Serum M-spike and transplant outcome in patients with multiple myeloma

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High dose therapy with autologous stem cell transplantation (HDT-ASCT) has prolonged survival in patients with multiple myeloma. Patients who achieve a complete response (CR) benefit the most from this form of therapy. Thus, achieving a CR is an important goal of therapy and it will be beneficial if the probability of achieving CR can be determined for any patient before transplant. Here we report that pretransplant monoclonal protein level (M-spike) was found to be an important predictor. Thus, we used knowledge of the rate of M-protein production by myeloma cells together with the clearance of the protein to estimate the pretransplant disease burden. We show that the pretransplant disease burden, based on the M-spike, is the only predictor for achieving CR. A simple function that describes this probability is presented. We also provide an estimate of the rate of tumor regrowth in patients who obtain a CR and in patients who only get a partial response with HDT-ASCT. The significant expansion of myeloma cells after HDT-ASCT is clearly evident. Clinical trials must be designed that take into account these kinetic aspects of the disease. (*Cancer Sci* 2007; 98: 1035–1040)

The advent of HDT-ASCT has improved the survival of patients with MM. HDT-ASCT is a safe procedure in centers experienced with this form of therapy and mortality can be as low as 1–2%.[1–3] The improved survival is partly due to a higher incidence of CR that can approach 40%, compared to what can be achieved with conventional therapy using melphalan–prednisone, VAD and its variants, Thal-Dex and melphalan–prednisone with thalidomide.[4–6] Given the impact of CR on survival[7–10] current therapy is designed to achieve CR in as many patients as possible. Thus, patients with a new diagnosis of MM without significant comorbidities are usually offered HDT-ASCT soon after initial diagnosis, although not all studies have shown an improvement in survival with HDT compared to conventional therapy.[11–13] Moreover, response rates for early *versus* delayed transplant are not significantly different but some patients might not be able to undergo a delayed transplant due to age, comorbidities or advanced disease.[14–16] In preparation for HDT-ASCT, and outside of clinical trials, patients usually receive cytoreductive therapy with either VAD (or its variants)[17,18] or Thal-Dex[19] as these agents neither damage the hematopoietic stem cell pool nor interfere with stem cell collection.[20]

MM is a unique neoplasm because the vast majority of patients have a detectable serum and/or urine M-protein that can be used to monitor the disease and its response to therapy. Sullivan and Salmon have used measurements of the rate of M-protein production and metabolism to estimate the burden and rate of tumor growth.[21] Tumor burden is an important prognostic parameter and incorporated directly or indirectly in the Durie–Salmon staging system[22] and the International Staging System.[23] To date, all attempts to estimate tumor burden have been based on indirect measurements such as β_2-microglobin[24,25] and percentage of bone marrow plasma cells.[26] However, β_2-microglobulin is cleared by the kidneys and levels increase with renal dysfunction, although this has been considered an advantage as it indirectly captures more advanced disease. Lactate dehydrogenase is elevated in only a small percentage of patients with MM and the bone marrow biopsy may or may not be representative of the extent of marrow infiltration due to patchy involvement. In this report we study the impact of the serum M-spike and *estimate* disease burden on the outcome of HDT-ASCT in myeloma. We show that disease burden based on the serum M-spike is the most important determinant for achieving a CR and develop a simple means to predict the probability of achieving CR with HDT-ASCT. Moreover, we estimate the kinetics of tumor regrowth after HDT-ASCT.

Materials and Methods

Patients. Patients with MM who undergo HDT-ASCT at the Mayo Clinic, Rochester (MN, USA) are maintained in a database that is continuously updated by the senior author. This database contains all the relevant demographic, clinical and laboratory characteristics of the patients. All patients give informed consent to be included in the database. Any patient who is considered for HDT-ASCT undergoes evaluation of disease status before transplant that includes measurements of the serum M-protein, bone marrow aspirate and biopsy with cytogenetic analysis and PCLI. Patients with a serum M-protein <0.1 g/dL were excluded from this analysis. This study was approved by the Mayo Foundation Institutional Review Board in compliance with both federal regulations and the Declaration of Helsinki.

Response definitions. The response criteria were as defined by Blade *et al*.[27] A CR was defined as the absence of monoclonal protein in the blood and urine as well as a negative immunofixation. In these patients, the return of immunofixation positive serum defined relapse. However, for tumor burden estimation, the date of the first measureable M-protein level after relapse was considered. In the case of patients who achieved a PR, progression was defined as a doubling of the serum M-protein level. In patients with a PR, the lowest serum M-spike after transplant was considered the new baseline when estimating the rate of tumor regrowth, and the time interval between the lowest M-spike and M-spike compatible with progression taken as the denominator.

Disease burden estimation. Plasma volume was estimated from the patients' height, weight and hematocrit using established nomograms.[28] Assuming that, on average, a malignant plasma cell produces M-protein at a rate $p \approx 12.1$ pg/day and the M-protein is cleared at a rate $k = 0.117$/day (i.e. 11.7%/day)[21,29] if $M(t)$ is the size of the serum M-protein and PV is the plasma volume, then disease burden at a given time, $N(t)$ is given by:

$$N(t) = \log\left[\frac{(1-k)}{p}M(t)PV\right] \qquad (1)$$

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Abbreviations: CR, complete response; HDT-ASCT, high dose therapy with autologous stem cell transplantation; LCR, less than complete response; MM, multiple myeloma; M-protein, monoclonal protein; M-spike, pretransplant monoclonal protein level; PCLI, plasma cell labeling index; PR, partial response; Thal-Dex, thalidomide–dexamethasone; TTP, time to progression; VAD, vincristine–doxorubicin–dexamethasone.

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Serial measurements of $M(t)$ can thus be used to estimate tumor burden both before and after ASCT. Serum samples that are negative on immunofixation imply that the disease burden is $<10^9$ cells[30] which therefore sets an upper limit for disease burden in patients who achieve CR. The difference between the pretransplant disease burden, N_{PT} and burden at day 100, N_{100}, when patients were re-assessed after HDT-ASCT, was operationally defined as the maximum decrease in tumor burden. For patients who achieved CR, tumor reduction was estimated as:

$$\Delta N(t) = N_{PT} - N_{100} \quad (2)$$

Similarly, the disease burden at the time of relapse N_E was calculated using Equation 1. The rate of increase in tumor burden that led to a diagnosis of relapse, in the time interval t between the two measurements is given by

$$R = \frac{N_R - N_{100}}{t} \quad (3)$$

For patients who achieved CR, given the log-linear relationship observed in responding patients, the lowest tumor burden N_E was estimated as a 2.38 log reduction in the tumor (justified by the results below), although this could be as high as 3.5 log. In these patients, the estimated rate of tumor regrowth was calculated as:

$$R_E = \frac{N_R - N_E}{t} \quad (4)$$

For purposes of statistical analysis, R and R_E were combined or treated separately as indicated in the text.

Statistical analysis. All statistical analyses were carried out using StatView (SAS Institute, Cary, NC). Comparisons between nominal variables were carried out using the χ^2-test, and differences between continuous variables were evaluated with the Mann–Whitney U-test. TTP was defined as the interval between ASCT and evidence of progression and was estimated using the product limit estimate of Kaplan and Meier. Differences in TTP between groups were evaluated with the log–rank test. TTP was chosen as a measure of the effectiveness of therapy in keeping with recent recommendations.[31] Univariate and multivariate analyses were carried out using the Cox proportional hazards method with sequential addition of parameters starting with the parameter associated with the highest χ^2. Parameters that remained statistically significant were retained but those that lost statistical significance were discarded.

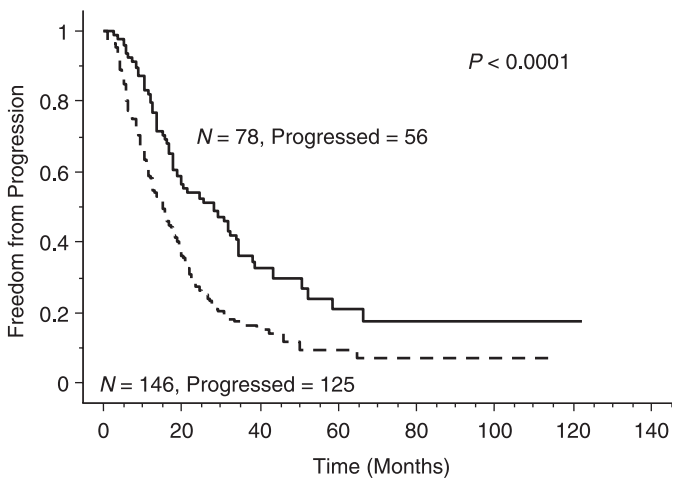

Fig. 1. Impact of achieving a complete response (CR) on time to progression. Multiple myeloma patients who achieved CR (solid line) had a median time to progression of 28 months compared to patients who did not achieve CR (dotted line) (15 months).

Data fitting. In order to obtain an equation for the probability to achieve CR as a function of the pretransplant disease burden, we sorted a total of 224 patients according to their disease burden. The log values for disease burden ranged from 10.27 to 12.45. Subsequently we binned the patients according to their log disease burden. Several binning intervals were tried, the overall results being robust to the binning details. Denoting by n the log of disease burden and by $p(n)$ the fraction of patients who achieved CR, a linear fit leads to $p(n) = 5.45–0.44n$ ($R^2 = 0.994$ and $p = 0.0002$). Unfortunately, such a simple expression does not capture some elementary properties expected from $p(n)$, namely, $p(n) = 1$ for $n < 9$, and $p(n) = 0$ for large n. However, the simple Fermi function $p(n) = [1 + e^{\beta(n-\alpha)}]^{-1}$ not only naturally includes the limiting behavior expected for $p(n)$ but also leads to an excellent fit of the binned data.

Results

Response to ASCT and TTP. The salient demographic, clinical and laboratory characteristics of this cohort of patients ($N = 265$) are presented in Table 1. By definition, all patients had a measurable serum M-spike (>0.1 g/dL). All patients had received prior therapy before ASCT, with 89.4% being treated with dexamethasone or a dexamethasone-containing regimen (e.g. VAD or Thal-Dex). In addition, 47% of patients were treated with at least two regimens, usually VAD followed by vincristine, carmustine, cyclophosphamide, melphalan and prednisone (VBMCP) that was started after stem cell collection. When they were evaluated at day 100, 78 patients had achieved CR (34.8%) and 146 (65.2%) had LCR. Patients who achieved CR had a significantly longer TTP (28 *versus* 15 months, $P < 0.0001$) (Fig. 1). In order to identify potential differences between CR and LCR patients, we compared the two cohorts for relevant demographic and laboratory parameters (Table 2). Only the

Table 1. Demographic, clinical and laboratory characteristics of the cohort of patients with multiple myeloma receiving high dose therapy with autologous stem cell transplantation (HDT-ASCT), *N* = 265

Characteristic	*n*	Median	Range
Sex, male	165	–	–
Age, years	265	56.45	32.6–71.2
Status at transplant	265	–	–
Plateau/response	89	–	–
Relapse	122	–	–
Primary refractory	54	–	–
Time to HDT-ASCT (months)	265	8.70	3.7–87.5
β_2-Microglobulin, μg/mL	261	2.68	0.9–15.2
PCLI, %	263	0.40	0.0–15.0
BMPC, %	265	20.00	0.0–95.0
LDH, U/L	253	165.00	65.0–1331.0
Serum M-spike, g/dL	265	1.98	0.1–10.36
Creatinine clearance, mL/min	265	76.50	20.0–164.0
Karyotype	259	–	–
Normal	181	–	–
Aneuploid	78	–	–
Durie–Salmon stage	265	–	–
II	75	–	–
III	190	–	–
International Staging System	165	–	–
Stage 1	67	–	–
Stage 2	53	–	–
Stage 3	45	–	–

–, not applicable; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase; M-spike, pretransplant monoclonal protein level; PCLI, plasma cell labeling index.

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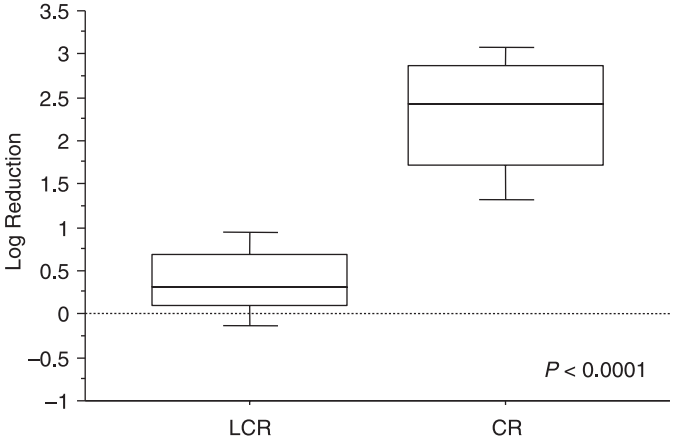

Fig. 2. Estimated log reduction in tumor burden with high dose therapy with autologous stem cell transplantation in multiple myeloma. Patients were divided into responders and non-responders. The median reduction in burden in patients who achieved complete response (CR) was 2.38 log. For those with less than complete response (LCR) this was 0.318 log ($P < 0.0001$).

serum M-spike correlated with the probability of achieving CR with HDT-ASCT ($P < 0.0001$, Mann–Whitney U-test).

Serum M-spike and response to ASCT. We hypothesized that the pretransplant serum M-spike is predictive of a response to HDT-ASCT due to a correlation with disease burden. Thus, we estimated the tumor burden before HDT-ASCT as described in the 'Methods'. The logarithm of the tumor burden before transplant correlates well with other, well established descriptors of tumor activity, including the percentage of bone marrow plasma cells ($P < 0.0001$) and β_2-microglobulin ($P < 0.0001$).

Tumor burden reduction with transplant. In an attempt to understand the response of MM patients to HDT-ASCT, we estimated the difference in tumor burden immediately before and at day 100 after HDT-ASCT. Patients who achieved CR had at least a median 2.38 log reduction in tumor burden, whereas the median tumor reduction in patients with LCR was 0.318 log ($P < 0.0001$, Mann–Whitney test) (Fig. 2).

Pretransplant tumor burden and response to HDT-ASCT. We hypothesized that the probability of achieving a CR was inversely related to disease burden. To test this hypothesis, we binned patients according to their disease burden (we denote by n the log of disease burden) and assessed the incidence of CR in each bin. As can be seen from Fig. 3, the probability of achieving a CR decreases with increasing tumor burden. We fit the observations into the well known Fermi function, where p is the probability and N is the tumor burden:

$$p(n) = \frac{1}{1 + e^{\beta(N-\alpha)}} \quad (5)$$

Our fitting gives $\alpha = 11.329$ and $\beta = 2.136$ ($R^2 = 0.9956$ and $p = 0.0038$), and accounts for the expected behavior of this probability function for low and large values of the disease burden.

Maximal response and relapse kinetics. The median reduction in tumor burden in patients who achieve a CR is probably higher than 2.38 log and more in the range of 3.5 as the detection limit of 10^9 sets an arbitrary ceiling for the cut-off. This would also be compatible with the dose–response curve for melphalan.[32] Thus, if patients with the highest tumor burden can achieve a 3.5 log reduction (Fig. 2), one expects that patients with the lowest tumor burden can achieve a similar reduction. Based on this assumption, we estimated the expected tumor burden after transplant in responders. However, for patients with a partial response, the lowest burden achieved after HDT-ASCT was

Table 2. Analysis comparing responders *versus* non-responders in patients with multiple myeloma receiving high dose therapy with autologous stem cell transplantation, $N = 224$

Characteristic	Status post-transplant		P
	CR	LCR	
Sex, male (%)	64	61.3	0.6930
Age, median, years	57.3	56.5	0.4380
β_2-microglobulin, μg/mL	2.505	2.705	0.9800
PCLI, median, %	0.4	0.4	0.5150
BMPC, median, %	23.0	20.0	0.0610
LDH, median, U/L	171.5	160	0.1460
CRP, median, mg/dL	0.4	0.4	0.3230
M-spike (g/dL)	1.225	2.595	<0.0001
Durie–Salmon stage, %	–	–	–
II	32.8	67.2	–
III	40.5	59.5	–
International Staging System	–	–	0.6072
Stage 1	43.6	40.0	–
Stage 2	34.5	30.6	–
Stage 3	21.9	29.4	–
Disease burden (log)	11.524	11.901	<0.0001
Cytogenetics	–	–	0.8522
Normal	70.6	69.4	–
Aneuploid	29.4	30.6	–
Disease status at transplant, %	–	–	0.5619
Plateau	42	33	–
Relapse	49.4	54.2	–
Primary refractory	8.6	12.8	–
Time to transplant, months	8.2	9.0	0.8570
Conditioning regimen (%)	–	–	–
MEL 200	58.6	63.5	–
MEL/TBI	35.6	31.3	–
Other MEL	4.5	5.8	–
HD-cyclophosphamide, %	–	–	0.5400
Mobilization	84	87	–

–, not applicable; BMPC, bone marrow plasma cells; CR, complete response; CRP, C-reactive protein; HD, high-dose; LCR, less than complete response; LDH, lactate dehydrogenase; MEL, melphalan; MEL/TBI, melphalan and total body irradiation; M-spike, pretransplant monoclonal protein level; PCLI, plasma cell labeling index.

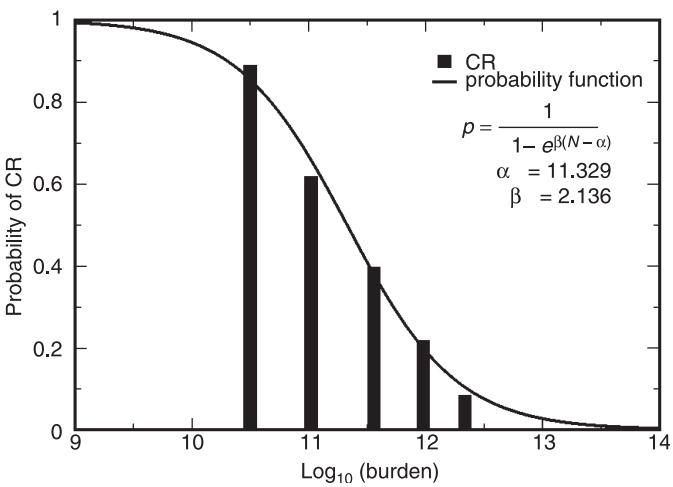

Fig. 3. Pretransplant tumor burden as a predictor of the probability for a complete response with autologous stem cell transplantation in multiple myeloma. As the tumor burden increases, the probability of complete response (CR) decreases considerably. Data fitted to the Fermi function, $R^2 = 0.994$ and $P = 0.0002$.

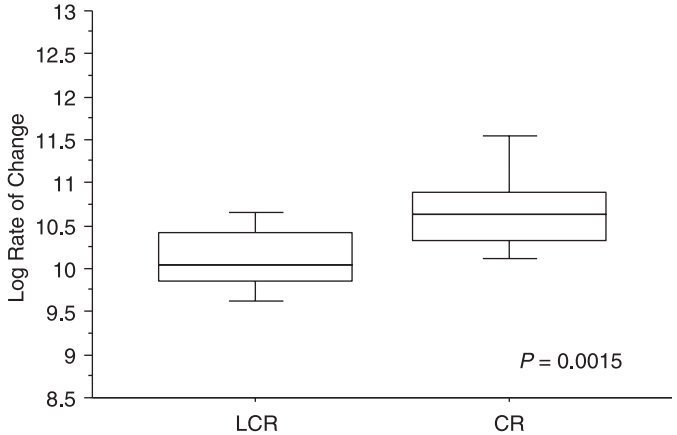

Fig. 4. Myeloma growth kinetics after transplant. In patients who achieve a complete response (CR) and have a lower tumor burden after transplant experience a higher rate of tumor growth as expected from the Gompertz function.

Table 3. Univariate analysis of parameters on time to progression in patients with multiple myeloma receiving high dose therapy with autologous stem cell transplantation, *N* = 209

Characteristic	Likelihood ratio	95% Confidence interval		*P*
Serum M-spike (g/dL)	1.139	1.017	1.275	0.0240
β_2-microglobulin, μg/mL	1.085	1.020	1.155	0.0149
C-reactive protein, mg/dL	1.052	1.013	1.093	0.0314
LDH, U/L	1.001	0.999	1.002	0.3716
Marrow plasma cells, %	1.015	1.009	1.021	<0.0001
Labeling index, %	1.186	1.118	1.257	<0.0001
Aneuploidy	2.374	1.782	3.164	<0.0001
Complete response	1.864	1.355	2.564	<0.0001

LDH, lactate dehydrogenase; M-spike, pretransplant monoclonal protein level.

measured. Knowing the size of the M-spike at relapse and the time of relapse relative to day 100, we determined the average increase in tumor burden for patients in both cohorts. Our results suggest that after a CR, the median rate of tumor regrowth is 4.33×10^{10} cells/day, but in patients with LCR, the rate is 1.14×10^{10} cells per day ($P = 0.0015$) (Fig. 4). A similar analysis using the conservative decrease in tumor burden of 2.38 log in patients who achieved CR gave similar results. Patients who achieved CR had a significantly higher rate of tumor replication compared to patients who did not achieve CR.

Multivariate analysis. Given the determining role of CR on TTP, we studied various parameters for their effect on TTP in both univariate and multivariate analysis. The results of the univariate analysis are presented in Table 3, and those for the multivariate analysis are reported in Table 4. Achieving CR is the most powerful and independent predictor of TTP (likelihood ratio [LR] = 2.131, $P < 0.0001$). In the multivariate analysis, the M-spike and achieving a CR could not be tested for independence due to their strong interaction (see Table 3).

Discussion

The advent of HDT-ASCT has significantly improved survival in patients with MM.[1–3,33,34] However, there is clear need for improvement in our therapeutic approaches. Data from several large studies has shown that patients who achieve CR have an

Table 4. Multivariate analysis on time to progression in patients with multiple myeloma receiving high dose therapy with autologous stem cell transplantation, *N* = 209

Characteristic	Likelihood ratio	95% Confidence interval		*P*
Aneuploidy	1.823	1.256	2.646	0.0016
Complete response	2.131	1.496	3.034	<0.0001
Labeling index	1.178	1.085	1.278	<0.0001
C-reactive protein	1.056	1.003	1.112	0.0400
Marrow plasma cells	1.008	1.000	1.016	0.0400

improved event-free survival compared to patients with LCR.[1–3,33,34] Our current study suggests that the estimated disease burden before ASCT is the most important determinant of CR with HDT. Patients with a lower disease burden have a higher probability of achieving CR and a longer TTP. This is compatible with what Rajkumar *et al*. reported for β_2-microglobulin.[35] The pretransplant disease burden is the only controllable variable as the PCLI and cytogenetic aneuploidy are characteristics of the disease and cannot be specifically targeted with current therapies. These results also illustrate the role of the PCLI, where high values identify kinetically active disease that will relapse faster and patients have a shorter TTP.[36] Our results suggest that patients with a low tumor burden and slow kinetics (e.g. low labeling index) benefit the most from HDT-ASCT. These observations complement those of Alexanian *et al*. who showed that achieving CR leads to longer TTP and that a serum M-protein < 1.0 g/dL before transplant is a predictor of CR.[10] Similar results have been reported by Nadal *et al*., where the size of the serum or urine M-spike and bone marrow plasmacytosis were the predictors of CR with HDT.[37] One could argue that it is easier to achieve CR in patients with a low serum M-spike and this has nothing to do with disease burden. However, this would suggest that patients with a low serum M-spike have a biologically different disease. Our intergroup comparisons do not support this argument (Table 2) although new technologies such as gene expression profiling might shed light on this possibility. To date, the importance of a low disease burden before transplant has been evaluated using surrogate markers. Here we provide a quantitative estimate of tumor burden before ASCT and correlate it with the outcome. Our results should not be interpreted as implying that pretransplant cytoreductive therapy is beneficial by improving CR rates and prolonging TTP. Such a question can only be addressed by properly designed clinical trials.

The availability of simple models to determine the outcome of therapeutic interventions is an important tool in the design of clinical trials. Such models help in risk stratification and identify patients who may or may not benefit from a given intervention. Patients who have a low probability of a response can be enrolled in experimental protocols designed to improve results in such 'high-risk' patients. In this report, we derive a simple function for the probability of an excellent response to HDT-ASCT in patients with MM. The function is based on tumor burden, a characteristic that has almost intuitive meaning and underlies all attempts at tumor staging and is a central tenet of oncology. Estimation of the tumor burden in most patients with MM is simple and based on parameters that are routinely measured in the management of these patients (see 'Methods'). The Fermi function, Equation 5, can then be applied to the tumor burden and the probability of achieving CR determined. Physicians can estimate this probability for each patient with the interactive tool provided at http://www.ciul.ul.pt/~pacheco/MM/calc.php. Of course, for any given probability of a response, the decision to proceed with HDT-ASCT is left to the patient and their treating physician. However, the probability of a response can

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be used in conjunction with the risk of morbidity and mortality to aid in decision making.

Cancer is a dynamic process where there is ongoing cell proliferation and death. Often it is difficult to estimate the rate of tumor growth *in vivo* and data from animal models might not always be representative of what happens in humans due to differences in the tumor microenvironment and allometric relationships in metabolic rate that vary across genera.[38] However, the underlying tumor dynamics are important for optimal design of clinical studies. Only recently has it been possible to appreciate the substantial tumor cell turnover in chronic lymphocytic leukemia, a disease often perceived as being due to the slow accumulation of neoplastic cells.[39] In this context, MM is perhaps unique because, in the vast majority of patients, the neoplastic cells secrete an M-protein that can be measured. Our results show that after HDT-ASCT, patients with myeloma have substantial cell turnover. We have to caution the reader that the tumor cell turnover reported are estimates, but they illustrate the dynamic nature of the disease after transplantation. For any tumor, the growth rate is not constant but decreases as the burden accumulates due to microenvironmental constraints. The expansion of the myeloma clone follows a Gompertz function[21] that is a consequence of both allometric principles and changes in the fraction of proliferating cells.[40–42] The higher rate of cell replication in patients who achieve CR compared to those who only achieved a PR is compatible with the underlying Gompertz function, because patients who achieve a PR have a higher burden after transplant and thus a slower rate of tumor growth (Fig. 4). Moreover, understanding the dynamics of the tumor in response to therapy illustrates that perhaps CR is not the only outcome we should look for in HDT-ASCT for myeloma. It is clear that as the tumor burden is decreased by therapy, regrowth occurs at a faster rate and might eliminate any potential benefit obtained despite increasing toxicity. Our preliminary studies on this aspect support this conclusion (Dingli *et al*., unpublished observations, March 2007).

The strength of any model depends on the assumptions on which it is based and our paper is no exception. Here we assume that on average, malignant plasma cells produce similar amounts of M-protein. This is justified by the observations of Sullivan and Salmon who evaluated *in vitro* protein secretion from plasma cells isolated from patients with MM.[21,29] In addition, we assumed that the clearance rate of the M-protein is constant and similar across patients. Immunoglobulins are cleared by cells of the reticulo-endothelial system and there is little evidence to support changes in clearance with disease activity. Moreover, the rate of antibody clearance is independent of serum concentration over a wide range of concentrations.[43] Needless to say, our model cannot be used for patients with non-secretory myeloma, although fortunately this is a minority of patients.

In conclusion, MM is a highly active tumor with substantial cell turnover after HDT-ASCT. The tumor burden before transplant is the best predictor of a CR after HDT and the probability of achieving a CR can be simply estimated from knowledge of the disease burden before the procedure. Patients who achieve a CR have a high rate of tumor regrowth and this provides a rationale for the current approaches to consolidate the results of HDT-ASCT with maintenance therapy.[12,44] The design of clinical studies must take into consideration these dynamic aspects of the disease for optimization of therapy.

Acknowledgments

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