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Long-term results of reduced-intensity conditioning followed by allogeneic transplantation in relapsed lymphomas

Patients affected by lymphomas relapsing after autografting or with refractory disease are often candidates for reduced-intensity conditioning (RIC) regimens followed by allogeneic stem cell transplantation (SCT). All the published series reported a 2 year progression free-survival of 60%, 40% and 30% in indolent, aggressive and Hodgkin's Lymphoma (HL), respectively. However, the long-term efficacy and toxicity of this strategy is still unknown. We report herein the long-term results of a prospective multicenter phase II trial at median follow-up of 5 years. A total of 194 relapsed/refractory lymphomas received the same RIC regimen (thiotepa, cyclophosphamide and fludarabine) followed by allo-SCT from matched sibling donors. Histologies were non-Hodgkin's lymphomas (NHL) [indolent (LG-NHL, n=68), including follicular lymphoma (FL, n=29), chronic lymphocytic leukemia (CLL, n=35), other (n=4); aggressive (HG-NHL, n=87), including B-cell phenotype (n=43); T-cell phenotype (n=28), mantle cell lymphoma (MCL, n=16)] and Hodgkin's lymphoma (HL, n=39); 133 (68%) of 194 patients (pts) had chemosensitive disease and 100 (52%) of 194 failed a previous autologous SCT. Median follow-up was 60 months (range, 15-113). At last follow-up, 116 pts are alive (59%) and 78 died from any cause [n=47 for disease progression, n= 30 for non-relapse mortality (NRM), n=1 not assessable]. The 5-year overall survival (OS) and progression-free survival (PFS) were 62% and 70% for LG-NHL, 61% and 59% for HG-NHL, and 42% and 19% for HL, respectively. The median time to relapse was 7 (range, 2-30), 4.5 (range, 1.6-33), and 5.5 (range, 0.4-42) months for LG-NHL, HG-NHL, and HL respectively. Pts with chemosensitive disease at allo-SCT had a 5-year OS and PFS of 69% and 61%, while those with refractory disease had a 5-year OS and PFS of 35% and 45%, respectively.

Disease status before allo-SCT significantly influenced long-term outcome in HG-NHL and HL [chemosensitive versus chemorefractory: 73% versus 32% (p<0.001) for HG-NHL; 64% versus 0% (p<0.002) for HL], but not in LG-NHL [chemosensitive versus chemorefractory: 65% versus 56% (p=0.43)], probably related to a stronger graft-versus-lymphoma effect in LG-NHL. Although, the 5-year PFS was significantly different between FL and CLL (85% versus 58%, p=0.04), the 5-year OS was not (71% *vs.* 56%, p=0.13). The OS and PFS were not significantly different between aggressive lymphoma of B- and T-cell origin [5 year OS: 67% versus 55%

(p=0.51); 5 year PFS: 63% versus 57% (p=0.45)], respectively. Overall, 30 pts died of transplant-related causes (n=13 infections, n=12 GVHD, n=1 VOD, n=2 MOF and n=2 second tumor) at median follow-up of 6 months (range, 0.8-60) with a 5-year cumulative incidence of 15%. The incidence of acute and chronic GVHD were 34% and 55%, respectively. Interestingly, only 27 of 116 (23%) pts are still receiving immune suppressive therapy. The incidence of second tumors was 2% in the pts surviving more than 6 months after allo-SCT (n=2 alive, n=2 death).

In conclusion, our long-term data with a median 5-year follow-up shows that: (i) pts with relapsed lymphomas could achieve long-term remission and are probably cured; (ii) non-relapse mortality is rather low; (iii) disease status before transplant is a critical determinant for long-term outcome.