731. CLINICAL AUTOLOGOUS TRANSPLANTATION: RESULTS: MULTIPLE MYELOMA: UPFRONT AUTOLOGOUS TRANSPLANTATION | NOVEMBER 29, 2018

Carfilzomib-Lenalidomide-Dexamethasone (KRd) Induction-Autologous Transplant (ASCT)-Krd Consolidation Vs KRd 12 Cycles Vs Carfilzomib-Cyclophosphamide-Dexamethasone (KCd) Induction-ASCT-KCd Consolidation: Analysis of the Randomized Forte Trial in Newly Diagnosed Multiple Myeloma (NDMM)

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Abstract

Background: Proteasome inhibitor (PI)-based induction and consolidation proved to be effective in newly diagnosed multiple myeloma (NDMM) patients (pts) eligible for melphalan 200 mg/m^2-autologous stem cell transplant (MEL200-ASCT). High response rates have been reported with the second-generation PI Carfilzomib in combination with Lenalidomide-dexamethasone (KRd) or Cyclophosphamide-dexamethasone (KCd).

Aims: The primary aim was to evaluate the efficacy and safety of KRd induction-ASCT-KRd consolidation (KRd-ASCT-KRd) vs 12 cycles of KRd (KRd12) vs KCd induction-ASCT-KCd consolidation (KCd-ASCT-KCd).

Methods: NDMM pts ≤65 years were randomized (1:1:1; stratification ISS and age) to: KRd-ASCT-KRd: 4 28-day cycles with KRd induction (Carfilzomib 20/36 mg/m^2 IV days 1,2,8,9,15,16; Lenalidomide

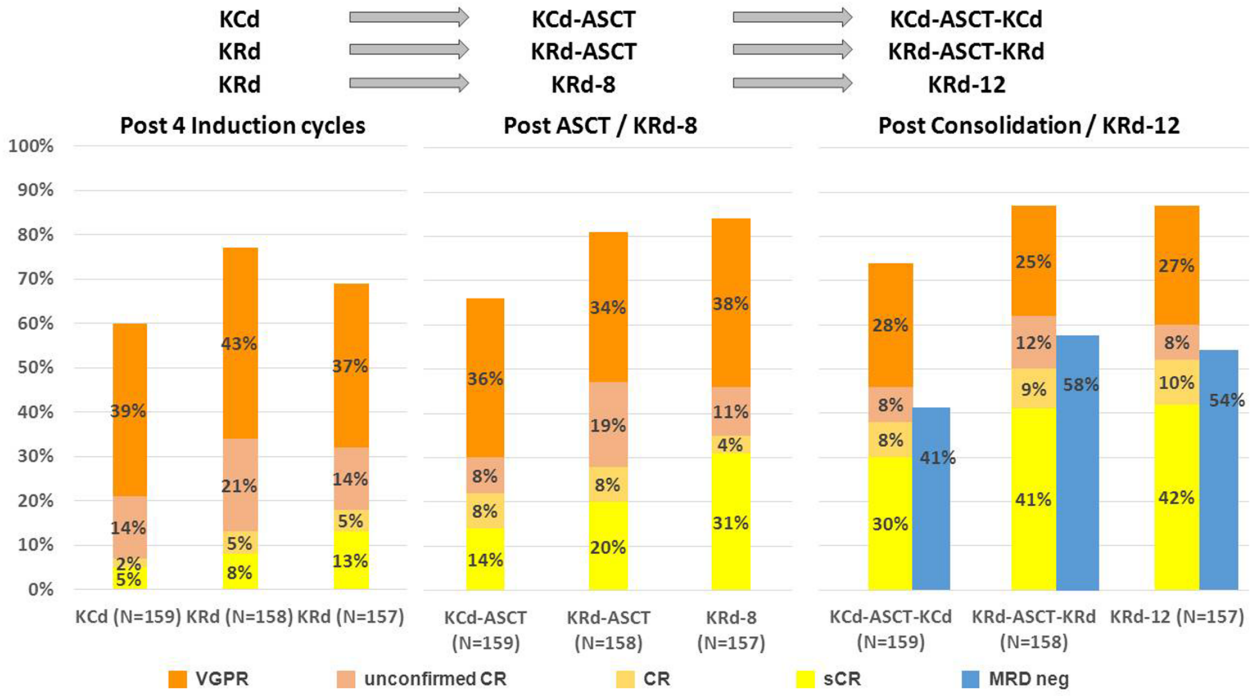
25 mg days 1-21; dexamethasone 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KRd consolidation cycles; KRd12: 12 KRd cycles; KCd-ASCT-KCd: 4 28-day induction cycles with KCd (Carfilzomib 20/36 mg/m^2 IV days 1,2,8,9,15,16; Cyclophosphamide 300 mg/m^2 days 1,8,15; dexamethasone 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KCd consolidation cycles. Thereafter, pts were randomized to maintenance with Lenalidomide alone or plus Carfilzomib. Centralized minimal residual disease (MRD) evaluation - 8-color second generation flow cytometry, sensitivity 10^{-5} - was performed in pts achieving ≥very good partial response (VGPR). Endpoints were pre-maintenance stringent complete response (sCR) and MRD negativity in intention-to-treat (ITT) analysis. Data cut-off was May 30, 2018.

Results: 474 NDMM pts were randomized (KRd-ASCT-KRd, n=158; KRd12, n=157; KCd-ASCT-KCd, n=159) and analyzed. Pts characteristics were well balanced. Median follow-up was 20 months. Depth of response improved during treatment (*Figure*). By ITT analysis, rates of pre-maintenance sCR was similar between KRd-ASCT-KRd (41%) and KRd12 (42%), and significantly higher than with KCd-ASCT-KCd (30%; P value KRd-ASCT-KRd vs KCd-ASCT-KCd=0.047; P value KRd12 vs KCd-ASCT-KCd=0.028). Similarly, rate of ≥CR was 49% with KRd-ASCT-KRd, 52% with KRd12 and 38% with KCd-ASCT-KCd (P value KRd-ASCT-KRd vs KCd-ASCT-KCd=0.041; P value KRd12 vs KCd-ASCT-KCd=0.014) and rate of ≥CR+unconfirmed CR (missing immunofixation confirmation) raised to 60% vs 63% vs 46% in the 3 groups, respectively; rate of ≥VGPR was 88% with KRd-ASCT-KRd, 86% with KRd12 and 74% with KCd-ASCT-KCd (P value KRd-ASCT-KRd vs KCd-ASCT-KCd=0.002; P value KRd12 vs KCd-ASCT-KCd=0.008). In multivariate analysis, the main factor affecting probability of achieving ≥VGPR, ≥CR or sCR was treatment with KRd-ASCT-KRd or KRd12 vs KCd, with no significant impact of ISS Stage or FISH abnormalities. In ITT analysis (MRD missing [31/395 VGPR pts, 8%] and <VGPR were considered as MRD positive), MRD negativity was again similar with KRd-ASCT-KRd (58%) and KRd12 (54%) and significantly higher than with KCd-ASCT-KCd (41%; P value KRd-ASCT-KRd vs KCd-ASCT-KCd=0.004; P value KRd12 vs KCd-ASCT-KCd=0.023); 82% vs 78% vs 88% of pts in the 3 groups, respectively, could maintain extended MRD negative status with 2 MRD negative results obtained apart ≥6 months (either pre-ASCT and post consolidation or post consolidation and during maintenance). During treatment (excluding ASCT) the most frequent grade 3-4 AEs were neutropenia (KRd-ASCT-KRd 20%, KRd12 10%, KCd-ASCT-KCd 16%), thrombocytopenia (KRd-ASCT-KRd 15%, KRd12 8%, KCd-ASCT-KCd 13%) and infections (KRd-ASCT-KRd 14%, KRd12 12%, KCd-ASCT-KCd 13%). Grade 3-4 dermatologic AEs (KRd-ASCT-KRd, 5% with KRd12 12%, KCd-ASCT-KCd 1%), increase in liver enzymes (KRd-ASCT-KRd 9%, KRd12 10%, KCd-ASCT-KCd 1%) and hypertension (KRd-ASCT-KRd 3%, KRd12 8%, KCd-ASCT-KCd 3%) were more frequent with KRd12. Rates of grade 3-4 cardiac AEs (KRd-ASCT-KRd 3%, KRd12

2%, KCd-ASCT-KCd 4%) and thrombosis (KRd-ASCT-KRd 1%, KRd12 2%, KCd-ASCT-KCd 2%) were below 5% in all arms. Discontinuation for AEs was similar in the 3 arms (KRd-ASCT-KRd 6%, KRd12 8%, KCd-ASCT-KCd 7%).

Conclusions: Rates of MRD negativity, sCR, ≥CR, ≥VGPR were significantly higher with KRd-ASCT-KRd and KRd12 vs KCd. At present, no differences in MRD and overall best response (sCR, ≥CR, ≥VGPR) were noticed between KRd-ASCT-KRd and KRd12; longer follow-up is needed to evaluate survival. Treatment was well tolerated. Updated data will be presented at the meeting.

Figure.



Disclosures

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* Asterisk with author names denotes non-ASH members.