Ibritumomab Radioimmunotherapy in Mantle Cell Lymphoma

a report by
Wojciech Jurczak

Department of Haematology, Jagiellonian University, Krakow

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General Considerations

It is difficult to establish the true incidence of mantle cell lymphoma (MCL), as there is an important difference between national lymphoma registers (2–4% of non-Hodgkin's lymphomas, NHL) and reports from reference centres (7–11%).[1,2] It may either reflect the diagnostic problems, where MCL is not properly diagnosed and reported as chronic lymphocytic leukemia (CLL) or clustering of the refractory/relapsing patients in the reference centres. The MCL diagnosis must therefore include flow cytometry (CD5+/CD19+/CD20+/CD23-), immunohistochemistry for cyclin D1 and cytogenetic analysis, in case of any doubts. The majority of patients are elderly males over 60 years of age. Prognosis of MCL lymphoma treated with conventional cytoxan, hydroxyrubicin, oncovin, prednisone (CHOP)-like chemotherapy regimens is unsatisfactory: most cases relapse and become resistant to treatment relatively early, with the average progression-free survival (PFS) and overall survival (OS) less than one and three years, respectively.[3]

Chemoimmunotherapy with Rituximab as an Initial Cytoreductive Regimen

Chemoimmunotherapy is a widely accepted first-line approach as rituximab increases response rate (RR) and prolongs PFS. In a German lymphoma study group (LSG) randomised comparison of CHOP with CHOP-R (with rituximab), CHOP-R increased RR from 72 to 92%, CR from 9 to 32% and PFS from 14 to 21 months, although still without a clear OS benefit.[4]

Although the addition of rituximab to the fludarabine, cyclophosphamide, mitoxantrone regimen (FCM-R) was superior to FCM in relapsed patients, most of the responses were shorter than 12 months.[5] A standard-dose chemoimmunotherapy is just not enough to cure MCL, and some kind of post-induction or consolidation treatment is necessary. For maximum effectiveness, whatever we offer to our patients should be incorporated into the first-line approach, before the resistance occurs. Most of MCL patients are either 'young' elderly patients or 'elderly' elderly patients. In the first group, an intensive therapy approach with subsequent transplant procedure is the treatment of choice.

Wojciech Jurczak is Head of the Lymphoma Team at the Department of Haematology, Jagiellonian University, Krakow, Poland, which is a referral centre for the whole south-eastern region of Poland, dealing with over 300 new lymphoma patients annually. He is also a Lecturer at the Lymphoma Expert Forum and a Board Member of the Medical School for Foreigners at Jagiellonian University. His main scientific interests are lymphoma immunotherapy and risk-adapted treatment strategies. Dr Jurczak is one of the initiators of the Polish Lymphoma Research Group, co-ordinating multicentre national trials in mantle cell lymphoma. He has contributed numerous scientific papers and abstracts to international peer-reviewed journals.

Dose Escalation for 'Fit' Patients

Autologous transplants as consolidation of the first-line therapy became a gold standard after the first generation of European MCL Network trials demonstrated a PFS benefit compared with INF maintenance (medium PFS 39 months versus 17 months, p=0.01).[6] In the ongoing second-generation trial, the role of the more intensive induction therapy is investigated, comparing CHOP-R with alternative CHOP-R/DHAP-R. High efficiency (PFS >70% at three years) of chemoimmunotherapy regimens containing intermediate-dose cytarabine was shown in phase II studies: alternative HyperCVAD-R/MA-R regimen developed in MD Anderson,[7] alternative MaxiCHOP-R/cytarabine-R followed by BEAM conditioned transplant investigated by Nordic MCL Group[8] and Milano high-dose sequential chemotherapy.[9] The results of the Nordic and Italian groups are particularly interesting, as they were both performed in a multicentre setting and there is a plateau of OS curves after the third year. Present Nordic Group protocol includes radioimmunotherapy (Z-BEAM) in a transplant-conditioning regimen for partial responders.

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Radioimmonotherapy Consolidation for 'Elderly' Elderly Patients?

The majority of MCL patients are not eligible for intensive therapy. In the ongoing second-generation European MCL Network trial, FC-R is compared with CHOP-R. Rituximab increases the response rate to literally all chemotherapy regimens, but the question of post-induction therapy to increase the quality of remission remains open. Data on rituximab maintenance in follicular lymphoma remain preliminary.[10] Involved field radiotherapy (IFRT) is effective in a localised disease, as demonstrated in a retrospective analysis from Vancouver (71% versus 25% OS at six years, p=0.01).[11] Until recently, total body irradiation (TBI), one of the transplant-conditioning regimens) was the only alternative at the advanced clinical stage. Radioimmunotherapy (RIT) is an efficient method of 'total tumour radiotherapy', and is feasible for elderly patients.

Ibritumomab tiuxetan (Zevalin) is a 90Y labelled radioimmunoconjugate binding to the CD20 antigen present on the surface of B lymphocytes. RIT combines the specificity of monoclonal antibodies (MoAb) with the efficiency of radiotherapy. Ibritumomab is administered intravenously

and, after a short distribution phase, most of the compound is bound in the tumour. Monoclonal antibodies are relatively big molecules, poorly penetrating enlarged, partly fibrosed lymph nodes and tissue lymphoma infiltrates. A single ibritumomab-tiuxetan molecule, with thousands of 90Y nuclides attached, is capable of killing several adjacent cells within the range of beta particles emitted by 90Y (about 5mm in the tissues). Compared with rituximab, ibritumomab is less selective: what is a desired effect in lymph nodes is a disadvantage in bone marrow. Haematological toxicity is a dose-limiting factor:[12] radioimmunotherapy is contraindicated in patients with an important bone marrow lymphoma infiltration (>25%), BM hypoplasia or peripheral cytopaenia (leukocytes <1000/ul, blood platelets <100,000/ul). Other side effects are rare and the therapy is exceptionally well tolerated in terms of quality of life.

Paradoxically, an antilymphoma effect of RIT may be greater in patients with a measurable disease than in micrometastasis or minimal residual disease. In very small tumours, with fewer antibodies attached, a crossfire effect is less pronounced. On the other hand, one should be realistic about the tumour burden that could be effectively treated with a single infusion of ibritumomab (about 2mg). In follicular lymphoma, complete responses were less frequent if lymph nodes were more than 5–7cm in diameter. Large asynchronic tumour masses (i.e. massive splenomegaly) may 'trap' most of the infused antibodies (known as the 'sink phenomenon'), decreasing the treatment's efficiency.

Summary of Clinical Trials with Radioimmunotherapy in Mantle Cell Lynphoma

The first attempts to use radioimmunotherapy in MCL were in relapsed/refractory cases (see *Table 1*). In MD Anderson, 22 patients, after failing from one to six previous therapy lines, were treated with ibritumomab.[13] Twenty-one out of 22 had previously received rituximab, five out of 22 bortezomib, and 14 out of 22 had relapsed after the HyperCVAD/MA regimen. None of the eight responders had bulky diseases, and the largest measurable lesion did not exceed 3cm. Similar results were confirmed by German Lymphoma Study Group (n=14, 33% RR, medium PFS 3.9 months).[14] The length of response would probably increase if patients were treated earlier within the disease course, after initial de-bulking chemoimmunotherapy. This consolidation approach was investigated by the Polish Lymphoma Study Group (PLRG), where 10 patients in two to five relapse were subjected to RIT after three to six cycles of FCM-R.[15] The response rate was high (RR = 9/10, CR = 4/10) with the medium PFS 7.5 months (see *Figure 1*). Haematological toxicity was more pronounced than in the MD Anderson and GLSG studies, with eight out of 10 patients developing grade 3–4 leucopaenia and thrombocytopaenia. Although initial chemotherapy may increase the PFS from 3.9 to 7.5 months, most patients subsequently relapse and ibritumomab does not seem to overcome the disease resistance once it occurs.

There are two multicentre studies, published in ASH and ASCO abstracts, investigating RIT as a consolidation of first-line therapy in MCL (see *Table 2*). In the Eastern Co-operative Oncology Group (ECOG) study,[16] 56 patients were subjected to brief chemotherapy (four cycles of CHOP-R) before ibritumomab. Only toxicity and response assessment data have been presented so far: RIT increased the overall RR from 72 to 84%, and tripled the CR rate from 14 to 45%. In a European PLRG trial, 20 patients were entered either at diagnosis or in PR (but not resistance) after first-line therapy. A fludarabine-based regimen was applied (three to six cycles of FCM-R) with further ibritumomab consolidation if an adequate cytoreduction was achieved. It was defined as a BM infiltration <20%, LN diameter <3cm and splenomegaly <15 cm. Radioimmunotherapy increased the CR rate over four-fold, from 20 to 85%, and most patients remained in remission for the next 1.5 years (see *Figure 1*). These early, fascinating results need a longer follow-up and must be confirmed in a multicentre phase III study, perhaps in the third generation of EMCL Network trials.

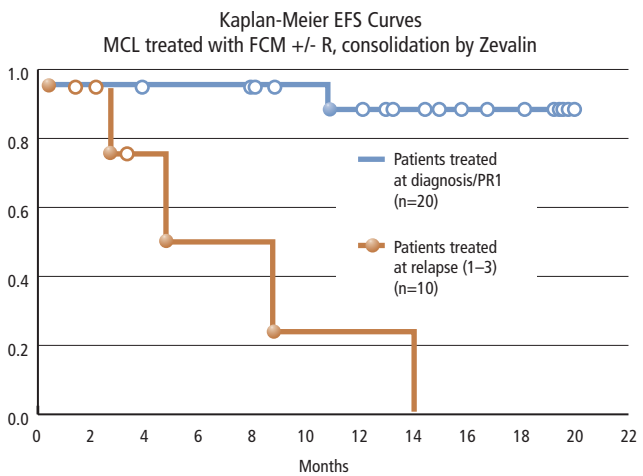
Table 1: Zevalin in Refractory/Relapsed Patients

Study	Patients	Protocol	Response	Median TTP
Youne et al. ASH 2005	Refractory/ relapsed n=23	Zevalin	RR 33% CR 22%	3–9 months 6 months
Weigert et al. ASH 2005	Refractory/ relapsed n=14 CR 8%	Zevalin 3 months	RR 30%	3 months
Jurczak et al. EHA 2006	Relapsed n=10	FCM-R (3–6), followed by Zevalin	RR 90% CR 40%	7–5 months 7–5 months

Table 2: Zevalin as a Consolidation Therapy in Mantle Cell Lymphoma First-line Treatment

Smith et al. ECOG ASCO 2006		4xCHOP–R	+	Zevalin
n=57	RR (%)	58%		84%
	CR (%)	14%		45%
Jurczak et al. PLRG ASH 2006		3–6xFCM–R	+	Zevalin
n=20	RR (%)	100%		100%
	CR (%)	20%		85%

Figure 1: Polish Lymphoma Study Group Mantle Cell Lymphoma Trial Results



Conclusions

Radiotherapy is an active treatment modality in MCL. Ibritumomab radioimmunotherapy is an interesting alternative to other consolidation methods. In younger patients subjected to intensive chemotherapy followed by autologous transplant, it may be an element of a transplant-conditioning regimen (i.e. Z-BEAM). In elderly patients, the role of zevalin consolidation should be further investigated in a phase III trial. ■

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Event Spotlight

34th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT)

Alberto Bossi, Congress President, and Ricardo Saccardi, Scientific Chair, look forward to the 2008 event.

Dear Colleagues, Members and Friends,

For many years now, haematopoietic stem cell transplantation (HSCT) has been the only form of cellular therapy employed at a clinical level. Its position between experimental biology and clinical application has resulted in an extraordinary plasticity in the associated technology, which has, in turn, demanded continuous development in the competencies of the specialists. In particular, the last 10 years have radically changed the setting, enabling procedures to cut through the barriers of age and tissue compatibility previously considered insurmountable. As a consequence, the choice of the best combination of cellular source, conditioning regimen and immunosuppressive treatment has become all the more intriguing. A careful evaluation of the emerging data, the development and support of investigational trials and an efficient diffusion of medical information continues to be an exciting task for the EBMT.

Pharmaceutical research has provided new, powerful tools for increasing both the safety and efficacy of our procedures, with an undeniable benefit to all our patients. A full and open collaboration with haematologists is needed in order to develop these evidence-based therapeutic strategies and to indicate the proper position of HSCT within them.

The concept of regenerative medicine has rapidly spread far and wide, both in the medical world and among the media. Despite the lack of strong evidence of efficacy, an increasing number of specialists have already launched clinical trials for the use of cellular progenitors for the treatment of non-haematological diseases. Bone marrow transplanters can provide these specialists with a unique heritage of experience in cellular collection, manipulation and delivery for clinical use; closer interaction with them might represent an unrepeatable opportunity for maintaining a key role in a field whose limits are still expanding, with huge potential in terms of clinical applications. EBMT has always been part of this background, creating a fundamental network for the best interaction between medical specialists, nurses, data-managers, cellular biologists and bio-engineers. The annual meeting has always reflected these accumulated experiences as part of an expanding EBMT heritage and our main aim is to maintain this standard of excellence. A special effort will be made to encourage the attendance of young scientists, in order to increase the basic scientific content of the meeting.

We are looking forward to hosting the meeting and to welcoming you to Florence in March 2008.

Alberto Bosi and Riccardo Saccardi

Source: EBMT.

Event Details

Date: 30 March – 2 April 2008
Location:
Fortezza da Basso, Florence, Italy
Further Information:
www.akm.ch/ebmt2008

Association Details

Address:
Executive Office, EBMT Secretariat
Villarroel 170
08036 Barcelona
Spain
E-mail: *admin@ebmt.org*
Tel.: *+34 93 454 9543*
Web: *www.ebmt.org*