"Focus on…" session: high-dose chemotherapy

098 THE NUMBER OF PREVIOUS TREATMENT LINES HAS NO IMPACT ON THE OUTCOME AFTER HIGH-DOSE THERAPY WITH AUTOLOGOUS STEM CELL RESCUE WITH BEAM FOR RELAPSED FOLLICULAR LYMPHOMA

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Background: The role of high-dose therapy with autologous stem cell rescue (HDT-ASCR) remains a major challenge in the management of patients (pts) with follicular lymphoma (FL), particularly in view of the undoubted clinical impact of rituximab and the advent of new therapeutic options such as reduced-intensity conditioning allotransplants. It was suggested that HDT-ASCR should be used not later than at 2nd response given the relatively high incidence of secondary myelodysplasia/acute myelogenous leukaemia (sMDS/AML) after using cyclophosphamide/total body irradiation (Cy-TBI) in heavily pretreated pts. However, it is not known if the number of previous therapy lines also influences prognosis in pts treated with BEAM for relapsed FL. This is currently of special relevance to decide the best timing for this therapy as it is pts who did not receive 1st line immunochemotherapy for FL that are presenting with recurrent disease.

Patients: From 1997 to 2008, 80 pts (41M/39F; median age: 51 yrs, range: 31-67), including 30 with transformed FL (tFL), received HDT-ASCR with BEAM for relapsed FL at our centre.

Results: The median time from diagnosis to HDT was 41 months (range: 4-165). The median number of previous treatment lines was 3, 61% of the pts having received >3. Thirty-eight pts (49%) received rituximab before HDT (only in 1 case as part of the 1st line therapy, in 28 as part of the salvage therapy before BEAM and in 4 as part of the HDT). There was a trend for a higher use of rituximab before BEAM in pts with FL (56%) in comparison with those with tFL (33%, p=0.05). After a median follow-up of 76 months (range: 14-160), 2 pts developed sMDS/AML. Five-year overall survival (OS) was 71% and progression-free survival (PFS) 44%. There were no differences in PFS or OS according to the number of previous treatment lines or episodes of disease. Likewise, histology at relapse did not impact on PFS or OS. Comparison with a historical control of pts treated with Cy-TBI revealed no significant differences in PFS or OS.

Conclusions: deferring HDT with BEAM until 3rd response does not impair OS in pts with FL.

		5-yr PFS	p-value	5-yr OS	p-value
Histology	FL (50)	43%	0.5	75%	0.13
	tFL (30)	45%		63%	
Episodes	1-2 (58)	47%	0.4	74%	0.11
	>=3 (22)	33%		61%	
Treatment lines	1-2 (31)	49%	0.5	79%	0.11
	>=3 (49)	41%		65%	
Prior rituximab	Yes (38)	50%	0.2	69%	0.6
	No (42)	40%		71%	
Conditioning regimen	Cy-TBI (132)	59%	0.06	65%	0.36
	BEAM (80)	44%		71%	

099 AUTOLOGOUS AND ALLOGENEIC STEM CELL TRANSPLANTATION FOR TRANSFORMED INDOLENT NON-HODGKIN LYMPHOMA: A REPORT OF THE CANADIAN BLOOD AND MARROW TRANSPLANT GROUP (CBMTG)

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Background: The outcome of patients with indolent non-Hodgkin lymphoma who have experienced transformation to an aggressive histology is poor despite current chemotherapy. The objective of this study was to determine whether autologous (AUTO) or allogeneic (ALLO) stem cell transplantation improve outcomes for these patients in the rituximab era.

Materials and Methods: This is a multicenter, retrospective cohort study of patients with biopsy-proven indolent B-cell non-Hodgkin lymphoma and simultaneous or subsequent biopsy-proven aggressive histology transformation, who were treated over the last 15 years at a participating CBMTG institution. Individual patient and disease characteristics, treatment and transplantation details, as well as outcomes were collected from each center and combined for analysis. A separate control group composed of cases with transformed lymphoma treated with conventional chemotherapy plus rituximab only, but not ALLO or AUTO, was identified using the BCCA Lymphoid Cancer database.

Results: A total of 375 patients were identified: 66 (18%) were treated with ALLO, 204 (54%) with AUTO, and 105 (28%) with chemotherapy. Median age at transformation was 45 (range 25-72) for ALLO patients, 53 (24-72) for AUTO, and 64 (30-87) for controls (p<0.001). Over 95% ALLO were myeloablative. The majority received 1 or 2 salvage chemotherapy regimens, which included rituximab in 52% ALLO, 59% AUTO, and 100% control patients. Compared to controls, patients eventually undergoing stem cell transplantation had improved 5-year post-transformation PFS (ALLO 47%, AUTO 48%, control 38%, p=0.033) but 5-year OS was similar (ALLO 49%, AUTO 56%, control 54%, p=0.276). Outcomes were similar following ALLO and AUTO, with 5-year post-transplant OS 46% vs. 50% (p=0.136) and PFS 46% vs. 48% (p=0.806). Transplant related mortality at 2 years was 32% for ALLO and 5% for AUTO.In patients undergoing ALLO, the addition of rituximab to salvage chemotherapy did not improve PFS or OS.In patients undergoing AUTO, the addition of rituximab to salvage chemotherapy improved both PFS (5y PFS 56% vs. 37%, p=0.007) and OS (5y OS 61% vs. 40%, p=0.015).

Conclusions: This analysis is the first large series to compare results of ALLO, AUTO and rituximab-based chemotherapy for TRIL. In this retrospective comparison, SCT appears to improve PFS though not OS over convention-dose chemotherapy. TRM was significantly greater in ALLO patients although OS was not statistically different. The addition of rituximab to salvage chemotherapy improves PFS and OS for patients who undergo AUTO, but not ALLO. Relapse and transplant-related mortality remain significant problems in this patient population. Prospective trials will be required to demonstrate the optimal therapy for this aggressive NHL.

100 AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) AS UPFRONT OR SALVAGE THERAPY FOR NON-CUTANEOUS T CELL LYMPHOMA (TCL): THE M.D. ANDERSON CANCER CENTER (MDACC) EXPERIENCE

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Background: Despite the advent of novel agents, outcomes of TCL with conventional chemotherapy are poor. We have previously reported encouraging results with ASCT (Rodriguez J, J Clin Oncol, 2001). Herein, we report our long-term experience in 126 patients (pts).

Patients and Methods: This is a retrospective analysis of TCL pts treated at our institution between 1986 and 2009. Median age was 49 years (range, 18 to 75), and 65% were males. Histologies included *1)* peripheral t-cell lymphoma not otherwise specified (PTCL-NOS=42), *2)* anaplastic large cell lymphoma (ALCL=47) of which 9 pts were ALK(+), *3)* angioimmunoblastic (AILT=15,), *4)* NK cell lymphomas (N=6,), Hepatosplenic TCL (HS-TCL=6,), others (n=10,).

Results: At transplant, 33% were in first remission (CR1), 51% had chemosensitive relapse, 16% had refractory disease. Most pts received BEAM or BEAM like (82%). With a median follow-up time of 39 months in surviving pts, actuarial overall survival (OS) and progression-free-survival (PFS) estimates were 39 %(95% CI,28-50), and 30%(95% CI 20-41)

Treatment related mortality (3 months) rate was 3%. Pts who received ASCT in CR1 had the best outcome regardless of histology. The 4-year OS and PFS rates for CR1 pts were 87% (95% CI 67-95), and 67% (95% CI 47-81), respectively, which compared favorably (p>0.05) to the pts transplanted in chemosensitive relapse (4-year OS and PFS rates of39% (95% CI 26-53), and 36% (95% CI 23-48), and to those who had refractory disease (4-year OS and PFS rates of24% and 15%. Risk factors for OS and

PFS were evaluated within the largest histological subgroups in our study (PTCL-NOS (n=42) and ACLC (n=40)). Among these 82 pts, age >50 years (p= 0.03), IPI of >1 (p=0.003), Prognostic Index for T-cell lymphoma (PIT) of >1 (p=0.008), prior exposure to >3 chemotherapy lines (p= 0.01), and refractory disease (p=0.01) were associated with a significantly worse OS. The same factors, with the exception of age, were associated with significantly worse PFS. We were not able to detect any difference in outcomes between ALK(-) and ALK (+) ACLC. The 4 yr PFS of pts with the various histologies were PTCL-NOS=48%, ALCL=38%, AILT=37%, NK TCL=67% and T-LBL=14%.

Conclusion: This is the largest single institution analysis to investigate the role of ASCT for TCL. Our review demonstrates that ASCT can produce induce long-term remissions in TCL pts when incorporated in an upfront strategy. Innovative strategies are instead needed for pts with relapsed disease.

101 LONG TERM DISEASE CONTROL AND OVERALL SURVIVAL AFTER EARLY DOSE INTENSIFICATION IN T-NHL DEPEND ON SPECIFIC ENTITIES

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In contrast to B-NHL, no standard therapy for T cell lymphoma exist so far. Nevertheless, CHOP-like therapies were used due to known effects in B cell lymphoma. In addition, the impact of dose intensification and first line high-dose therapy with autologous stem cell transplantation (ASCT) is even less well defined. Here we present longterm follow up data from a single center experience with early dose intensification and first line high dose therapy/ASCT in subsequently treated patients with T-NHL. From 12/1986-07/2009 a total of 113 patients newly diagnosed with T-NHL were treated at the University Hospital Freiburg. The median age of the entire cohort was 56 years (range: 18-90) and the specific diagnoses included: PTCL,NOS (n=46), AILD (n=25), ALCL,ALK negativ (n=26), ALCL, ALK positiv (n=7), and others (n=11). Initial chemotherapy included anthracycline based/CHOP-like regimens in most of the cases. If no complete remission could be achieved by CHOP-like protocols only, early intensification mainly with VIPE/VCPE (epirubicin 50mg/m^2, etoposide 500mg/m^2, cisplatin 50mg/m^2, ifosfamide 4g/m^{2}or cyclophosphamide 1350mg/m^2) or DHAP regimens and primary autologous stem cell transplantation after BEAM (66.6% of all ASCT) was initiated. After a median follow-up of 59.7 months the 5-year overall survival (OS) of the entire group was 53,1%. In detail, 5y-OS for specific diagnoses were 62,8% for PTCL,NOS, 45,1% for AILD and 48,6% for ALCL, ALK neg.. Among those, patients with PTCL,NOS frequently (32/46=69,6%) presented with advanced (stage III/IV) disease. With the mentioned therapeutic approach, 31 (68,9%) PTCL,NOS patients experienced a first complete remission (CR1) after induction therapy. Primary high-dose therapy with ASCT did not result in a significantly improved 5-OS (64,6% versus 60,1%, p=0.9). Nevertheless, cumulative 5 year relapse rate (RR) for patients in CR1 was significantly worse for patients not undergoing autologous transplantation (68,0% versus 15,6%, p=0,0046). Very similar results were observed in patients with ALCL, ALK neg.: 5y-OS with/without primary ASCT was 60,8% versus 38,5% (p=0.64); cumulative 5-year RR for patients in CR1 was 11,1% versus 40,0% (p=0.26), respectively. In contrast, in patients with AILD primary therapy with ASCT resulted in a significantly improved 5-year OS (87,5% versus 21,8%, p=0.01). These longterm follow up data show that chemotherapy with primary high dose intensification in patients with T-NHL results in improved disease control. Nevertheless, the effect depends on the underlying specific T cell disease.

102 UPDATE OF THE NORDIC MCL2 TRIAL UPDATE: 10-YEAR SURVIVAL 57% FOLLOWING INTENSIVE IMMUNOCHEMOTHERAPY AND ASCT, BUT LATE RELAPSES DO OCCUR

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Introduction: The concept of Mantle cell lymphoma (MCL) as an incurable disease has been questioned. In spite of the high risk characteristics of the 160 patients of the Nordic MCL2 Trial of first-line intensive immunochemotherapy followed by BEAM and autologous stem cell transplantation (ASCT) (31% with Ki-67 expression ≥29 and 19% blastoid/pleomorphic) the first results based on 3 years median observation were encouraging, with no relapse after 5 years[1]. Here we present an update after median 6 years observation time.

Results: The overall survival (OS) is now 57% at 10 years, but a continuous pattern of relapse has emerged, leading to 10-year event-free survival (EFS) and response duration of 42% and 54%, respectively. The MCL International prognostic index (MIPI)[2,3] remained highly predictive of all endpoints. By the MIPI-biological, incorporating Ki-67, no events have occurred in the low-risk group later than 3 years after the start of treatment, leading to a 10-year EFS of 75% compared to 25% in the high-risk patients. Molecular remission duration < 1 year was associated with a much shorter clinical response duration (median 2.5 years) than > 1 year. In multivariate analysis of EFS, performance status, Ki-67 expression, age and white blood cell count had independent significance.

Conclusion: A 10-year survival of 58% in aggressive MCL is highly encouraging, but late relapses warrant trials to improve treatment of MIPI high-risk patients and of maintenance treatment.

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103 TOTAL BODY IRRADIATION (TBI) IN THE CONDITIONING REGIMEN OF AUTOLOGOUS STEM CELL TRANSPLANTATION REDUCES THE RISK OF RELAPSE OF MANTLE CELL LYMPHOMA TRANSPLANTED IN PARTIAL REMISSION: A RETROSPECTIVE STUDY FROM THE LYMPHOMA WORKING PARTY OF THE EBMT

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The use of TBI in the conditioning of ASCT for MCL is decreasing despite the high sensitivity of MCL cells to radiotherapy. In this retrospective study from the EBMT registry, we access the role of TBI in the conditioning of ASCT for MCL. We analyzed 488 patients who underwent an ASCT between 2000 and 2008 in complete or first partial remission (CR/PR1) and who were registered within the EBMT data-base with complete MedB forms available. Pre-transplant characteristics of patients were: median age of 55 years (range 29-65), 93% presented with disease stage III/IV, 75% had received Rituximab (R) and/or HD-Cyt. At transplant, 333 patients (68%) were in CR and 155 (32%) in PR1. Conditioning regimen for ASCT included TBI in 160 patients (32.6 %) and a BEAM-based chemotherapy in 92% of the remaining 328 patients. With a median follow-up of 28.5 months, median overall and progression free survival (OS and PFS) of all patients were 101 and 57 months, respectively. Disease status at transplant appeared as the most potent predictive factor of PFS (HR= 1.59, 95%CI 1.16-2.20, p=0.004) and relapse incidence (RI) (HR=1.62, 95%CI 1.14 -2.30, p= 0.0065) but had no impact on OS. We found that the use of R+HD-Cyt before ASCT was associated with a higher CR rate (OR with both drugs versus without = 1.76, 95% CI 1.05-2.95, p=0.03). Since we found a significant interaction between the use of TBI and disease status on the incidence of relapse, all further analysis were stratified on disease status at transplant. OS, PFS and RI of patients transplanted in CR were not impacted by the use of TBI. In contrast, patients transplanted in PR1 with TBI had a prolonged PFS as compared to those transplanted without TBI (median PFS 50 months versus 33 months, respectively, p=0.14). The use of TBI in PR1 patients was the only predictive factor of reduced relapse incidence in multivariate analysis (HR=0.524, 95% CI 0.284-0.966, p=0.038). In conclusion, this retrospective series of autografted MCL points out the need for improving CR rates after induction chemotherapy in this disease. However, in patients who can not achieve a better response than PR at transplant, the use of TBI or other radiotherapy-based conditioning regimen should still be considered.