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S249 SELECTIVE JAK2/IRAK1/ACVR1 INHIBITOR PACRITINIB BEFORE REDUCED-INTENSITY CONDITIONING ALLOGENEIC STEM CELL TRANSPLANTATION IN MYELOFIBROSIS: FINAL ANALYSIS OF THE PHASE II HOVON-134 TRIAL

Topic: SCT clinical

Ruben Van Dijck*[1], Ron Van Der Holt[1], Ellen Meijer[2], Timothy Devos[3], Mette Hazenberg[2], Marjolein Van Der Poel[4], Dimitri Breems[5], Lien Deleu[6], Michel Schaap[7], Peter André Willem Te Boekhorst[1]

[1]Hematology, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Hematology, Amsterdam University Medical Center, Amsterdam, Netherlands; [3]Hematology, Leuven University Hospitals, Leuven, Belgium; [4]Hematology , Maastricht University Medical Center, Maastricht, Netherlands; [5]Hematology, Ziekenhuisnetwerk Antwerpen, Antwerpen, Belgium; [6]Hematology, Az Delta, Roeselare, Belgium; [7]Hematology, Radboud University Medical Center, Nijmegen, Netherlands

Background:

Allogeneic stem cell transplantation (alloSCT) remains the only curative treatment option for patients with myelofibrosis (MF). The selective JAK2/IRAK1/ACVR1 inhibitor pacritinib (PAC) is effective in reducing spleen size and MF-related symptoms. We hypothesize that, because of its differential kinome profile, PAC pre-treatment before alloSCT improves outcomes in MF patients, potentially by diminishing NF-kB regulated inflammatory cytokine and graft-versus-host disease (GVHD) and by reducing the rate of primary (PGF) and secondary graft failure (SGF).

Aims:

Primary objective was to investigate the effect of pre-transplant PAC on the outcomes of alloSCT with uniform conditioning regimen in MF. Primary endpoint was the proportion of patients with a failure (PGF, SGF, grade 3-4 acute GVHD, and death of any cause) within 180 days post-transplant. Secondary endpoints included the safety profile of PAC, response rate, relapse and non-relapse mortality (NRM).

Methods:

MF patients (primary, post-ET, post-PV) aged 18-70 years with an intermediate-2 or high risk DIPSS Plus score and platelet count ≥25x109/L were included to receive 3-4 cycles of PAC (BID 200 mg, 1 cycle 28 days, stopped one day before conditioning) before proceeding to alloSCT with busulfan, fludarabine and anti-T lymphocyte globulin (Grafalon-Neovii) conditioning. Ruxolitinib treatment was allowed if it was stopped before initiation of PAC. Patients with disease progression or without a suitable HLA-identical sibling donor or 10/10 matched unrelated donor went off protocol before alloSCT. GVHD prophylaxis consisted of mycophenolate mofetil (day 0 to 28) and cyclosporine A (day -3 to 100, followed by tapering).

Results:

61 eligible patients (64% JAK2 mutated and 62% JAK2-inhibitor naïve) were included, of whom 38 (62%) proceeded to alloSCT according to protocol and completed a minimum of 6-month post-transplant follow-up. 23 (38%) patients went off protocol before alloSCT (adverse events, not PAC related [n=4] and possibly PAC related [n=2], progressive disease [n=1], death [n=2], no suitable donor [n=7] or other reason [n=7]), of whom 2 (9%) continued PAC in follow-up and 20 (87%) still received an alloSCT (off protocol). Of the transplanted patients within the protocol, 6 (16%) had an event for the primary endpoint: one (3%) SGF and 5 (13%) deaths (all NRM). Three patients received a stem cell boost or donor lymphocyte infusion before an event at day 180 could have occurred. Figure 1 shows overall survival from inclusion and GVHD-free, relapse-free survival post-transplant

after a median follow-up of 32.9 months (range, 9.4-52.7). The 1-year cumulative incidence of acute GVHD grade 3 or 4 was 3%, while moderate and severe chronic GVHD were 38% and 24% respectively. 3-4 cycles of PAC resulted in a symptom response (>50% reduction in MPN-SAF-TSS) before alloSCT in 31% of patients, and a reduction of spleen size below the lower costal margin from median 9 cm (interquartile range [IQR], 5-14) to median 4 cm (IQR, 3-10). PAC dose modification for hematological and gastro-intestinal toxicity was necessary in 9 (15%) and 2 (3%) patients, respectively; 39 (61%) patients were able to tolerate the 200 mg BID dose throughout the treatment period.

Summary/Conclusion:

Treatment with the JAK2/IRAK1/ACVR1 inhibitor PAC at a 200 mg BID dose is a safe and effective pre-transplant strategy for patients with MF. In this phase II HOVON-134 trial, we have shown a low incidence of 6-month post-transplant failure (including PGF, SGF, grade 3-4 acute GVHD and death) compared with historical controls.