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Clinical Features of Long Surviving Patients during Treatment for Multiple Myeloma

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Abstract

Data of patients still alive 10 years after initial treatment for multiple myeloma (MM) were collected by 13 Italian hematological centers from January 2020 to December 2022. Routine work-up at diagnosis and type of treatment of 201 patients were analyzed from December 2023 to March 2024. At the time of the analysis, 89% of patients were alive, with a mean survival

of 156 months. Biochemical data at diagnosis were not different from those reported in an unselected myeloma population, but severe, irreversible renal damage was absent. About half the patients attained complete remission (CR) after one or two lines of treatment. After the first line of therapy, 80% of patients experienced a treatment-free period of no less than two years. A small number of patients (13%) required a single line of therapy, although they were not in continuous CR (CCR); about 28% of patients received more than four lines of treatment. These and other data suggest that CR is statistically associated with probability of long-term survival although this does not seem to be a necessary or sufficient condition for attaining long-term survival; on the other hand, persistent chemosensitivity and slow progressive disease appear to be the most important factors characterizing the clinical profile of long-term survivors, suggesting kinetic and genetic features that remain stable in time.

Keywords: Multiple myeloma; Long survivors

Dedication: This paper is dedicated to the memory of our colleague and gentlewoman Silvana Capalbo, whose initial participation and enthusiasm has been determinant for our work.

Introduction

The survival of patients affected by multiple myeloma (MM) has increased as a result of the therapeutic options able to increase quality and quantity of response in any phase of the disease, with acceptable and manageable toxicity [1]. However, achieving long-term survival is a target not yet common for all patients, and reports describing unselected populations are scant [2-12], also due to the difficulty of recovering data from long periods of observation. Retrospective analyses can offer interesting hints for discussion about the impact of treatments on patients' survival, as they analyse data of persons who actually achieved a long-term remission and not of people who are likely to become long-term survivors. Following a preliminary report on a smaller population [13], we describe the results of an Italian multicenter retrospective analysis of patients surviving over ten years since their first chemotherapy for MM, aiming to identify their clinical features and treatment course.

Patients and Methods

In January 2020, an invitation to collect data of patients still living more than 10 years after initial treatment for MM was made to hematological Italian centers. A previous diagnosis of solitary plasmacytoma was the only exclusion criterion. The data collected included standard biochemical work-up at diagnosis, treatment lines and response duration, uninvolved polyclonal immunoglobulin and leukocyte counts at the last follow up. Data were collected from medical records and communicated anonymously in order to be analysed , until December 2022. Nevertheless, ethical approval was requested to Ethics Committees of all participating centers.

Results

After approval by the Ethics Committee of the promoting center, 13 out 100 centers provided data of 203 patients. Of these, 201 were analyzed. Two Ethics Committees denied approval on the grounds that the statistical assumption was insufficient.

In our population both sexes were equally represented (M/F =1); median age was 52 years (r.:33-82). At time of the analysis (Dec.2023) 89% of patients were still alive. Mean survival was 156 months, r.:118-339. MGUS duration longer than two years was reported in almost 60% of cases (58% vs.42%, respectively). Monoclonal heavy and light chains were: Gk 50%, Gλ 14%, k 11%, Ak10%, λ 6%, Aλ 5%, non secreting 2%, Dλ 1%, Mk 1%. Almost two thirds of the patients were not severely anemic (Hb<10 vs.>10g/dL: 32%vs.68%; mean Hb 11g/dL, r.: 7-17). Normal serum LDH levels were reported in almost half of patients (normal

vs. abnormal LDH: 42%vs. 58%; mean : 262 IU/L, r.: 72-693), and most patients had normal serum creatinine levels (creatinine <1,2 vs.>1,2mg/dL: 81% vs. 19%, mean creatinine 1 mg/dL, r.: 0,5-2,5). One patient with creatinine 8 mg/dL recovered after induction. As many as 67% of the patients presented bone lesions. Durie & Salmon stage: IA 8%, IIA35%, IIB 5%, IIIA 42%, IIIB 10%. IPSS >1: 35%. At the last follow up, mean lymphocyte counts were 1650/mmc (r.: 140-4460), mean neutrophil counts were 2950/mmc (r.: 400-9300), and mean uninvolved Ig concentrations were 860 mg/dL (r. 50-10000, n.=95).

First Line Therapy: Table 1 shows the main data and outcome of first line therapy. About 60% of the patients were treated with single or double high dose regimens and autologous rescue: half of them received maintenance therapy with interferon or thalidomide or its derivatives (IMIDS) in equal parts. In induction, IMIDS were employed in 52% of the patients, proteasome inhibitors (PI) in 35%. No one was treated with allogeneic transplant. About 40% of the patients were in CR after the first line, with mean remission duration of 119 months (r.: 3-330): of these, 46% received a second line and 28% attained a second CR. About 50% of the patients in CR were in continuous CR (CCR: 43/88). The number of patients who received only one line of treatment (n.=69; 34%) was higher than that of patients in CCR (n.=43; 21%), therefore 26 patients (13%) were in stable non complete remission. About 40% of the patients did not attain a complete response and 12% were in stable or progressive disease. Seventeen patients were refractory to initial treatment: five of them never reached CR after additional treatment, four of them were still alive at the time of data collection. After the first line, 80% of the patients did not require further therapy for at least two years.

Table 1: Characteristics and outcome of first line treatment

Characteristics and outcome of first line treatment		
	n.	%
Chemotherapy	85	42
single auBMT	53	27
double auBMT	63	31
alloBMT	0	0
Outcome		
CR	88	44
VGPR	52	26
PR	37	18
SD	7	3
PD	17	9
post-auBMT maintenance		
Yes	51	56
No	65	44
TTNT		
> 10 years	83	41
> 8 years	99	49
> 5 years	124	62
> 2 years	160	80

CR: Complete Remission; VGPR: Very Good Partial Remission; PR Partial Remission; PD: Progressive Disease; auBMT: Autol-

ogous Bone Marrow Transplant; alloBMT: Allogeneic Bone Marrow Transplant ; TTNT: Time To Next Treatment

Second Line: Table 2 shows the main data and outcome of second line therapy, which was received by 131 patients: IMIDS were employed in 46% of cases, PI in 49%. Autologous transplant in relapse was used in about 10% of patients, allogeneic transplant in 7 patients.

Table 2: Characteristics and outcome of second line treatment

Characteristics and outcome of second line treatment		
	n.	%
Chemotherapy	106	53
auBMT	19	9
alloBMT	7	4
No further treatment	69	34
Outcome		
CR	29	22
VGPR	31	23
PR	30	23
SD	19	15
PD	22	17

CR: Complete Remission; VGPR: Very Good Partial Remission; PR Partial Remission; PD: Progressive Disease; auBMT: Autologous Bone Marrow Transplant; alloBMT: Allogeneic Bone Marrow Transplant ; TTNT: Time To Next Treatment

Mean number of therapy lines received by patients treated by auBMT as first line treatment (n.= 116) is less than those received by patients treated in first line by non-transplant procedures (n.= 85): 2.5 vs 3.2, respectively; Mann-Whitney test: p 0.03.

Table 3 shows the number of treatment lines of the whole population. About one third of the patients received only one line of treatment, one fourth received two lines, about 13% three lines. Twenty eight percent of the patients received more than three lines of treatment (mean: 8, r. 4-14) .

Table 3: Number of treatment lines

Number of treatment lines		
n.of lines	**n. of pats.**	**%**
1	69	34
2	50	25
3	25	13
>or =4	57	28

Discussion

The statistical significance of retrospective studies can be negatively influenced by several factors usually absent in prospective observations [14]. In particular, in retrospective studies variables potentially affecting outcome may not have been recorded or missing data may reduce the statistical significance. Adequate sample size, control groups and reliable statistics can reduce the

biases; however, collecting and analysing relevant data may allow for a more accurate assessment of past events and outcomes. This is why we chose to analyse the effects of treatment, which undoubtedly affects the survival. The above aspects could explain the little interest for retrospective analyses also verified in the current study, where about 10% of the national centers accepted to participate. However, the costs of prospective randomized studies are almost invariably supported by companies whose interests can interfere with the study design and consequently with its results. Retrospective analyses are inexpensive, -often at zero cost, as in our case,- and independently affordable by any center: they should be encouraged, because if consistent with equivalent experiences, the statistical significance of the results of retrospective analyses can be increased. Retrospective surveys could be further facilitated by less bureaucracy: ethical approval for collecting anonymous routine data seems redundant and probably unnecessary. In our study, considering time and resources spent on administrative procedures and the approval denied by two committees, ethical consent ended up being an obstacle more than a resource.

The results of our inquiry show the profile of long surviving myeloma patients as being younger people with balanced percentage of men and women, with not particularly long MGUS duration, with prevalence of monoclonal immunoglobulin types similar to those reported at diagnosis in the general myeloma population [15], often anemic at diagnosis and with frequent bone involvement, with normal or mildly impaired renal function. The absence of severe renal damage or of patients in dialysis associate these conditions to worse prognosis [4]. Durie & Salmon (DS) stage and IPSS score appear irrelevant for prognosis, but DS stage seems generally accepted as operational criterion: only 8% of patients were treated in stage IA.

The clinical history of long surviving patients can be an interesting starting point to try to understand the effects of therapy. Chemotherapy unquestionably determines survival. Thirty four percent of the patients lived more than 10 years after a single line of chemotherapy, 62 % of whom in CR. After the first line of treatment, 44% of the patients attained CR, that on average was long (mean: 119 months, r.: 3-330). About half the patients (56%) attained CR after the first or the second line of treatment. After first line, 80% of the patients did not require further therapy for a minimum of two years, 50% of the patients did not require further therapy for eight years.

Forty four patients survived more than 15 years (mean : 224 months, r.: 180-339); half of them were in CR after first line (CR vs. non-CR: 21/44), three quarters of them (n.=32) received single (n.=17) or double (n.=15) autologous transplant. Fifteen of these 44 patients received a single line of therapy, 12 two lines, 3 three lines, 14 more than three lines.

The impact of chemotherapy in relapse is relevant: one fourth of the patients (26%) survived more than 10 years thanks to four or more lines of therapy. Taken together, all these observations suggest that CR is statistically associated with the probability of long survival [2,4,6,7,11] but it is not a necessary nor sufficient condition for attaining long-term survival, while persistent chemosensitivity and slow progressive disease appear as the most important factors related to good prognosis [3,8,9,12], suggesting kinetic and genetic features that remain stable in time [16].

The genetic data available for our patients are few and do not allow statistically significant correlations. Table 4 shows chromosomal findings and the results of FISH analysis of 53 patients at diagnosis; 42% of them showed normal karyotype at diagnosis. The presence or the absence of chromosomal aberrations did not correlate with the number of treatment lines received (χ^2 0,7; p 0,3).

Table 4: Chromosomal findings and FISH analysis of 53 patients at diagnosis

	number ofpatients	**associated alterations**
normal karyotype	24	
del (13q)	18 1	del 1q

del (17p)	3 1 2 1	 trisomy 17 del 13q del 13q
t (11,14)	4 1 2	 del 13q t(11,14) and chrom. 11 polysomy
miscellaneous	2 1 1	polisomy 11 aneuploidy 5 ampl 1q

Our inquiry did not include questions on quality of life, although it is reasonable to think that patients who need less therapy experience better quality of life [17].

Conclusion

The clinical and biochemical profile at diagnosis of patients surviving over ten years after initial treatment for MM appears similar to that of the general myeloma population, but the former are relatively younger, not affected by severe renal damage and show good and persistent therapeutic response in any phase of the disease. Chemosensitivity and slow progressive disease more than depth of the response seem the main characteristics of this still too small percentage of patients, suggesting a stable genetic background. Worthy underlining is also the fact that one fourth of the patients live longer than 10 years thanks to the administration of more than three lines of therapy. Although difficult to perform, prospective studies of long-term survivors in multiple myeloma could strengthen the findings of retrospective observations, and furthermore they could more precisely focus on the impact of genetic profiling.

Declarations

Ethical Approval

Ethical approval was obtained by the Ethics Committee of the promoting center (University Federico II of Naples) in April 2020 (n.89/20)

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Competing Interest

Not applicable

Data Availability

Data files available on request

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