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Case report

Patterns of relapse and outcome of elderly multiple myeloma patients treated as front-line therapy with novel agents combinations ☆

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ABSTRACT

We report the characteristics of relapse, treatment response, and outcomes of 145 elderly patients with multiple myeloma in first relapse after front-line treatment with VMP or VTP. Reappearance of CRAB symptoms (113 patients) and more aggressive forms of disease (32 patients) were the most common patterns of relapse. After second-line therapy, 75 (51.7%) patients achieved at partial response and 16 (11%) complete response (CR). Overall survival was longer among patients receiving VMP as front-line induction (21.4 vs. 14.4 months, $P=0.037$), in patients achieving CR (28.3 vs. 14.8 months; $P=0.04$), and in patients without aggressive relapse (28.6 vs. 7.6 months; $P=0.0007$).

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1. Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and presents primarily in elderly patients, with a median age at manifestation of approximately 72 years in Europe [1,2]. The number of older patients with this disease is expected to rise over time as a consequence of the increased life expectancy of the normal population. In recent years, the introduction of novel agents such as thalidomide, lenalidomide, and the proteasome inhibitor bortezomib has changed the management of elderly myeloma patients and extended overall survival (OS) times in all age categories supporting the use of modern anti-myeloma therapy independent of age [3,4].

Despite this improvement in OS, MM remains incurable and the majority of patients ultimately relapses and require further therapy. Thus, knowledge of relapse patterns and management of relapsed disease is a critical aspect of MM treatment and an

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important area of ongoing research [5]. Moreover, the optimal sequence or combination of post relapse therapeutic strategies remains unclear, and information is needed on the efficacy of each treatment, especially in the second-line setting. In this regard, previous reports focused on patients relapsing after conventional chemotherapy or autologous stem cell transplantation [6–8], and such data on elderly patients in the era of novel therapies is limited.

With the aim of understanding whether exposure to novel agents based induction affected the efficacy of subsequent therapy we have conducted a post hoc subgroup analysis of 145 patients with MM in first symptomatic relapse previously included in the GEM2005MAS65 Spanish trial. Front-line therapy in this trial consisted of bortezomib, melphalan, and prednisone (VMP) or bortezomib, thalidomide, and prednisone (VTP).

2. Methods

The Spanish GEM05MAS65 trial lasted from March, 2006 to October, 2008 and included 260 patients from 63 Spanish centers. At study entry, every patient was aged 65 years or older and had newly diagnosed, untreated, symptomatic, measurable MM. These patients had received a homogeneous induction treatment consisting either in bortezomib, melphalan, and prednisone (VMP) or bortezomib, thalidomide, and prednisone (VTP). Design of the study and treatment arms have been extensively described elsewhere [9–11]. Briefly, patients were upfront randomized to receive induction with 6 cycles of VMP or VTP. One hundred and seventy eight patients completed the six induction cycles and were randomly assigned to maintenance therapy with bortezomib plus prednisone (VP, $n=87$) or bortezomib plus thalidomide (VT, $n=91$) [9–11].

As of December 31st, 2013, 164 patients of the GEM05MAS65 trial had suffered disease relapse or progression. One hundred and forty-five (88%) received second line therapy and form the basis of this study. Nineteen (12%) patients were excluded due to asymptomatic relapse at time of analysis (11 patients), no data at relapse (6 patients) and early death after relapse without receiving second-line therapy (2 patients) (Fig. 1).

2.1. Definitions

Response to salvage therapy and clinical relapses were evaluated according to the International Myeloma Working Group (IMWG) criteria, but near complete response (nCR) category, as defined by disappearance of monoclonal protein at routine electrophoresis but positive immunofixation, was added [12]. Biological relapse was defined as progressive, asymptomatic increase in M-component and clinical relapse was defined as evidence of organ dysfunction and reappearance of CRAB features. For the purpose of this article, aggressive relapse was considered when the patient presented extramedullary plasmacytomas, plasma cell leukemia or severe renal failure requiring hemodialysis at time of relapse.

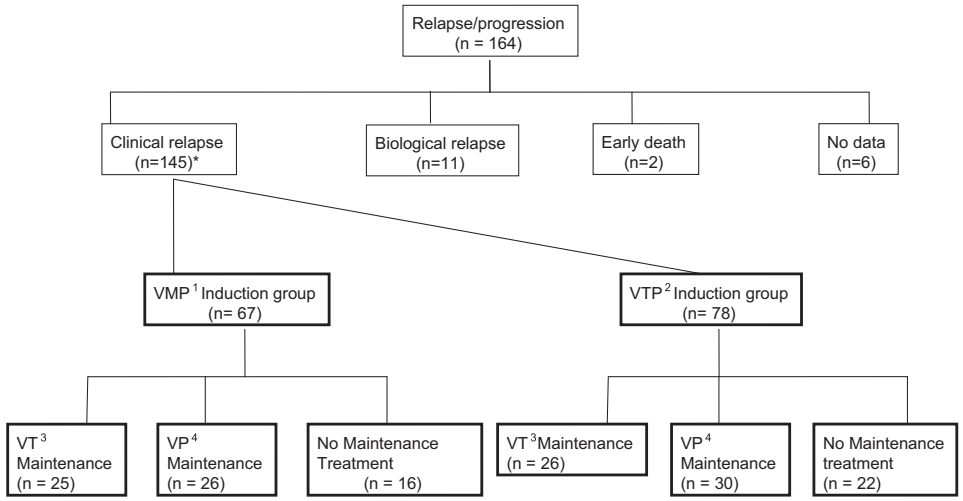
2.2. Statistical analysis

The proportions of patients with a given set of characteristics were compared by the chi-square test or by the Fisher exact test. The chi-square and Fisher exact tests were also used, as appropriate, to compare overall response, complete response (CR), and nCR between both groups. The duration of PFS was calculated from the start of the second line treatment to new disease progression, death from any cause, or reference date (December 31, 2013). Patients who were alive and discontinued the study without evidence of disease progression were censored at the last evaluation for assessment of PFS. OS was calculated as the time from start of the second line treatment until death from any cause, or censored at the last reference date. PFS, and OS were plotted according to the Kaplan–Meier product-limit method with comparisons made by the log-rank test. All patients were followed until death or reference date (December 31, 2013). All statistical analyses were performed with version 3.0.1 of R software (The R Project for Statistical Computing) [13].

3. Results

3.1. Characteristics of patients at relapse

Median age at time of relapse in the overall series was 74.4



*In 31 (21.3%) clinical relapse was preceded by a period of biological relapse.
1.Bortezomib/Melphlan/Prednisone
2.Bortezomib/Thalidomide/Prednisone
3.Bortezoimb/Thalidomide
4.Bortezomib/Prednisone

Fig. 1. Flow diagram of relapsed patients.

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