role of rituximab retreatment in relapsed DLBCL has, therefore, not yet been established. Analysis of long-term follow-up of the GELA study included 399 previously untreated patients; age 60-80 years, with diffuse large B-cell lymphoma. Of the 399 patients, 202 (50.6%) experienced relapse or progression, including 125 (63%) in the CHOP arm and 77 (38%) in the R-CHOP arm. Subsequently, 22 (20%) of the 109 treated patients in the CHOP arm and 9 (12%) out of 73 in the R-CHOP arm received rituximab-containing salvage chemotherapy. In the final analysis, patients treated with a rituximab-containing salvage regimen had a 2-year survival of 58% compared with 24% for those treated without rituximab (p=0.00067). Importantly, in the CHOP arm, the benefit of the addition of rituximab at time of salvage therapy is statistically significant (p=0.002), whereas it is not statistically significant in the R-CHOP arm (p=0.23). However, only 9 patients received a second regimen with rituximab in the R-CHOP arm, hence it is not possible to draw any conclusions from this trial regarding the benefit of rituximab re-treatment.

The ongoing multicenter phase III CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study, aims to further guide the choice of salvage chemotherapy in diffuse large B-cell lymphoma (DLBCL) and assess the role of rituximab maintenance after autologous stem cell transplantation (ASCT). Patients are first randomized between ICE (ifosfamide, carboplatin, etoposide) and DHAP (dexamethasone, ara-C and cisplatin), both combined with rituximab (R-ICE or R-DHAP). Patients are stratified on the basis of prior exposure to rituximab, relapsed versus refractory disease, and relapse less than or greater than 12 months from front-line therapy. After three courses, responders are treated by ASCT with BEAM conditioning (carmustine, etoposide, cytarabine, melphelan). A second randomization then allocates patients to maintenance treatment with rituximab or observation. A recently reported interim analysis of 200 patients of a planned total of 400 shows that the factors affecting EFS include second line aaIPI (39% *vs.* 56%), relapse less than 12 months since first-line treatment (36% *vs.* 68%), and prior rituximab exposure (34% *vs.* 66%).[9] This heralds an important conundrum, suggesting that patients, who do not respond to rituximab containing regimens as first-line, may be much more difficult to salvage with rituximab containing chemotherapy. Hence, the benefit of rituximab in salvage is well established in rituximab-naïve patients, while its efficacy in retreatment remains questionable. The GEL/TAMO study in this issue is the first comprehensive analysis of the efficacy of rituximab in salvage therapy in patients with prior exposure, relevant to the current standard of care.[5]

Prognostic factors

Patients who fail first-line therapy may be categorized into three distinct groups; relapsing after complete remission, partial responders with persistent disease, and refractory patients. The outcome is significantly different in each subgroup. True refractory patients occasionally benefit from salvage regimens but generally have a poor outlook. Partial responders will sometimes benefit from non-cross resistant salvage regimens and might be offered autologous stem cell transplant. In a pooled analysis of over 7,400 patients from various GELA studies, significantly better EFS and OS have been seen in patients with partial remission or late relapse as compared to early treatment failures or refractory patients. Hence, early identification of these subgroups that might benefit from more aggressive front-line therapy would be critical. In the study presented here, apart from the previous exposure to rituximab, the most significant adverse prognostic factors were the presence of bulky disease, primary refractory disease, and s-aaIPI at the time of R-ESHAP of greater than 1, as well as administration of less than three

Table 1. Comparative response rates and progression-free survival with rituximab containing salvage regimens in relapsed/refractory DLBCL undergoing ASCT.

Salvage regimen	Response rates	Progression-free survival
R-DHAP-VIM-DHAP *vs.* DHAP-VIM-DHAP[6]	75% *vs.* 54%; p=0.01 (OR)	52% *vs.* 31%; p<0.002 (2-year post-ASCT)
R-ICE vs. ICE (historical controls)[7]	53% *vs.* 27%; p=0.01 (CR)	54% *vs.* 43%; p=0.25 (2-year post-ASCT)
R-ESHAP *vs.* ESHAP[8]	73% *vs.* 62%. (OR)	38% (actuarial 5 year) *vs.* NR

R: rituximab; DHAP: dexamethasone, high-dose cytarabine and cisplatin; VIM: etoposide, ifosfamide, methotrexate; ICE: ifosfamide, carboplatin, etoposide; ESHAP: etoposide, solumedrol, cytarabine and cisplatin; OR: overall response; CR: complete response; NR: not reported; ASCT: autologous stem cell transplant).

cycles of R-ESHAP. As suggested in the final analysis, the response rate to R-ESHAP was independent of prior rituximab exposure, although patients with primary refractory disease at the time of R-ESHAP had very low CR and OR rates (8% and 33% respectively), those patients in first PR or relapsed disease showed a high response rates, similar to that of rituximab naïve patients.[5] Primary refractory disease, as evidenced by PET data and high-risk s-aaIPI, have been found to be independent adverse risk factors for response and OS by other investigators, and the data presented by Martin *et al*. underscores the importance of alternative treatment strategies including experimental therapeutics in such patients.

Rituximab resistance

Rituximab resistance, a growing concern, has been best characterized in follicular lymphoma. The exact mechanism of such resistance is not entirely clear, although several tumor-associated and host-associated mechanisms have been proposed. Low serum levels or rapid monoclonal antibody metabolism, poor surface CD20 antigen expression, alterations of intracellular signals, inhibition of complement mediated cytotoxicity, and variations in cell-mediated immunity have all been implicated in cases of resistance.[10] As is evidenced by response to radioimmunoconjugates, surface CD20 expression seems to be preserved in relapsed follicular lymphoma, and is likely not changed in aggressive lymphomas. Zelenetz *et al.*, in a small retrospective analysis of 71 patients with transformed lymphoma treated with a single dose of iodine 131 tositumomab, showed an OR rate of 39% with 25% CR. The median duration of response was 20 months.[11] Based on these data, Morchhauser *et al.* performed a Phase II trial of yttrium-90 ibritumomab tiuxetan in transplant-ineligible elderly patients with first relapsed or primary refractory DLBCL. The patients were stratified according to prior rituximab exposure. In the final analysis, the OR rate was 44%, but only 19% of patients with prior rituximab exposure responded.[12] Martin and colleagues observed poor survival with rituximab containing salvage regimen in patients previously exposed to rituximab. One possible explanation is that R-CHOP failure is a predictor of antibody-refractory disease in DLBCL, hence retreatment with immunotherapy or radioimmunotherapy is not useful and alternative strategies, including novel small molecule targeted therapy, and improvement in conditioning regimens would be required.

Role of ASCT in post-rituximab era

The aforementioned PARMA trial,[4] now published over a decade ago, remains the only randomized trial comparing ASCT versus salvage chemotherapy. Since then, rituximab has become standard of care in both front-line therapy, and as part of salvage regimens, not used in the PARMA trial. Furthermore, PET scan, which has been incorporated in the modern response criteria, was not used. Exclusion of primary refractory disease and patients with less than a PR response are other limitations of the PARMA trial. Martin and colleagues, using R-ESHAP demonstrate more evidence of improved response rates with rituximab containing salvage regimens. Given the improved response rates to rituximab containing salvage therapy, are the results of the PARMA trial still valid? The rituximab treated relapsed patients may represent a truly refractory disease and not benefit substantially from ASCT.

The results from the GEL/TAMO study need to be in viewed in the perspective of its limitations. First, more patients in the R- group received previous chemotherapy that has not been defined. Could it be possible that these patients were treated with a non-anthracycline based and possibly an inferior chemotherapy? This is important when assessing the final impact of R-ESHAP, as these patients might represent a subgroup that would respond particularly well to front-line chemotherapy with an anthracycline. Second, patients with previous ASCT were included in the analysis, confounding results thereof. These patients have historically been poorly responsive and potentially incurable with further therapy. In addition, conditioning regimens and use of maintenance rituximab would need to be accounted for in these patients. Third, more patients in the R+ subgroup had B-symptoms, an established poor prognostic factor, although in the multivariate regression analysis, B-symptoms were not reported to be a factor. Fourth, although both subgroups of patients had similar numbers of primary refractory patients, can the R- be truly considered to be primary refractory, given the robust responses to rituximab containing first-line therapy? Finally, this is a retrospective analysis from a multicenter study, and would be difficult to confirm in a prospective manner in the post-rituximab era. Further evaluation of this hypothesis may result from the confirmatory CORAL study.

Future directions

Future directions to improve outcome in the post-rituximab era will include improvements in salvage regimens with the use of biologics and targeted therapy, better conditioning regimens, and consideration of maintenance therapy.

Similar to the experience with salvage regimens, no single preparative regimen has been shown to be superior. Most regimens historically have incorporated total body irradiation, which has been shown to provide superior disease control, despite significant concerns for cardiopulmonary toxicity and secondary malignancies. More recently, chemotherapy-only regimens such as BEAM, BEAC and CBV have been commonly used. With the success of non-myeloablative radioimmunotherapy in second line therapy, there has been considerable interest in combining them with the standard preparative regimens. Press *et al*. first established the feasibility of high dose radioimmunotherapy prior to autologous transplant in lymphoma.[13] Subsequently several studies have used myeloablative radioimmunotherapy with promising results. Vose *et al.* in a Phase II trial used Iodine 131 tositumomab in 40 patients with relapsed and chemosensitive DLBCL. After a median follow-up of 28 months, the 3-year PFS and OS were 70% and 81% respectively.[14] Alousi *et al.*

added yttrium-90 ibritumomab tiuxetan to high-dose rituximab delivered peritransplant plus BEAM and compared this to historical controls receiving high-dose rituximab plus BEAM alone in 25 patients with DLBCL. The radioimmunoconjugate combination appeared superior to results seen in historical controls, especially in patients with high IPI scores and residual PET-avid disease.[15] In both these studies, most patients had been exposed to rituximab in prior treatments. The BMT CTN group in the United States is currently conducting a Phase III trial comparing BEAM and iodine 131 tositumomab to BEAM plus rituximab as conditioning for ASCT of relapsed DLBCL.

Maintenance rituximab post-ASCT has also been evaluated as a means to reduce minimal residual disease. Khouri *et al.*[16] and the Stanford group[17] have independently reported on the improvement in DFS and OS rates with use of rituximab post-ASCT. The majority of patients in these trials were rituximab-naïve, and there was a substantial increased risk of prolonged neutropenia and hypogamaglobulinemia. The results of the ongoing CORAL study will provide valuable information regarding the efficacy and toxicity of maintenance rituximab post-transplant, especially in patients with prior rituximab exposure.

Improving the antibody-dependent cytotoxicity of rituximab, mediated through improved binding of the Fc portion of the mAB to FcR found on the accessory cells, while taking into account the well described functional polymorphisms of the FcR in humans is an important step in improving rituximab resistance. Monoclonal antibodies with varied FcR, such as ocrelizumab and rhuMAb v114, are associated with higher antibody-dependent cytotoxicity compared to rituximab, and show promising results in Phase I and II studies. Humanized anti-CD20 antibodies, veltuzumab and ofatumumab have demonstrated efficacy in rituximab refractory indolent lymphoma and are undergoing pivotal Phase III evaluations. Novel antibody targets are being identified given the initial success of anti-CD20 therapy. These include antibodies against CD22, CD40, the B-cell-activating factor of the TNF family (BAFF), and receptors for TRAIL (TNF-α-related apoptosis-inducing ligand, also known as Apo2L).[18]

Further understanding of the genetic subtypes and the associated gene-expression profiles, with subsequent evolution of targeted drugs, will lead to individualized therapy based on protein expression. Identification of biomarkers such as BCL-2 expression will be valuable in choosing appropriate first-line and salvage therapy. Gene expression profiling has identified several potential therapeutic targets such as protein kinase C, which modulates downstream signaling via NF-κ B pathway. In a Phase II study of 55 patients with relapsed/refractory DLBCL, treatment with enzastuarin, a protein kinase C inhibitor, resulted in 8 patients remaining free from disease progression for more than four cycles of therapy.[19] This agent is currently being evaluated as maintenance after R-CHOP induction for DLBCL. The great interest in tumor angiogenesis and inhibition of the VEGF pathway, with bevacizumab in relapsed aggressive lymphoma is supported by increased *VEGF* gene expression in activated B-cell and refractory lymphoma. Bevacizumab is being evaluated in both Europe and in the US in consideration with R-CHOP. The survival pathways of BCL-6 and p53 are up-regulated in DLBCL. Inhibition of DNA deacetylation by HDAC inhibitors results in suppression of both of these pathways.[20] Use of HDAC inhibitors in many hematologic malignancies and solid tumors have been shown to improve response rates. Trials in relapsed/refractory DLBCL with HDAC inhibitors are ongoing. Finally, fostamatinib disodium, an inhibitor of Syk kinase shows promising activity in DLBCL cell lines, and is now in early Phase I/II trials.[20]

Conclusions

The treatment paradigm in patients with relapsed and refractory diffuse large B cell lymphoma is still being defined. Outcome after failure of R-CHOP induction chemotherapy continues to be dismal, and efforts to define patients with refractory disease and early relapse will be crucial. Autologous stem cell transplant following high-dose chemotherapy remains the standard of care but will need to be revisited in the post-rituximab era. Salvage therapy of choice and the role of rituximab remain to be elucidated, and the results from the CORAL study are eagerly anticipated. Novel targeted therapeutics are evolving, and further incorporation of these agents into induction or salvage treatments will be the key in future.

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Allogeneic stem cell transplantation for thalassemia major

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Allogeneic hemopoietic stem cell (HSC) transplantation in thalassemia major has been a cornerstone of the development of cell-based therapies[1] and a matter of passionate debate during the '80s and early '90s.[2] The aim of HSC transplantation in thalassemia is to replace the ineffective endogenous thalassemic erythropoiesis with an effective allogeneic substitute and to obtain a lasting, permanent, clinically effective correction of the hemolytic anemia[3,4] and of the transfusion-associated pathologies, including iron overload. The large Pesaro experience demonstrated that this target has been achieved (Figure 1).

The issue of HSC transplantation in genetic disease is much different from that of HSC transplantation in malignancies. In the case of thalassemias, a graft versus leukemia effect in not required but the expansion of the erythroid compartment together with the enhanced immunological activity likely related to repeated transfusions result in the risk of graft rejection and disease recurrence being higher[5] than those observed for malignant diseases.

Application of transplantation world-wide

The HSC transplantation therapeutic approach pioneered by the Pesaro group[5-11] is now applied widely worldwide. The European Group for Blood and Marrow Transplantation (EBMT) has established the hemoglobinopathy registry which now contains detailed epidemiological data on over 3,000 patients. Since the early '90s, between 133 and 197 transplants per year have been registered (Figure 2).

The EBMT registry highlights the pioneering role of the Pesaro group in this field (Figure 3) and shows the wide diffusion of the procedure after 1993 (the year in which Professor Lucarelli gave the Ham-Wasserman lecture at the St. Louis ASH meeting).

Medical therapy for thalassemia major

Medical therapy of thalassemia is one of the most spectacular medical successes of the last two decades. Thalassemia has been transformed from a lethal disease of infancy into a chronic disease of adulthood[12] with a dramatic increase in both survival and life expectancy. An Italian retrospective study clearly demonstrated the enormous progress for patients born in the last two decades compared with patients born in earlier decades (Figure 4).

In recent years we have witnessed spectacular advances in our knowledge of iron overload pathophysiology, which have been accompanied by a substantial improvement in quality and availability of diagnostic capability, and by the development of new,