



Chapter 5

Improving survival in patients with transformed B-cell non Hodgkin lymphoma: consolidation with ⁹⁰Yttrium ibritumomab tiuxetan-BEAM and autologous stem cell transplantation

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Recently, Eide et al. suggested an important role for high dose chemotherapy followed by autologous stem cell transplantation (AuSCT) in patients with histologically transformed B- cell non-Hodgkin's lymphoma (1) . However, this prospective study was conducted in the pre-rituximab era, therefore the results can not be translated to patients who would currently be treated with rituximab-containing chemotherapy regimens prior to AuSCT.

In our center a cohort of 32 patients with transformed B- cell non-Hodgkin's lymphoma has uniformly been treated with rituximab-containing reinduction therapy from 2006 onwards. Of these 32 patients 25% did not reach at least partial remission (PR, defined as a decrease in tumor diameter of at least 50% on CT scan).

We hereby present the results of the 24 patients proceeding to AuSCT following conditioning with ^{90}Y trium-ibritumomab tiuxetan-BEAM and AuSCT (Z-BEAM: ^{90}Y trium-ibritumomab tiuxetan=Zevalin[®] dose 0.4 mCi/kg (maximum 32 mCi) on day -15, carmustine 300 mg/m² on day -6, etoposide 100 mg/m² every 12 hours and cytarabine 200 mg/m² once daily on days -5 to -2 and melphalan 140 mg/m² on day -1.)

Histologic confirmation of transformation was defined as a diagnosis of diffuse large B cell lymphoma (DLBCL) in patients with either a previous (n=19) or simultaneous (n=5) histologic diagnosis of follicular lymphoma (FL) according to the WHO classification (2). Importantly, patients with DLBCL with indolent lymphoma in the bone marrow only were excluded as a superior outcome has been reported in these patients (3).

Similar to Eide's series, patients were eligible for AuSCT at the time of first diagnosis of transformation (n=15) or after subsequent relapse (n=9). Unlike in Eide's series, all 24 patients were treated with rituximab during the re-induction regimen. Eleven patients were treated with R-CHOP and 13 with R-DHAP. However, unexpectedly, the addition of rituximab to chemotherapy did not result in an improved response rate before AuSCT as compared to Eide (75% in our versus 72% in Eide's series). A possible explanation might be that pre-treatment with rituximab leads to rituximab resistance, as 15/24 patients had been treated with rituximab prior to re-induction therapy. Moreover, it can be hypothesized that histologic transformation itself confers rituximab resistance. Several mechanisms of rituximab resistance in lymphoma have been suggested, such as downregulation of CD20 expression and polymorphisms of FcR or complement components leading to diminished ADCC or CDC response. Lastly, up-regulation of signalling pathways and anti-apoptotic proteins has been implicated in causing

rituximab resistance. Unfortunately, specific mechanisms conferring resistance in transformed lymphoma are unknown (4).

Currently, the median follow up of all patients undergoing AuSCT after conditioning with Z-BEAM is 20 months (range 6-56). Five patients relapsed after respectively 6, 10, 11, 23 and 23 months. None of the patients who were rituximab-naïve before re-induction therapy have relapsed. Progression free survival at 2 years is 80% and overall survival is 100% until now.

Radioimmunotherapy did not lead to additional toxicity as compared to our previous experience with BEAM conditioning: TRM was 0%, median time until neutrophil recovery ($> 0,5 \times 10^9/l$) was 15 days and until platelet recovery ($>20 \times 10^9/l$) 15 days ($> 50 \times 10^9/l$: 24 days). Patients who experienced relapse following AuSCT had sufficient bone marrow capacity to undergo salvage treatment. They were rescued with either an allogeneic transplantation (n=2, 1 for a relapse of DLBCL, 1 for a relapse of FL) or chemoimmunotherapy (n=2, 1 for relapse of DLBCL, 1 for relapse of FL). One patient with relapsed FL did not require treatment yet.

We added radioimmunotherapy to AuSCT conditioning because it adds a new treatment modality in an inherently radiosensitive disease and allows escalation of radiation dose to tumor sites without additional toxicity to uninvolved organs. Indeed, the addition of ⁹⁰Yttrium-ibritumomab tiuxetan (Zevalin®) and ¹³¹Iodine tositumomab (Bexxar®) to high dose conditioning regimens for AuSCT has led to promising results (estimated 2-year OS of 65-85%) in high risk NHL patients. However, these studies comprised only a few transformed lymphoma patients (total n=15, ref 5-7). Our series is the largest consisting of transformed lymphoma patients only, who were uniformly treated with Z-BEAM and AuSCT. The follow up is still short, but importantly, the survival rate of 100% at 2 years compares favourably to the 2-year overall survival of 73% reported by Eide who performed AuSCT without the addition of radioimmunotherapy .

Although it is still unclear whether patients who respond well to (re)induction with chemoimmunotherapy benefit from upfront consolidation with AuSCT, both the study from Eide and our results strongly suggests an additive effect of consolidation with AuSCT on survival in this patient group. Moreover, we show an impressive outcome by the addition of radioimmunotherapy with ⁹⁰Yttrium-ibritumomab tiuxetan reaching a 2-year PFS of 80% (Eide 50%) and a 2-year OS of 100% (Eide 73%) Unfortunately, the superiority of consolidation with Z-BEAM and AuSCT over consolidation with BEAM



and AuSCT or rituximab-based chemotherapy only is unlikely to ever be substantiated by a randomized controlled trial, considering the low incidence of transformed B cell NHL. However, it is important to realize that the outcome we here describe in patients being treated with Z-BEAM compares favourably with the 5 year OS of 57% in the study of Al Tourah using rituximab-based chemotherapy only (8). Certainly, when taking into account that these patients were all rituximab-naïve and that PFS and OS were 100% on last follow up in our rituximab-naïve patients. In addition, when comparing our data to Eide, addition of rituximab to induction chemotherapy did not increase response rate, highlighting the need for radioimmunotherapy.

Although not compared head to head, our data strongly support the incorporation of radioimmunotherapy in the treatment of patients with transformed B cell non Hodgkin's lymphoma.

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