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Response to first-line chemotherapy and long-term survival in patients with multiple myeloma: results of the MM87 prospective randomised protocol

A. Riccardi[a,*], O. Mora[a], C. Tinelli[b], C. Porta[a], M. Danova[a], S. Brugnatelli[a], D. Grasso[a], B. Tolcà[a], R. Spanedda[c], A. De Paoli[d], L. Barbarano[e], L. Cavanna[f], M. Giordano[g], C. Delfini[h], G. Nicoletti[i], C. Bergonzi[j], E. Rinaldi[k], L. Piccinini[l], E. Ascari[a], for the Cooperative Group of Study Treatment of Multiple Myeloma

[a]*Medicina Interna e Oncologia Medica, Università and Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, 27100 Pavia, Italy*
[b]*Direzione Scientifica, Università and Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, 27100 Pavia, Italy*
[c]*Istituto di Ematologia, Università di Ferrara, 44100 Ferrara, Italy*
[d]*Divisione di Medicina II, Ospedale di Legnano, 20025 Legnano, Italy*
[e]*Divisione di Ematologia, Ospedale di Niguarda, 20100 Milano, Italy*
[f]*Divisione di Medicina I, Ospedale di Piacenza, 29100 Piacenza, Italy*
[g]*Servizio di Oncologia, Ospedale S. Anna, 22100 Como, Italy*
[h]*Divisione di Ematologia, Ospedale di Pesaro, 61100 Pesaro, Italy*
[i]*Semeiotica Medica, Università Cattolica di Roma, 00168 Roma, Italy*
[j]*Divisione di Medicina II, Ospedale di Cremona, 26100 Cremona, Italy*
[k]*Divisione di Medicina I, Ospedale di Magenta, 20013 Magenta, Italy*
[l]*Istituto di Oncologia, Università di Modena, 41100 Modena, Italy*

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Abstract

In this study we evaluated whether a good response to conventional chemotherapy, i.e. a significant tumour reduction, is a prerequisite for improved survival in multiple myeloma (MM). Between January 1987 and March 1990, 341 consecutive previously untreated patients with MM received chemotherapy within the prospective, multicentre, randomised Protocol MM87. Of these, 258 patients were evaluable for both response and long-term survival and 244 (94.6%) have died. The median survival of all patients was 40 months (6–162 months). The median survival did not differ between patients who had complete response (CR) (50 months (9–162 months)), partial response (PR) (46 months (8–147 months)) or stable disease (SD) (41 months (7–135 months)). The median survival was shorter (13.6 months (6–135 months)) ($P<0.0001$) in patients whose disease progressed while they were receiving first induction chemotherapy. Causes of death were more frequently ($P=0.04$) related to MM in patients who had progressive disease (PD) than in patients who had a CR or PR or SD. The main clinical and laboratory characteristics were similar in the four groups. These data indicate that patients who maintain SD during first-line chemotherapy have a prognosis similar to that of patients who attain a response. Only patients whose disease progresses have a distinctly worse outcome.

Keywords: Multiple myeloma; Conventional chemotherapy; Response; Survival

1. Introduction

Response to therapy (usually chemotherapy), i.e. tumour reduction, is the cornerstone of phase II trials, with the related belief that this is a prerequisite for prolonging survival in phase III trials. The results of recent trials have partially questioned this concept. In advanced breast cancer, a greater median rate of responses, and especially of complete responses, is obtained with higher rather than with lower doses of anthracyclines, but the advantages with regard to duration of survival are much less clear-cut than response

* Corresponding author. Tel.: +39-0382-527985; fax +39-0382-526223.
E-mail address: a.riccardi@smatteo.pv.it (A. Riccardi).

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rate [1]. In addition, median survival is increased only marginally and not significantly by therapies that double the response rate, but cause greater toxicity, in advanced colorectal cancer [2] and in chronic lymphocytic leukaemia [3].

In this report, we examine the relationship between response and long-term survival in a large series of patients with multiple myeloma (MM) who were treated between 1987 and 1990.

2. Patients and methods

Between January 1987 and March 1990, 341 patients with previously untreated MM entered the prospective, multicentre, randomised Protocol MM87 [4], that included first- and second-line treatments.

The protocol was approved by the Clinical Research Review Board of the Department of Internal Medicine at Pavia University Medical School.

2.1. Summary of treatment

Criteria for diagnosis are reported elsewhere [4]. Patients were staged [5] and randomised for both induction and maintenance therapy.

A less or more aggressive first-line induction policy was adopted for stage I and III patients, respectively. Stage I patients were randomised between receiving melphalan and prednisone (MP) at disease progression or immediately after diagnosis. Stage III patients were randomised between receiving MP or peptichemio, vincristine and prednisone (PVP). Peptichemio is the sarcolysin molecule, i.e. m-{di-(2-chloroethyl)-amino}-L-phenylalanine, covalently bound to six peptides in order to combine alkylating and antimetabolic effects. In a randomised study [6], PVP proved to be more effective than MP in inducing responses in MM.

Patients with stage II disease were uniformly treated with MP [4].

Response was evaluated after six courses of MP or four courses of PVP, according to the criteria detailed below.

Within each stage, patients who had a complete or partial response were randomised between either receiving additional courses of induction therapy until a maximum reduction in the monoclonal component (MC) (i.e. the plateau phase) was achieved and then stopping all cytostatics until relapse, or continuing therapy indefinitely until relapse, as a maintenance therapy.

Patients who were resistant to one regimen or progressed or relapsed during maintenance with this regimen were crossed over to the other regimen, as a second-line therapy. So, patients who were originally treated with MP for induction were treated with PVP and patients originally treated with PVP were treated with MP. Patients who achieved a response to second-line treatment continued maintenance therapy with the same drugs until relapse. No patient underwent stem cell transplantation.

2.2. Response evaluation

Patients were evaluated for response at the end of first induction therapy, i.e. after six courses of MP or four courses of PVP, according to slightly modified clinical criteria adopted by the SECSG (Southeastern Cancer Study Group) [7]. The criteria were the following: (a) reduction in MC; (b) decrease in bone marrow plasma cells (BMPC) of at least 20% or return to less than 20%, as evaluated on bone marrow (BM) imprints before and after treatment; (c) a 20 g/l rise in Hb concentration in anaemic patients (Hb <110 g/l) sustained for more than 4 weeks; (d) return of serum calcium and blood urea nitrogen (BUN) to normal values; (e) elevation of serum albumin up to or greater than 30 g/l in the absence of other causes of hypoalbuminaemia; (f) absence of progression of skeletal lytic lesions.

Complete response (CR) was defined as a $>50\%$ reduction in MC and a response in more than half of the other parameters. A partial response (PR) was defined as a 25–50% reduction in MC and a response in more than half of the other parameters. Progressive disease (PD) was defined as a $>25\%$ increase in MC and/or an increase in BMPC of at least 20% and/or worsening of laboratory parameters (mainly haemoglobin, serum calcium and BUN) and/or of skeletal lytic lesions. Minor response or stable disease (SD) was the failure to fulfill the above criteria for CR, PR and PD, i.e. these patients experienced a $<25\%$ decrease or increase in MC.

Relapse was defined as a $>50\%$ increase in the plateau level of MC and/or an increase in the size and/or number of skeletal lytic lesions.

2.3. Data collection

Just after first randomisation, a protocol entrance form had to be completed (specifying data which validated the diagnosis and the stage) and a photocopy sent to the co-ordinating centre. Every 6 months, the entrance form was updated and cooperative group meetings were held regularly in Pavia.

The main clinical results of the MM87 Protocol have been detailed from data analysis collected in May 1993, when 59% of patients had died [4].

In June 2000, a re-analysis of survival and causes of deaths was carried out. Medical form records and death certificates were searched.

2.4. Statistical evaluation

Statistical analysis was performed using non-parametric tests, after checking data distribution by Shapiro–

Wilk's test, and so data were expressed as medians and interquartile ranges. Comparisons between two groups were performed using the Mann-Whitney U test and comparisons between more than two groups were performed using the Kruskal–Wallis ANOVA test. Differences in frequencies were evaluated by chi-squared statistics or Fisher's Exact test, as appropriate. Survival analysis was based on Kaplan–Meier estimates and differences between groups were evaluated using the log-rank test. A P value of less than 0.05 was considered to indicate statistical significance. All tests were two-sided. Analyses were performed with Statistica for Windows Software (StatSoft Inc. 2001, Tulsa, OK, USA).

3. Results

The results obtained are detailed in Tables 1 and 2 and in Figs. 1 and 2.

Table 1
Main clinical features of patients with multiple myeloma who had complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) on first-line chemotherapy

	Patients with CR	Patients with PR	Patients with SD	Patients with PD	P value
	n (%)	n (%)	n (%)	n (%)	
Patients	60 (100)	69 (100)	95 (100)	34 (100)	
M/F	28/32 (47)/(53)	34/35 (49)/(51)	47/48 (49)/(51)	21/13 (62)/(38)	NS
IgG	32 (53)	45 (65)	63 (66)	23 (68)	NS
IgA	19 (32)	12 (17)	21 (22)	6 (18)	NS
IgD	1 (2)	1 (1)	2 (2)	0 (0)	NS
IgM	0 (0)	0 (0)	1 (1)	0 (0)	NS
LC	6 (10)	9 (13)	7 (7)	5 (15)	NS
Not secreting	2 (3)	2 (3)	1 (1)	0 (0)	NS
K/L	36/24 (60)/(40)	39/30 (56)/(43)	57/38 (60)/(40)	23/11 (68)/(32)	NS
$\beta 2 \leqslant 40$ mg l^{-1}	14/37 (38)	19/38 (50)	29/60 (48)	7/24 (29)	NS
ECOG/WHO $\leqslant 2$	56 (93)	67 (97)	92 (97)	32 (94)	NS
Stage I	7 (12)	16 (23)	23 (24)	6 (18)	NS
Stage II	17 (28)	26 (38)	26 (27)	9 (26)	NS
Stage III	36 (60)	27 (39)	46 (48)	19 (56)	NS
Initial therapy:					
no therapy[a]	4 (6)	6 (9)	5 (5)	2 (6)	NS
MP	39 (65)	45 (65)	68 (72)	26 (76)	NS
PVP	17 (28)	18 (26)	22 (23)	6 (18)	NS

LC, light chain; β2, β2 microglobulin; MP, melphalan and prednisone; PVP, peptichemio, vincristine and prednisone; NS, non-significant; M, male; F, female; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; K/L, kappa/lambda chain.
[a] These were stage I patients who were randomised to receive no therapy at diagnosis and were treated with MP at progression [4].

Table 2
Main laboratory features of patients with multiple myeloma who had complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) on first-line chemotherapy

	Patients with CR	Patients with PR	Patients with SD	Patients with PD	P value
	Median (range)	Median (range)	Median (range)	Median (range)	
ESR (mm 1st h)	109 (9–180)	72 (2–151)	78 (4–160)	91 (5–160)	NS
Hb (g l^{-1})	110 (56–153)	114 (55–170)	111 (53–149)	111 (57–152)	NS
WBC ($\times 10^9$ l^{-1})	6.5 (3.0–11.7)	6.0 (2.5–16.0)	5.7 (2.3–19.3)	5.6 (2.8–21.1)	NS
PLT ($\times 10^9$ l^{-1})	229 (98–429)	238 (110–484)	228 (23–440)	174 (116–430)	NS
Serum creatinine (mg $l^{-1)}$	11 (6–90)	10 (6–3.3)	10 (6–113)	11 (6–35)	NS
Albumin (g l^{-1})	38 (22–52)	39 (23–53)	385 (20–62)	38 (24–48)	NS
Serum MC (g l^{-1})	42 (9–90)	32 (6–82)	29 (7–111)	32 (7–115)	NS
Residual normal Ig (%)	0.38 (0.08–1.5)	0.36 (0.06–1.7)	0.31 (0.08–1.64)	0.34 (0.1–1.9)	NS
Alkaline phosphatase (Ul^{-1})	1400 (170–5090)	1260 (210–4170)	1200 (210–4260)	1210 (410–7290)	NS
Uric acid (mg l^{-1})	60 (32–170)	55 (24–111)	57 (20–131)	55 (16–116)	NS
Serum Ca^{++} (mg l^{-1})	93 (74–142)	94 (80–118)	93 (72–144)	92 (80–162)	NS
Urinary Ca^{++} (mg 24 h^{-1})	15.7 (1.6–70)	12.57 (1.1–148)	14.35 (2.0–96)	12.5 (2.2–171)	NS

WBC, white blood cells; PLT, platelets; MC, monoclonal component.

3.1. Evaluable patients

At the time of this analysis (June 2000), 258 of the 341 patients originally recruited were evaluable for both response and survival. Their main clinical and laboratory characteristics are summarised in Tables 1 and 2.

With respect to the 1993 analysis [4], 17 additional stage I patients have been evaluated for response, in that they were originally randomised to no treatment and subsequently progressed and were treated (after a median period of 60 months).

The reasons why 78 patients are not evaluable for response are detailed in Figs 1–3 and are refusal of treatment (2 patients), insufficient data for establishing response (9 patients), lost to follow-up before response could be assessed (9 patients), stage I patients randomised to no treatment (23 patients) and early death, i.e. death before response could be assessed (35 patients) (see Figs. 1–3).

5 additional patients (2 with CR, 1 with PR, 1 with SD and 1 with PD) have been lost to follow-up after a median time of 65 months (10–98 months) and it is not possible to ascertain whether they are still alive.

Of the 258 patients who were evaluable for both response and survival, 244 (94.6%) have died and the

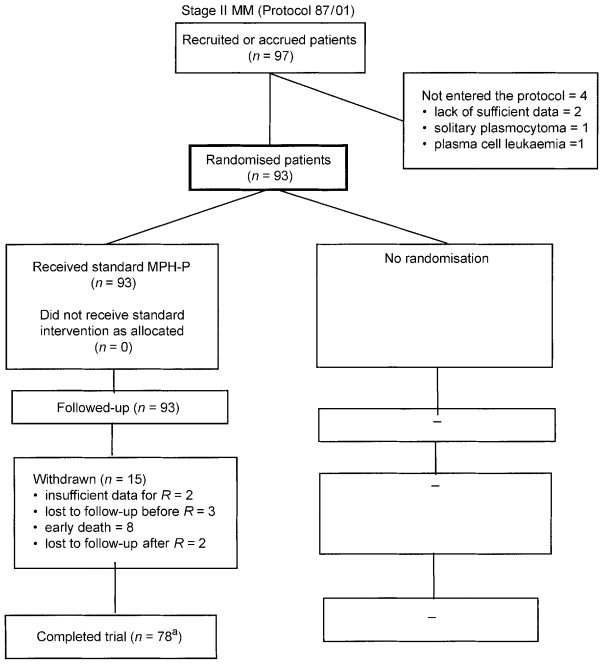

Fig. 2. Flow chart of the progress of patients through the trial that evaluated the relationship between response and long-term survival in MM (adapted from Ref. [27]). [a]Overall, 78/93 patients with stage II MM were evaluable for both response and long-term survival, according to the criteria of Protocol MM 87.

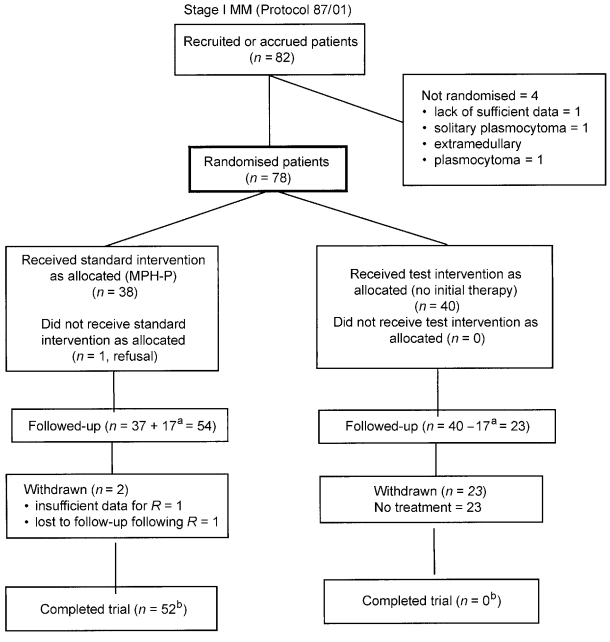

Fig. 1. Flow chart of the progress of patients through the trial that evaluated the relationship between response and long-term survival in MM (adapted from Ref [27]). [a]These 17 patients were added for evaluation of responses in the following up of Protocol 87/01, in that they were originally randomised to no initial therapy and subsequently progressed and were treated with MPH-P; these patients have been subtracted from the cohort of patients who were randomised to no initial therapy; [b]Overall 52/78 patients with stage I MM were evaluable for both response and long-term survival; according to the criteria of Protocol MM 87. R, response; MM, multiple myeloma.

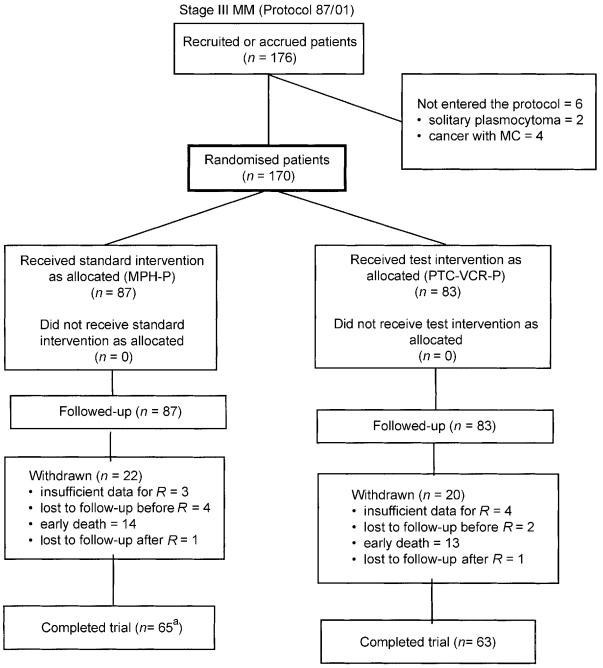

Fig. 3. Flow chart of the progress of patients through the trial that evaluated the relationship between response and long-term survival in MM (adapted from Ref. [27]). [a]Overall, 128/170 patients with stage III MM were evaluable for both response and long-term survival, according to the criteria of Protocol MM 87. PTC-VCR-P, peptichemio, vincristine and prednisone.

median follow-up of the remaining 14 (5.4%) surviving patients is 138 months (121–162 months).

3.2. Survival according to response

Overall, 86.8% (95% Confidence Interval (CI): 82.1–90.5) of patients had a CR, PR or SD following first induction chemotherapy and 13.2% (95% CI: 9.4–17.8) had progressive disease. The CR, PR and SD rates were 23.2% (95% CI: 18.3–28.6), 26.8% (95% CI: 21.7–32.5) and 36.8% (95% CI: 31.0–42.8), respectively.

After a median follow-up of 134 months, the median survival of all 258 evaluable patients is 40 months (6–162 months) (Fig. 4).

There were no differences in median survival among patients who had CR (50 months (9–162 months)), PR (46 (8–147 months)) or SD (41 months (7–135 months)) following first induction chemotherapy. These survival rates were significantly higher than those in patients whose disease progressed while they were receiving first induction chemotherapy (13.6 months (6–135 months)) ($P<0.0001$) (Fig. 4). The survival of patients with SD was significantly longer than that of patients with PD ($P<0.0002$).

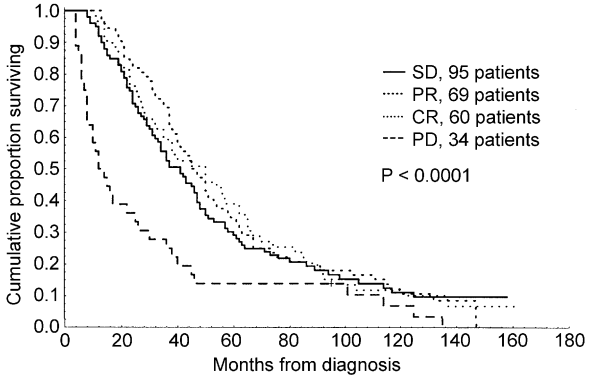

Fig. 4. Survival of patients with multiple myeloma according to the four types of response to first-line chemotherapy. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

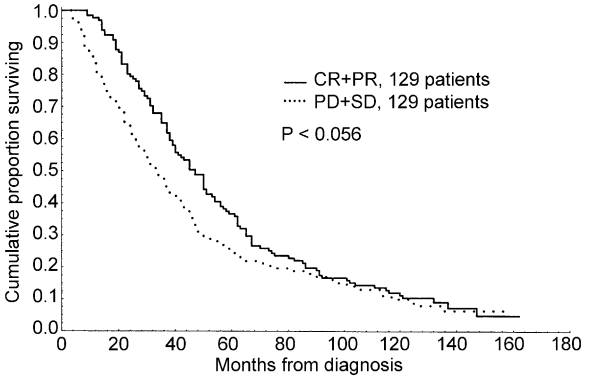

Fig. 5. Survival of patients with multiple myeloma according to two groups of response to first-line chemotherapy (abbreviations as in Fig. 4).

When the survival of patients with either a CR or PR was compared with that of patients with either SD or PD, the survival advantage of the former (46 months (range 8–162 months)) over the latter (33.5 months (range 6–135 months)) group approximated, but did not reach the level of statistical significance ($P=0.56$) (Fig. 5).

The intensity of treatment was quite similar in the four groups of patients. In fact, first-line therapy was completed in 81.9, 83.6, 84.0 and 78.4% ($P=$NS) of patients who had CR, PR, SD and PD, respectively. Second-line therapy was completed more frequently in patients with CR, PR, SD (83.2, 85.6 and 80%, respectively) than in patients who had PD (62.8) ($P=0.008$).

3.3. Patients' characteristics according to response

Overall, there were no major clinical nor laboratory differences between patients who had CR, PR and SD, and had similar survival.

3.4. Causes of death

The causes of death were ascertained in 174 of the 244 patients who died and divided into related (mainly infections, renal insufficiency and hypercalcaemia) and unrelated to MM. There were no differences in the causes of death among patients who had a CR, PR or SD following first-line chemotherapy, both related (72.2, 69.6, and 75.8%, respectively) and unrelated (24.2, 31.4 and 24.2%, respectively) to MM. With respect to these patients, a greater number (94.1%, $P=0.04$) of patients who had PD during first-line chemotherapy died of causes related to MM.

4. Discussion

This study focuses on two aspects of conventional chemotherapy of MM. First, it indicates that benefits from the initial treatment are gained not only by patients who achieve major responses (i.e. either CR or PR), but also by patients who experience minor response or whose disease remains stable (i.e. experience a $<25\%$ decrease or increase in MC) during treatment. Second, only patients whose disease progresses while receiving treatment are to be considered severe chemotherapy failures, and therefore effort should be made to promptly identify these patients. As a matter of fact, the median survival of patients who achieved minor response or SD was similar to that of patients who obtained major responses and significantly better than that of patients with PD. These data are in keeping with those recently reported with a shorter follow-up [8].

The relevance of minor responses must be taken into account when the survival benefit of chemotherapy is

evaluated. The questionable correlation between complete and partial response rates and survival reported in single MM studies, as already discussed [8], as well as in a dedicated meta-analysis [9], could be explained by the fact that minor responses are included among non-responses, i.e. therapy failures. Actually, a number of patients considered as therapy failures have minor responses or SD and probably gain benefit from chemotherapy. Depending on the precise definition of minor response or SD, these patients account for different percentages of non-responders (for example, they represented 36.8% and 18% of patients in our and in Oivanen's series). The relevance of minor responses or SD in favouring survival, as suggested in some studies [10–13]), is illustrated, in our series, by the fact that the survival of the grouped patients who had either SD or PD approaches that of the grouped patients who had either CR and PR (Fig. 5).

In MM, a kinetic reason for the poor correlation between the degree of response to chemotherapy and survival, unproven in this study, could be that a number of chemotherapy-refractory, kinetically-quiescent cells persist in responsive patients following tumour debulking. If the gompertzian growth curve model is accepted, these relatively few residual cells are rapidly recruited into the cell cycle after chemotherapy is discontinued [14,15]. Their proliferation rate is expected to be greater than that of the larger bulk of cells in patients with minor response or stable disease, leading to a more rapid relapse. In patients with progressive disease, there is no recruitment, in that resistant cells are proliferating and increase the clinical disease irrespective of chemotherapy treatment.

The inadequate evaluation of minor responses, including the status of stable disease, could add to the general problem of determining a relationship between an increased response rate and a survival advantage. The clinical relevance of minor responses is possibly also underestimated, in chronic lymphocytic leukaemias [3] and advanced breast [1] and colorectal [2] cancers. In fact, in randomised studies, survival is similar (present study [1,3,8]) or only marginally increased [2] in either the arm who attained a high or a low complete plus partial response rate, as conventionally defined. This could indicate that minor responses and/or disease stabilisation play a role in prolonging survival in the arms attaining low percentage of major responses.

Another general explanation for the poor correlation between response and survival is that compared with the objective overall survival measure, response is more subjective, with confounding factors deriving from the interpretation of laboratory and/or radiological tumour measurements (in MM these include changes in MC, BMPC%, Hb, serum calcium, BUN, albumin concentration and skeletal lytic lesions) and the lack of external reviewers (especially in multicentre trials). Hence, the relationship between response, a partially subjective parameter, and survival, an objective parameter, cannot be expected to be completely unequivocal.

Finally, other reasons are probably implicated. As a studied example, in colorectal cancer the new modalities of administering fluoropyrimidines decrease, compared with bolus fluoropyrimidines, the odds of failure to respond by 50%, but decrease the odds of death by only 6%. Overall, this means that the final treatment outcome, i.e. survival, is only partially accounted for by response rate to the first treatment [2]. Second- and third-line therapies, duration of response, tumour grade and performance status could play relevant, although poorly assessable, roles.

The other practical, relevant finding of this study is the very poor prognosis of patients who progress during the initial chemotherapy and usually die, as expected, from causes directly related to the disease, especially infections, renal insufficiency and hypercalcaemia. These patients must be promptly identified, to be switched to another treatment, such as thalidomide [16] or high dose chemotherapy schedules, thus avoiding unnecessary toxicity.

The reasons for resistance are poorly known, both in MM and in the overwhelming majority of other neoplasias. Biological factors are putative biological causes and must be evaluated within controlled clinical trials. In MM, these include the low proliferative activity [14,17] and the presence of aneuploid clones [18,19], most of which have a multiple drug resistant (MDR) phenotype [20], as well as plasmablastic cytology [21], *c-myc*, *N-ras* and *k-ras* oncogene mutations [22,23], CD19, CD28, CD36 and LFA-1 (alpha L beta 2-integrin) expression [24], increased interleukin-6 (IL-6) production [23,25] and VLA-4 (very late antigen) and VLA-5 integrin expression [26].

Overall, this study, as well as that of Oivanen and colleagues [8], could contribute to a better definition of the role of chemotherapy in MM. Patients having minor responses or stable disease on first-line chemotherapy probably increase the number of those who benefit, i.e. should be considered with those who have major responses. On the other hand, patients who progress during treatment deserve special attention, in that their prognosis is greatly worsened, and they therefore must be promptly identified using a detailed phenotypic and genotypic analysis.

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