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Plateau phase in multiple myeloma: an end-point of conventional-dose chemotherapy

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ABSTRACT

Background and Objective. **In multiple myeloma (MM) patients treated with conventional chemotherapy, the attainment and duration of a plateau phase seems to affect survival more than the degree of response to initial treatment. The aims of this study are: 1) to analyze within a cohort of previously untreated MM patients the incidence and the duration of the plateau phase; 2) to correlate it with the presenting features; 3) to assess its impact on survival.**

Design and Methods **A series of 146 consecutive MM patients treated with conventional chemotherapy were evaluated for this study. Of 146 patients, 102 responded (13 achieving complete response, 21 partial response, and 68 minimal response), and 44 showed less than minimal response or a progression. A plateau phase was documented in 115 patients (comprising all responders and 13 non responders. The median plateau phase duration was 21.6 months. The majority of patients received intermittent cycles of chemotherapy (melphalan or interferon) during the plateau phase. In multivariate analysis, lytic lesions, response, and time to the best response (TBR) correlated with the attainment of a plateau, while stage, response as a whole, and TBR showed a significant correlation with the duration. In contrast, the type of response did not correlate with either the attainment or the duration of plateau. To analyze the prognostic impact of presenting features, response to therapy and plateau we used a hierarchical model for survival. The analysis showed that the response to therapy and the duration of plateau significantly affect the survival.**

Interpretation and Conclusions. **In multiple myeloma a plateau phase of at least 6 months' duration has a higher impact on survival than the degree of response to conventional chemotherapy so plateau duration could be used as target of therapeutic trials. The best way to maintain the plateau phase remains, however, undefined.**

Key words: multiple myeloma, plateau phase, conventional therapy

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Cytotoxic treatment currently available for multiple myeloma (MM) relieves or temporarily eliminates symptoms and improves survival. There is, however, no evidence that the chemotherapeutic strategies adopted up to now are curative.[1-4] After conventional chemotherapy, the median survival of patients with MM is three years or less, while better survival has been reported with high-dose chemotherapy supported by autologous stem cell transplantation.[5-7] A cure is occasionally achieved by allogeneic transplantation, even though the mortality related to this approach is still high.[8,9] The main difficulty in MM, however, remains the evaluation of the response to treatment, whose quality is usually considered strictly linked to the percentage fall of the M-component.[10] Conventional-dose chemotherapy with melphalan, for instance, results in a complete remission in less than 10% of patients. More frequently the patients obtain a stable state which is known as the *plateau phase*. This is usually defined as 3 to 6 months of clinical stability, stable paraprotein levels regardless of the degree of percentage decrement of M protein, and transfusion independence.[11] However, all the studies comparing the classic combination of melphalan and prednisone with multidrug protocols, in spite of higher percentages of complete remissions, have failed to demonstrate that the more intensive treatments are superior in terms of overall survival.[1-4,12-14]

This has led some authors to attribute a greater importance to the attainment of a plateau phase and to assess its predictive value for survival.[15-20]

The aims of this study were: a) to analyze the incidence and the duration of the plateau phase within a cohort of 146 MM patients treated with conventional-dose chemotherapy; b) to evaluate the prognostic significance of presenting features in predicting the achievement of a stable state and survival; c) to assess the impact of the plateau phase on survival.

Design and Methods

Between 1985 and 1992 we observed 177 consecutive previously untreated myeloma patients. Thirty-one patients were excluded from the study for the following reasons: 15 *early deaths*, 13 lost during follow up, and 3 whose initial biochemical parameters were not

evaluable. The following criteria, indicated by the *Chronic Leukemia-Myeloma Task Force* for diagnosis of MM were used: *major criteria,* a) serum M-protein concentration >3.5 g/dL (IgG) or >2.0 g/dL (IgA) and/or Bence Jones proteinuria > 1 g/24 hours; b) bone marrow plasma cells > 30%; *minor criteria,* a) bone marrow plasma cells between 10-30%; b) osteolytic bone lesions; c) serum M-protein concentration < 3.5 g/dL (IgG) or < 2.0 g/dL (IgA) and/or Bence Jones proteinuria < 1 g/24 hours; d) reduction of normal serum immunoglobulins. A diagnosis of MM was accepted if at least one major criterion plus one minor one or three minor criteria were fulfilled.[11] Staging was performed according to Durie and Salmon.[21] The WHO scale was used to assess the patient's performance status. Bone lesion extension was evaluated using skeleton X-ray. Biological studies conducted for initial evaluation included bone marrow aspiration and/or biopsy, serum and urine electrophoresis, immunologic typing of the myeloma immunoglobulin (M-component) and normal immunoglobulins as well as blood cell count and serum biochemistry. For the 146 evaluable patients the following parameters were computed for their prognostic value on survival: age, disease stage, performance status, radiological bone lesions, white blood cell count, platelet count, M-component type and level, bone marrow plasmacytosis, hemoglobin levels, calcium, erythrocyte sedimentation rate (ESR), creatinine, and Bence Jones proteinuria. In addition, primary chemotherapy, response to therapy, and time to reach the best response (TBR), were included. All but three patients, treated only with low-dose steroid, started conventional chemotherapy: melphalan (MPH) or cyclophosphamide (CTX) plus prednisone. VAD-like combination protocols, including anthracyclines, were used in only 4 patients. The criteria published by the *Chronic Leukemia-Myeloma Task Force* were applied for evaluation of response.[11] A complete response (CR) was defined as a reduction of the initial serum M-component concentration and Bence Jones proteinuria by >75% accompanied by normalization of renal function, anemia, and hypercalcemia, and by clinical improvement. A partial response (PR) was considered achieved if the M-component in serum and urine was reduced to 75-50%, and a minimal response (MR) when the reduction was of 50-25%. A response less than MR or disease progression during treatment was defined as non-response (NR). Patients who fulfilled the response criteria within 12 weeks after the start of therapy were classified as *early responders*, the others as *late responders*.

The duration of the plateau phase was calculated from the achievement of the best response until a 50% increase occurred in paraprotein above the plateau level in two subsequent determinations obtained 1 month apart, or until any sign appeared of disease progression such as hypercalcemia, bone lesions, renal failure, not controllable with the ongoing chemotherapy.

During the plateau phase patients underwent periodic serum biochemistry controls; bone marrow aspiration or skeletal X-ray were performed only in doubt of progression. Maintenance therapy until disease progression was performed in most patients: 79 patients were treated with MPH or CTX, alone (39 pts) or in combination with vincristine (40 pts), 21 with IFN (in 6 pts as a single agent, in 15 in combination with chemotherapy), 23 patients were only submitted to periodic examinations, and 8 were not evaluable.

Statistical analysis

Descriptive statistics (mean and standard deviation, SD) were used to summarize data for continuous variables and percentages of patients for categorical variables. The primary endpoint was time to tumor-related death. Secondary endpoints were time to the occurrence of a plateau and its duration. The covariates were selected because of their potential association with either one of the two outcomes: death or the presence of a plateau. Cox proportional hazard regression was used to model time to death; patients surviving were censored at the last follow-up time. During the observation period, the occurrence of a plateau and of a response, and the type of response were treated as time dependent covariates. Patients showing a plateau were classified into the appropriate category from the time of the best response to the time of progression of the disease or to the end of the observation when no progression occurred.

Bivariate associations between any covariate and the primary outcome were assessed. Those showing a p value < 0.1 were retained for multivariate analysis. Concerning the survival, for modeling purposes the covariates were grouped into several categories (clinical or laboratory features, response to therapy, plateau phase), based on their timing within the diagnostic and therapeutic process.

The clinical variables included the stage according to Durie and Salmon. Laboratory variables included bone marrow plasmacytosis, albuminemia, creatininemia, type of monoclonal component and platelet levels. The type of response was further considered as well as the occurrence of a plateau. A series of hierarchical proportional hazard models was constructed, in which each category of covariates was successively added. The first model included only the stage of the disease and the final model included the 4 groups of covariates. Differences between models were tested with the log likelihood ratio statistics. Explained variation of the different models was calculated using Magdala statistics.[22]

Univariate and multivariate Cox models were used to assess the association of the presenting covariates with time to occurrence of a plateau. The same covariates were related to duration of plateau by means of a multiple regression model. The variables significant

at $p = 0.1$ at univariate analysis were included in the multivariate model. Backward stepwise selection (p-value to stay in the model = 0.1) was then applied. Stata 5.0 (StataCorp 1997, College Station, TX, USA) statistical software was used for the computation.

Results

The main characteristics of the 146 patients are summarized in Table 1. One hundred and two patients achieved a response (13 CR, 21 PR, 68 MR) after a mean of 8.8 months from the start of chemotherapy and 44 did not show a response. Among patients defined resistant to first line treatment, 9 had stable disease and 35 were in progression. The median survival of responding and not responding patients, analyzed through a Cox model considering response as a time-dependent variable, differed significantly (44.3 vs 29.3 months, p=0.002). Among responders, survival did not differ significantly in relation to the type of response.

In order to evaluate the impact of presenting features on the attainment of a plateau phase univariate and multivariate statistical analyses were performed. In univariate analysis, age (p=0.05), lytic lesions (p=0.01) and time to the best response (p=0.01), were significantly correlated with the attainment of a 3 month plateau phase. In multivariate analysis, lytic lesions, response and TBR maintained a statistical significance. In univariate analysis, Hb level (p=0.02), platelet level (p=0.05), bone marrow plasmacytosis (BMPC) (p=0.001), TBR (p=0.05), and stage (p=0.03), significantly correlated with plateau duration. Multivariate logistic regression selected stage, response as a whole and TBR as the most significant independent factors for plateau duration.

The degree of response did not statistically influence the achievement or duration of plateau phase. In fact, the incidence of a plateau phase was similar among patients with CR or PR and those with MR (Table 2). Furthermore, even in the group of patients categorized as non-responders, 9 patients had stable disease for more than 6 months and 3 of them for more than 24 months. Multivariate analysis confirmed a lack of correlation between the level of response and the achievement of plateau or its duration. Of the 96 patients attaining a minimum of 6 months' plateau, 63 showed disease progression, 18 are still alive with stable disease, 11 died during MM plateau phase, and 4 were lost to the follow-up.

We also evaluated the prognostic impact of the plateau phase on survival considering it as a time dependent variable. As shown in Figure 1, the attainment of a plateau phase was strikingly correlated with a longer survival.

We then tried to divide patients into groups according to duration of the plateau phase. No survival advantage was seen in patients with a plateau phase of less than 3 months with respect to those in progression (p=0.4). Similarly, no survival difference was present between patients with a plateau phase of less than 3 months and those with a plateau lasting from 3 to less than 6 months (p=0.8). Therefore, patients not achieving a plateau, with < 3 months and with 3 to < 6 months plateau duration were considered as a single group. Patients whose plateau phase lasted more than 6 months duration were categorized into two groups: one of 6-24 months and one of more than 24 months. As shown in Table 3, it appears that patients with more than 24 months of plateau have a strikingly important survival advantage over patients with less than 6 months of plateau (p=0.00001) or with patients with a plateau between 6 and 24 months (p=0.0001). However, the survival of patients with a plateau lasting 6-24 months differed significantly from that of those with a plateau of < 6 months (p=0.002) (Figure 2).

Table 1. Main characteristics of 146 patients evaluated for plateau phase.

Sex M/F		76/67
Median age		58 (range 33-84)
Performance status		
0-1		99
2-4		47
Stage*		
I		42
II		31
III		73
MC		
IgG		93
IgA		33
IgD		2
BJ		13
Non-secretory		5
Blood counts and serum biochemistry		
Hemoglobin	< 8.5 g/dL	31
Platelets	< 150×10^9/L	24
Creatinine	> 2 mg/mL	18
Urea	> 50 mg/mL	21
Calcium	> 12 mg/mL	8
BMPC >50%	53	
Bone lesions		
no lesions		71
lytic lesions		75

*MC: M-component; BJ: MM Bence Jones; BMPC: bone marrow plasma cells; *Stage according to Durie & Salmon (1977).*

Table 2. Correlation between duration of plateau phase and the level of response in 146 MM patients.

Response to first line therapy	*< 6 months*	*≥6 and ≤24 months*	*>24 months*	*Total no. of patients*
CR or PR	5 (15%)	13 (38%)	16 (47%)	34
MR	10 (15%)	27 (40%)	31 (45%)	68
NR	35 (79%)	6 (14%)	3 (7%)	44
All patients (%)	50 (34%)	45 (31%)	51 (35%)	146

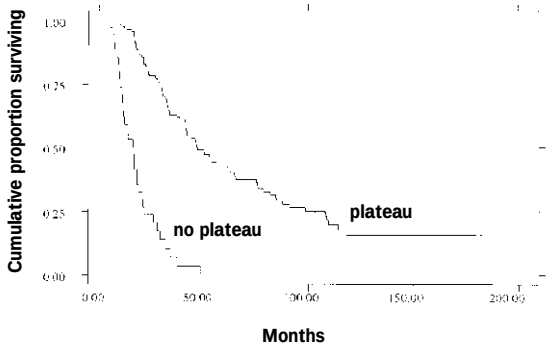

Figure 1. Survival curves in relation to the achievement of a plateau phase. The difference between the two groups is strikingly significant (p=0.00001).

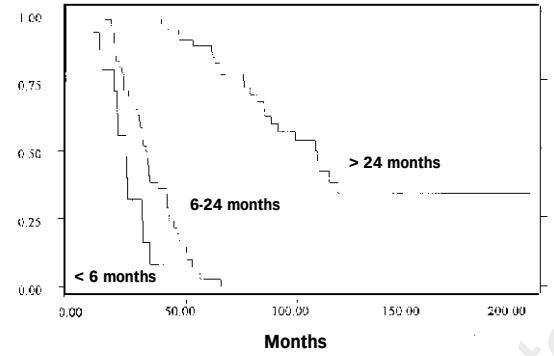

Figure 2. Survival curves of 146 MM patients in relation to the duration of plateau phase. Survival of each group differs significantly from the others (p=0.0001)

To analyze the prognostic impact of the presenting features, response to therapy and occurrence of plateau, we used a hierarchical model for survival. The analysis shows that each step is important even though the plateau (considered as attainment and duration) has a greater influence on survival (Table 4).

Discussion

We performed this study, in a cohort of 146 evaluable MM patients, to evaluate the clinical relevance and the prognostic significance of the plateau phase.

The concept of a plateau phase was first introduced by Salmon[23] through kinetic studies. He demonstrated that the plateau phase results from a balance between the cytoreductive effect of chemotherapy and the expansion of the growth fraction of the neoplastic clone. Its importance was further underlined by Durie *et al.*[24] and Alexanian *et al.*[25] They introduced the concept of *unmaintained remissions* hypothesizing the plateau phase as an indolent state in which plasma cells are dormant, probably unsensitive to any treatment. So they concluded that it is possible, through a selection of patients, to identify those who would not benefit from further therapy.

Table 3. Duration of plateau phase and survival in 146 patients with multiple myeloma. Progressive disease regardless of chemotherapy is attributed to a plateau of 0 months.

Duration of plateau (months)	*N° of patients*	*Median survival (months)*
0 - < 6	50	18.8 (10.2-29.7)
6 - ≤ 24	45	31 (21.2-41.9)
> 24	51	108 (75.7-not reached)
Overall	146	38

Table 4. Hierarchical models for survival analysis.

Models	*Loglikelihood*	*Likelihood ratio test* chi-square (df)*	*p*
Stage	- 449.98	–	–
Stage+Lab. variables	- 441.11	17.75 (8)	0.0232
Stage+Lab. variables+ response to therapy	- 427.82	26.57 (3)	0.0000
Stage+Lab. variables+ response to therapy+plateau	- 372.53	110.59 (3)	0.0000

**tests difference between consecutive models.*

Although these efforts have stressed the importance and the predictive power of plateau phase, most authors have been paying attention to the achievement of a more profound response rather than considering the plateau phase itself as an end point. However, until now, in spite of a higher percentage of complete remissions, no substantial improvement in survival has been shown to be derived from polychemotherapy approaches rather than from MPH plus prednisone.[1-4,13]

The first goal of this study was to evaluate which parameters correlate with the attainment and the duration of the plateau phase. Data reported in the literature about this item are contradictory. Oivanen reported high Hb level as the only presenting characteristic significantly correlated with achievement of a plateau phase.[19] Joshua *et al.*,[18] on the other hand, reported high Hb, high albumin, lower β_2 microglobulin and lower incidence of Bence Jones excretion as features typically present in patients who obtained a long stable phase. Other authors[18,25] reported the stage and the percentage fall of paraprotein as important parameters. In the effort to distinguish between the attainment and the possibility of maintaining a stable phase, we performed a double analysis with the initial parameters, the response to therapy, and the TBR. In univariate analysis, age and lytic lesions correlated with the achievement of plateau, while Hb,

platelet count, BMPC, and stage correlated with its duration. This means that a low-burden myeloma is much more likely to be a durable, stable disease. Response to initial treatment, as a whole, and time to the best response, subsequently considered, proved to be significantly related to plateau. In contrast, we did not find any effect of the type of response on the duration of the plateau or survival. The 8.8 months mean time taken to reach the best response was similar to the 9 months reported by Joshua,[18] the 8.8 months of McLennan,[26] and the 9.2 months of Oivanen.[19] In multivariate analysis, response and time to best response proved strongly related to a stable state.

In our study, we found no differences in terms of survival between the group of patients with a plateau lasting less than 6 months and those who had MM in progression. This differs from the period of at least 3 months reported by Oivanen.[19] Patients with a plateau lasting between 6 and 24 months had a significantly better survival than those with a shorter stable period. A more significant advantage was found for patients with a plateau phase >24 months (Table 3). The median duration of the plateau (21.6 months) was longer than the 13 months reported by Joshua,[18] but is in line with the 19.5 months reported by MacLennan,[26] and the 18 by Oivanen.[19]

To evaluate how survival is affected by the presenting features, response to therapy and occurrence of plateau, we used a different statistical approach. Through this statistical method, we tried to re-examine the usual diagnostic and therapeutic itinerary followed during the course of multiple myeloma. The analysis shows that each step is important even though the response to therapy (as a whole) and the plateau (considered as attainment and duration) have a greater influence on survival. This is consistent with the plateau phase having a central role which could be considered as an end-point of conventional chemotherapy.

The other unresolved problem is whether and, if so, how maintenance chemotherapy influences the plateau phase. As known, the plateau phase is an indolent state in which cells are essentially dormant, so that, as suggested by some authors,[19,24] chemotherapy is probably useless in this phase. In our study, the majority of MM patients underwent maintenance chemotherapy with MPH or IFN, alternating with *unmaintained periods*. Belch *et al.*[27] concluded that maintenance MPH offers no advantage to patients who have had a stable response to treatment and that unmaintained patients retain their sensitivity to initial treatment in case of relapse. At the same time, they underline the necessity of close monitoring in order to restart therapy when MM begins to escape from the plateau phase since the probability of attaining a response is significantly less when patients are symptomatic. It is, therefore, not yet definitely established whether to and how to maintain the plateau phase. It is equally controversial how to predict which patients will have a prolonged plateau phase.[28,29] Even though different variables seem to positively correlate with a long plateau phase, careful follow-up seems to be the only safe means of monitoring the course of the disease.

In conclusion, in multiple myeloma a plateau phase of at least 6 months has a greater impact on survival than the quality of response to conventional chemotherapy and this phase could be used as a target of therapeutic trials. The best therapeutic strategy for patients in a stable state is, however, yet to be defined.[30]

Contributions and Acknowledgments

AC was responsible for the conception of the study and its design, data handling, and writing of the paper. AN and ML contributed to the design of the study, to data handling and writing of the paper. PZ, LA contributed to the data collection. CB participated in the review of the paper. CK performed the statistical analyses. The order of the authors is related to their contribution.

Disclosures

Conflict of interest: none.

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