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Continuous therapy in standard- and high-risk newly-diagnosed multiple myeloma: A pooled analysis of 2 phase III trials

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ABSTRACT

Background: Risk-adapted therapy is a common strategy in curable hematologic malignancies: standard-risk patients receive less intensive treatment, whereas high-risk patients require a more intensive approach. This model cannot be applied in multiple myeloma (MM), which is still incurable.

Continuous treatment (CT) is a key strategy for MM treatment, since it improves duration of remission. However, the role of CT according to standard- or high-risk baseline prognosis remains an open question.

Patients and methods: We performed a pooled analysis of 2 phase III trials (GIMEMA-MM-03-05 and RV-MM-PI-209) that randomized patients to CT vs fixed-duration therapy (FDT).

Results: In the overall patient population (n = 550), CT improved progression-free survival1 (PFS1) (HR 0.54), PFS2 (HR 0.61) and overall survival (OS) (HR 0.71) vs FDT. CT improved PFS1 both in R-ISS I (HR 0.49) and R-ISS II/III patients (HR 0.55). Four-year PFS1 was 38% in R-ISS II/III patients receiving CT and 25% in R-ISS I patients receiving FDT, with similar trends for PFS2 and OS. High-risk patients benefited more from proteasome-inhibitor plus immunomodulatory-based CT than immunomodulatory alone.

Conclusion: Good prognosis patients receiving FDT lose their prognostic advantage over high-risk patients receiving CT and high-risk patients may benefit from more intensive maintenance including proteasome inhibitors and immunomodulators.

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1. Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder representing 1% of all cancers and 13% of all hematologic tumors (Howlader et al., 2013). The introduction of novel agents (thalidomide, bortezomib and lenalidomide) into clinical practice greatly improved the outcome of MM patients in the last decades (Kumar et al., 2008). Currently, treatment of newly-diagnosed MM (NDMM) patients is differentiated according to transplant-eligibility. One of the standards of care in transplant-ineligible patients is continuous therapy (CT) with lenalidomide plus low-dose dexamethasone (Rd) until progression (Facon et al., 2017). More recently, the addition of bortezomib to Rd proved to be superior to Rd alone as induction treatment in patients without an immediate intent to transplant (Durie et al., 2017). Of note, in this trial, both bortezomib-Rd and Rd induction arms were followed by Rd CT. Another standard of care is bortezomib-melphalan-prednisone (VMP) for 9 cycles.

CT with bortezomib has been also evaluated. In transplant-ineligible patients, bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT) maintenance showed a progression-free survival (PFS) and overall survival (OS) advantage over VMP with no maintenance (Palumbo et al., 2014a, 2010).

Again in transplant-ineligible NDMM patients, a Spanish phase III trial showed a remarkable median PFS of 35 months and a 5-year OS of 58% with bortezomib-prednisone or bortezomib-thalidomide maintenance after bortezomib-based induction (Mateos et al., 2012).

In transplant-eligible patients, an induction treatment with proteasome inhibitors plus immunomodulatory agents (IMiDs)/chemotherapy followed by high-dose melphalan and autologous stem-cell transplantation (ASCT) is the standard (Palumbo and Cavallo, 2012). Post-transplantation lenalidomide approximately doubled PFS in all randomized clinical trials performed so far, and a recent meta-analysis showed an advantage in OS as well (Attal et al., 2016, 2012; Jackson et al., 2016; McCarthy et al., 2012; Palumbo et al., 2014b). Post-transplantation maintenance with bortezomib has also been evaluated. In the phase III Hovon-65/GMMG-HD4 trial, bortezomib-based treatment before and after ASCT showed a PFS advantage compared with classical cytotoxic induction therapy followed by post-ASCT thalidomide maintenance (Goldschmidt et al., 2018). Of note, the negative prognostic effects on PFS and OS of deletion 17p13 and baseline renal impairment were abrogated in patients receiving bortezomib-based CT. In another phase III trial, post-ASCT maintenance with thalidomide-bortezomib showed a PFS advantage over interferon alpha-2b and thalidomide maintenance (Rosiñol et al., 2017).

The rationale of implementing CT in patient's care is to enhance the results of upfront induction/consolidation therapy, preventing or delaying tumor progression and eventually death. Although efficacy data about CT strongly support its use, there are still some unanswered key questions. In curable hematologic malignancies, risk-adapted therapy is commonly applied: standard-risk patients may be cured with less intensive and shorter duration of treatment, which can minimize the risk of drug-related adverse events; whereas high-risk patients require more intensive regimens. In MM, this model may not be applicable, since the disease is still incurable. The goal of this study was to dissect the role of CT in standard- and high-risk NDMM patients, to specifically evaluate if CT could be avoided in standard-risk patients.

2. Methods

2.1. Patients and treatment

We performed an individual patient data pooled analysis of two phase III clinical trials (GIMEMA-MM-03-05 and RV-MM-PI-209) coordinated by the same principal investigator, in which NDMM patients were randomly assigned to CT or fixed-duration therapy (FDT) with novel-agents (Table S1). The two studies were approved by the institutional review boards of each participating center and are registered at ClinicalTrials.gov. All patients provided written informed consent before entering the source trials. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Patient prognosis was defined according to the revised International Staging System (R-ISS), which combines the International Staging System (ISS), baseline cytogenetics and LDH (Palumbo et al., 2015a). FDT was defined as an upfront treatment (induction/consolidation) for up to 1 year, CT was defined as an upfront treatment (induction/consolidation) followed by maintenance lasting at least for 2 years. Both definitions are based upon an intention-to-treat (ITT) population. Details of the inclusion/exclusion criteria of the source studies have been previously published (Palumbo et al., 2014a, 2014b, 2010). A detailed description of the treatment is given in the Supplementary Appendix. Briefly, the GIMEMA-MM-03-05 trial included NDMM elderly ASCT-ineligible patients, who were randomized to receive 9 cycles of VMPT followed by 2 years of VT maintenance versus 9 cycles of VMP with no maintenance (Palumbo et al., 2014a, 2010). The RV-MM-PI-209 trial included NDMM ASCT-eligible patients, who received induction therapy with 4 cycles of Rd and then were randomized to consolidation with two courses of melphalan 200 mg/m^2 followed by ASCT (MEL200-ASCT) or six 28-day cycles of oral chemotherapy plus lenalidomide. In this trial, patients were also randomized to maintenance with lenalidomide versus no maintenance after consolidation (Palumbo et al., 2014b).

In both trials, the median follow-up time was > 4 years.

2.2. Statistical analysis

The primary endpoints were PFS1, PFS2 and OS in the ITT population eligible for CT vs FDT (detailed endpoints definition in the Supplementary Appendix) according to patients' baseline prognosis (R-ISS I-standard risk vs R-ISS II/III-high risk) (Palumbo et al., 2015a).

Data of the two trials were pooled together and analyzed. Patients enrolled but not eligible for CT vs FDT were excluded. Because patients were randomly assigned at study enrolment, to specifically assess the effect of CT we included all patients alive and progression-free after 10 months from random assignment, which corresponds to the average duration of induction/consolidation in the two trials (landmark analysis). Baseline R-ISS Stage assessment was based on the International Myeloma Working Group guidelines (Palumbo et al., 2015a).

Time-to-event endpoints were calculated from the time of inclusion in the landmark analysis and were analyzed using the Kaplan–Meier method. Treatment groups were compared with the log-rank test. Stratified log-rank test was used for comparisons within groups. The Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and the 95% confidence intervals (CIs) for the main comparisons; the Grambsch and Therneau test was used for testing the proportional hazard assumption. To account for potential confounders, the Cox models for the comparison CT vs FDT were adjusted for the trial effect, best response pre-maintenance, R-ISS stage and Easter Oncology Cooperative Group performance status (ECOG-PS). Subgroup analyses were performed using interaction terms between treatment and each of the covariates included in the Cox model. All HRs were estimated with their 95% confidence intervals (95% CI) and two-sided p-values.

Data were analyzed using SAS software (Version 8.2) and R (Version 3.1.1).