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ORIGINAL ARTICLE

# Study of the frequency and reasons for discontinuation of different lines of treatment in patients with multiple myeloma

Alicia Senín[1] · Francesc García-Pallarols[1] · Randa Ben Azaiz[1] · Laia Martínez-Serra[1] · Sara Montesdeoca[1] · David Román[1] · Mariana Ferraro[1] · Ivonne Párraga[1] · Carlos Besses[1] · Eugenia Abella[1]

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## Abstract

The availability of new agents for the treatment of multiple myeloma has allowed the use of multiple lines of treatment, but a percentage of patients do not reach to receive this combination because of toxicity and early death. In this regard, a cross-sectional European study evaluated the management of different lines and discontinuation of treatment in 7635 patients from seven countries in routine clinical practice, finding that 39% of European patients do not receive a second line and that only 4% of patients reach third line in Spain, a figure that is striking when comparing with the rest of the countries. We analyze the frequency and causes of treatment discontinuation in a series of 108 patients from a Spanish University hospital showing that the main reason for permanent treatment discontinuation after finishing first line was to have a response, while death due to disease progression accounted for the main reason in subsequent lines of therapy, with its frequency increasing according to the number of lines received. Additionally, in our longitudinal study, we estimated, using a competitive risk analysis, that 22% of patients would not receive a second line of therapy at 60 months and 47% would not reach third line, also at 60 months, showing a marked discrepancy with the results reported in the cross-sectional European study. Although based on limited data, our results suggest the convenience of validating the findings of cross-sectional studies conducted in large cohorts.

**Keywords** Multiple myeloma · Lines of treatment · Discontinuation · Competitive risk analysis

## Introduction

The introduction in the last decade of new agents and combinations for the treatment of multiple myeloma (MM) has increased the life expectancy of patients and the consequent use of multiple lines of treatment [1–6].

Nevertheless, data from real world clinical practice is scarce, since the majority of studies are carried out in the context of clinical trials. A recent observational European study evaluated the frequency and causes of treatment discontinuation in 7635 patients from seven countries in routine clinical practice [7, 8]. This study showed that up to 39% of patients do not receive a second line of therapy and explored the causes of treatment discontinuation in each line.

However, it is not known if treatment discontinuation is permanent or not, and its cause. On the other hand, the low percentage (4%) of patients who reached the third line in Spain is striking when compared to the rest of the countries.

To the best of our knowledge, no study has assessed the causes of permanent treatment discontinuation in real clinical practice. This paper analyzes the frequency and causes of treatment discontinuation in a series of 108 patients diagnosed of MM between 2010 and 2017 in a university hospital of Barcelona.

## Methods

The clinical and biological characteristics of 108 patients diagnosed with MM between January 2010 and March 2017 were retrospectively collected in a tertiary referral hospital.

✉ Alicia Senín
60014@parcdesalutmar.cat

[1] Hematology Department, Hospital del Mar-IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Universidad Autónoma de Barcelona, Barcelona, Spain

**Table 1** Disease and clinico-biological characteristics of 108 patients

| | *n* (%) |
|---|---|
| Age (years) | |
| < 65 | 21 (19.5) |
| 65–75 | 36 (33.5) |
| > 75 | 51 (47) |
| Sex | |
| Male | 58 (54) |
| Type of MM | |
| IgG | 55 (51) |
| IgA | 26 (24) |
| BJ | 20 (21) |
| IgD | 3 (2) |
| Other | 2 (2) |
| Onset, *n* = 104 | |
| Acute renal insufficiency | 13 (12) |
| Pathological bone fracture | 17 (16) |
| Bone pain | 24 (23) |
| Anemia | 18 (17) |
| Smoldering MM | 11 (10) |
| Other | 21 (20) |
| ISS, *n* = 106 | |
| ISS1 | 33 (30.5) |
| ISS2 | 38 (35) |
| ISS3 | 35 (32) |
| ISS-R, *n* = 83 | |
| ISS1-R | 19 (8) |
| ISS2-R | 44 (41) |
| ISS3-R | 20 (18.5) |
| Cytogenetics, *n* = 69 | |
| Normal | 24 (22) |
| del 17p | 9 (8) |
| *t* (4;14) | 9 (8) |
| *t* (14;16) | 2 (2) |
| cr1 gain | 8 (7) |
| Complex karyotype | 4 (4) |
| Other | 13 (12) |

In order to reproduce the design of the aforementioned European study, both cross-sectional and longitudinal analyses of the cohort were carried out. For the transversal analysis, patients were classified according to the last line of therapy received at the time of the analysis, including palliative treatment with prednisone. Those patients who did not receive a subsequent line of treatment were studied for the causes of treatment discontinuation. These causes could be permanent, disqualifying the patient from receiving further therapy, or transitory, that did not disqualify patients from receiving further therapy in the future. The causes of permanent discontinuation were limiting toxicities, death from different causes, or lost to follow-up. Discontinuation was transitory in the case of response or ongoing treatment. For the longitudinal analysis, all treatments received and the number of cycles administered were collected for every patient. Overall survival was computed with the Kaplan-Meier method and, in each line, median time to next treatment (TNT), defined as the time interval between the start of two consecutive lines, was estimated. Furthermore, a competitive risk analysis [9] was carried out to estimate the projected proportion of patients receiving a second and a third line of therapy, with death, limiting toxicities, or lost to follow-up acting as competitive events. All statistical analysis were performed using SPSS 22.0 (SPSS, Chicago, IL) except for the competitive risk analysis, which was performed using the etm package [10] in R version 3.3.2 [11].

## Results

The clinical-biological characteristics of the series are summarized in Table 1. Forty-seven percent of patients were > 75 years at diagnosis and 75% of the series (*n* = 81) was not eligible for autologous bone marrow transplantation (BMT), either due to comorbidities or age at diagnosis. Around 20 to 30% of patients met high-risk criteria according to ISS and ISS-R scales [12, 13], and 30% of the series also showed high-risk cytogenetics [*t*(4;14), *t*(14;16), del(17p), complex karyotype or chromosome 1 aberrations] [14].

**Table 2** Treatment received in each line and number of patients who permanently discontinue treatment in each line

| | 1st line *n* = 108 | 2nd line *n* = 73 | 3rd line *n* = 44 | 4th line *n* = 23 | 5th line *n* = 10 |
|---|---|---|---|---|---|
| Number of cycles* | 6 (1–18) | 6 (1–29) | 5 (1–45) | 2.5 (1–16) | 3 (1–16) |
| Median treatment duration* (months) | 6.6 (0.4–26.41) | 5.7 (0–40) | 4 (0.1–15.5) | 3 (0–16) | 1.8 (0.1–11) |
| Median TNT* (months) | 16 (12.1–20.5) | 15 (11–18.8) | 13 (10.1–17.4) | 3 (0.6–5.7) | – |
| Number of patients who permanently discontinue treatment | 35 (32) | 29 (27) | 21(20) | 13 (12) | 10 (9) |

*TNT* time to next treatment

*Median and range

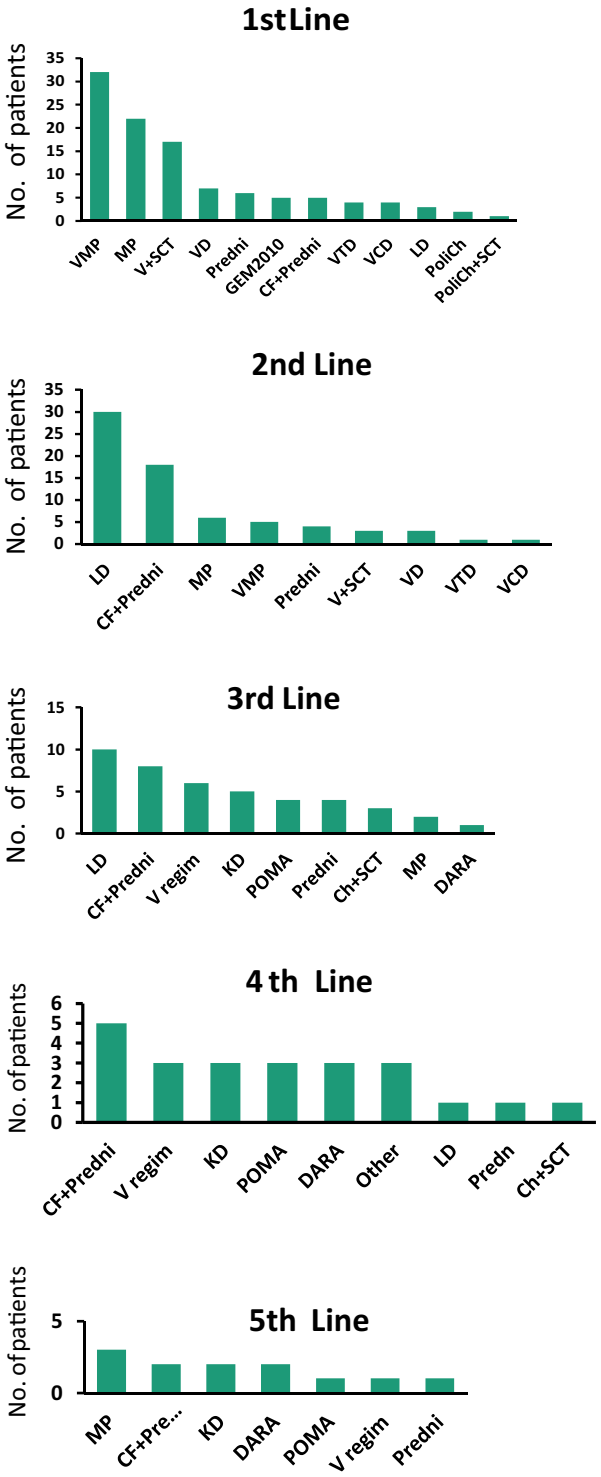


**Fig. 1** Type and frequency of different treatments in each line. VMP, Velcade melphalan prednisone; MP, melphalan prednisone; V+SCT, Velcade-based regim followed by autologous stem cell transplantation; VD, Velcade dexamethasone; Predni, prednisone; GEM2010, Velcade melphalan prednisone and maintenance with lenalidomide dexamethasone; CF, cyclophosphamide; VTD, Velcade thalidomide dexamethasone; VCD, Velcade cyclophosphamide dexamethasone; LD, lenalidomide-dexamethasone; Poly-Ch, polychemotherapy; SCT, autologous stem cell transplantation; KD, carfilzomib-based regims; POMA, pomalidomide-based regimes; DARA, daratumumab-based regimes

In the cross-sectional analysis, all patients ($n = 108$) received a first line of therapy and 35 of them (32%) did not receive a second line. Seventy-three patients received up to a second line of treatment and 29 of them (27% of the overall series) did not receive a third line. Forty-four patients received up to a third line and 21 of them (19% of the series) did not receive a fourth line. Twenty-three patients received a fourth line of treatment and 13 of them (12% of the series) did not receive a fifth line. Finally, ten patients received a fifth line of therapy and none a sixth line (Table 2). A greater treatment discontinuation rate was observed in subsequent lines of treatment.

The type and frequency of treatments administered in each line of therapy is summarized in Fig. 1. In first line, 12% of patients were eligible for an autologous BMT while 10% was only eligible for palliative treatment after diagnosis. Bortezomib (V)-based regimen was administered in 50% of patients, melphalan prednisone (MP) was given to 20% of patients, and only 5% of patients were enrolled in a clinical trial (CT).

In second line, the most frequent treatment administered was lenalidomide-dexamethasone (LD), whereas only 4% of patients were eligible for an autologous BMT. Up to 30% of patients were treated with cyclophosphamide (CF) and/or prednisone.

In third line, LD was also the most frequently used scheme. Remarkably, 22% of the treatments administered in this line used newly available agents (carfilzomib, pomalidomide, and daratumumab). These agents were used in up to 33% and 50% of patients in fourth and fifth line of therapy, respectively.

The number of cycles administered was similar in the first three lines of therapy, showing a decrease in subsequent lines. A progressive decrease in median treatment duration and treatment free interval between lines was also observed. Median TNT was of 16 months in first line, 15 months in second line, and 13 months in third line (Table 2).

## Treatment discontinuation causes: cross-sectional study

In the cross-sectional study, we selected, in each line, those patients not receiving further therapy, in order to assess whether this treatment discontinuation was permanent. The reasons for not receiving further therapy in each line are summarized in Table 3.

The most frequent cause of treatment discontinuation in first line was to have achieved a response to treatment (31% of discontinued cases). The frequency of treatment discontinuation due to this cause decreased progressively in subsequent lines, to such an extent that no lasting responses were observed in fourth and fifth lines. Treatment interruption due to progressive disease-related death

accounted for 14% of discontinuations in first line, increasing its frequency in subsequent lines, until 40% or more in third and subsequent lines. Treatment interruption due to therapy-related death (mainly infections) was a common cause in all lines (ranging from 11 to 17%). Secondary neoplasms and other causes (myocardial infarction, acute pulmonary edema) of death accounted for 10% of treatment discontinuations in first and second line of therapy. Limiting toxicities disqualifying from further treatment (pneumonitis, psychosis) were scarcely observed in all lines (ranging from 3 to 5%).

### Survival and competitive risk analysis: longitudinal analysis

With a median follow-up of 2.35 years, 53 patients died. Progressive disease was the cause of death in half of them. Twenty-one percent of patients died because of another neoplasm, 6% due to toxicity, and 13% from other causes. The frequency of deaths was higher in the last lines of treatment (16% in first line vs 50% in fifth line of treatment).

Median overall survival of the series was 3.67 years (2.3–5.1), being poorer in patients older than 75 years (2.4 years), in comparison with 4.7 and 5.5 years in patients between 65 and 75 years and those younger than 65 years, respectively.

The projected 60-month probability of receiving a second line of therapy, estimated with a competitive risk analysis, was 78% (95% CI, 68 to 83%) (Fig. 2), while the probability of receiving a third line was 53% (68% of the 78% remaining) (Fig. 3). Accordingly, an estimated 22% and 47% of patients would not receive, respectively, a second and a third line of therapy mainly due to toxicity or death.

## Discussion

In the present study, a cohort of 108 patients from a tertiary referral hospital was analyzed both retrospectively and cross-sectionally about the frequency and causes of treatment discontinuation. The aforementioned European study analyzing the routine clinical practice in 7635 patients served as a reference and we studied the reproducibility of its main findings in our cohort [7, 8].

Median age at diagnosis was 74 years (40–89), with 47% of patients being > 75 years in comparison with 22% observed in the European study. In the same line, the frequency of patients eligible for autologous BMT in our cohort was only of 27%, in contrast to 44% of eligible patients observed in the European study.

In our series, the most frequent treatment administered in first line was Bortezomib, as in the European study. VMP and MP were the predominant schemes used in first line (30% and 20% of patients, respectively), mainly due to advanced age, frailty, and a high index of comorbidities in our patients. Only 12% of patients received VTD and BMT in first line, a scheme that was more frequently used in the European study [7, 8]. In second line, the most frequent scheme was LD (41%), in a similar proportion to that reported by Yong et al. Nevertheless, it should be noted an important use of cyclophosphamide and corticoids in this line (29%), according to the frailty of our series. For subsequent lines, both series showed a predominant use of new agents (daratumumab, carfilzomib, and pomalidomide).

Yong et al. [8] observed a decrease in treatment duration and in treatment-free intervals according to the number of administered lines, whereas in our series, this trend is only observed in advanced lines of therapy. This finding could be explained by the significant use, in our series, of continuous schemes such as CF or LD in second and third lines of therapy. In advanced lines, we have observed a short TNT according to the natural evolution of the disease and probably, to the low tolerance of treatment in our elderly patients, leading to dose reduction, lower efficacy, and faster progression.

We also analyzed the frequency and motives of treatment discontinuation in each line, after detecting some limitations in the European study by Raab et al. and Yong et al. [7, 8]. Observation of 39% of patients who do not receive a second line of treatment in Europe is based on the transversal finding of 61% of patients who received treatment in the moment of the study. However, this figure does not take into account that

**Table 3** Reasons for not receiving further therapy in each line

| Patients that do not receive a subsequent line | 1st line $n = 35$ | 2nd line $n = 29$ | 3rd line $n = 21$ | 4th line $n = 13$ | 5th line $n = 10$ |
|---|---|---|---|---|---|
| Persisting response | 11 (31) | 4 (14) | 2 (8) | 0 | 0 |
| Treatment ongoing | 7 (20) | 10 (35) | 7 (33) | 5 (38) | 5 (50) |
| Death due to MM progression | 5 (14) | 5 (17) | 8 (40) | 5 (41) | 4 (40) |
| Treatment-related deaths | 4 (11.5) | 5 (17) | 3 (14) | 2 (16) | 1 (10) |
| Death due to other causes | 4 (11.5) | 2 (7) | 0 | 0 | 0 |
| Death due to another neoplasm | 3 (9) | 3 (10) | 0 | 0 | 0 |
| Treatment-related limiting toxicities | 1 (3) | 0 | 1 (5) | 1 (5) | 0 |

*MM* multiple myeloma

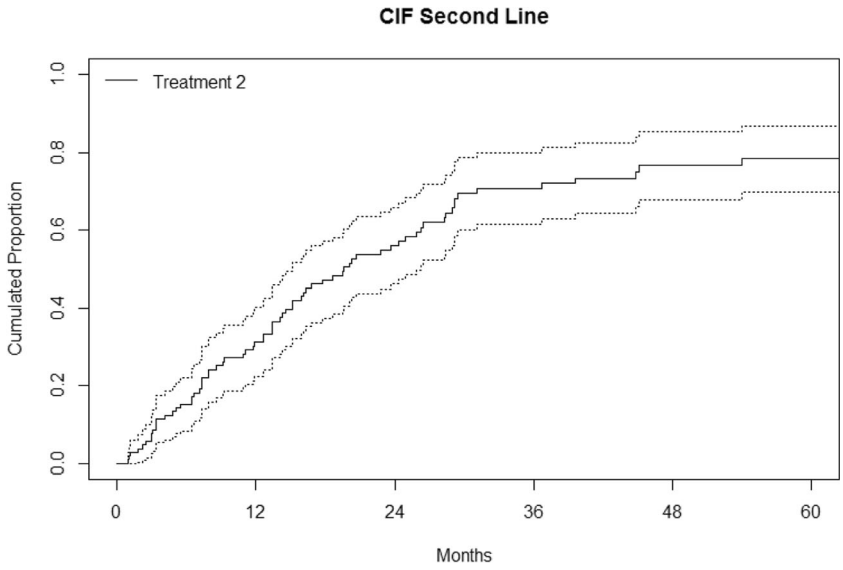


**Fig. 2** Estimated probability of receiving a second line of treatment. *CIF* Cumulative Incidence Function

those patients currently in response after first line and those with their first line ongoing may be eligible for a second line in the future. Moreover, the causes of treatment discontinuation listed are not necessarily permanent, such as treatment holidays or transient toxicity.

In our series, we observed, in the cross-sectional study, that 32% of our patients did not receive a second line of therapy. Nevertheless, this result is overestimated, since it does not take into account, as Raab et al., that patients under treatment or in response may be eligible for future treatments [7]. In order to provide a finer estimate of the proportion of patients not receiving a second line in our cohort, we performed a competitive risk analysis, a methodology that accounts for the events that compete with the event of receiving a subsequent line: limiting toxicity, death, and lost to follow-up [10]. Considering this setting, the estimated probability of not receiving a second line at 60 months was 22%, and that of not receiving a third line, also at 60 months, was 47%.

Our data from the cross-sectional analysis was similar to that of the European series (61% vs 68% receiving a second line, 38% vs 41% receiving a third line, 15% vs 21% receiving a fourth, and only 1% in both series receiving a fifth line of therapy). These similarities would suggest the use of a competitive risk analysis in the European cohort.

Another significant finding in the European study is the marked discrepancy of the proportion of patients receiving a third line in Spain (4%) versus the rest of Europe (39–60%). In our cohort, that is older and with more comorbidities than the cohort of patients included in the European study, 41% of patients in the transversal analysis are observed to receive a third line. In the longitudinal study, a projected 47% of patients would receive a third line of therapy at 60 months, a

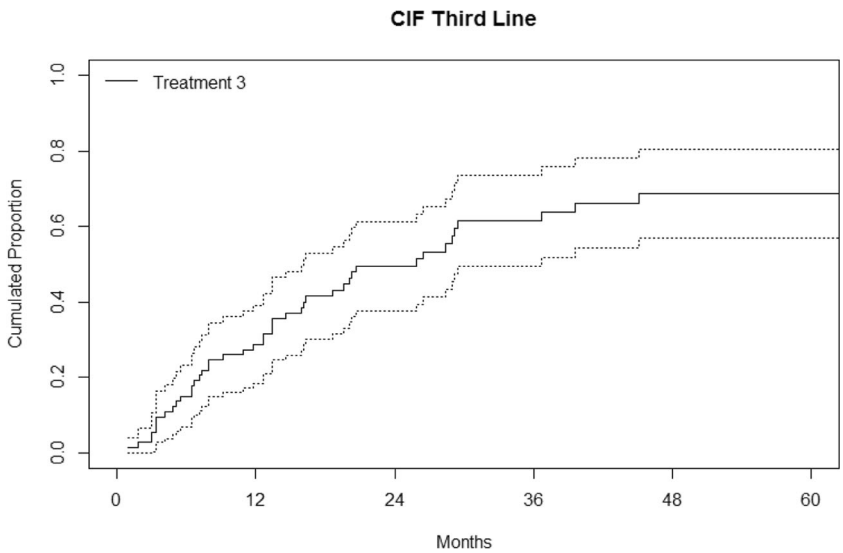


**Fig. 3** Estimated probability of receiving a third line of treatment. *CIF* Cumulative Incidence Function

figure more closely related to that reported by Raab et al. for other European countries. This suggests a possible selection bias for the Spanish population of the European study.

Finally, the causes of treatment discontinuation considered by Raab et al. and Yong et al. are not only limited to definitive treatment discontinuations, the outcome of more clinical interest [7, 8]. Nevertheless, both studies reported similar frequencies and causes of treatment discontinuation. Overall, response rates decrease in subsequent lines, while progression, toxicity, and worsening of patient's general condition increase according to the number of lines of administered therapy. In our series, the death rate in all lines of treatment was higher than that reported by Yong et al. and Raab et al., which seems remarkably low [7, 8].

In spite of being based on a cohort with a limited number of patients ($n = 108$), we believe that the findings of the present study may be taken as relevant, since they offer an overview of real clinical practice in a group of MM characterized by an old median age and by the presence of several concomitant comorbidities.

## Conclusions

In the present study, the main reason for permanent treatment discontinuation after first line was to have reached a response, while death due to disease progression accounted for the main reason for permanent treatment discontinuation in subsequent lines, with its frequency increasing according to the number of lines received (ranging from 14% in first line to 41% in fifth line).

In our series, we estimated, using a competitive risk analysis, that 22% of patients would not receive a second line of therapy at 60 months, in contrast to 32% observed in our transversal analysis and, most remarkably, the 39% reported in the aforementioned European study.

Although based on limited data, the marked discrepancy of some of our results with those reported in the European study suggests the convenience of further confirmation of these findings in other series.

**Authors contribution** AS, EA, RBL, and FG-P designed the study, collected data, performed the statistical analysis, and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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### Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all patients for being included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.



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