CORRESPONDENCE

Reduced Intensity Conditioning and Allogeneic Stem-Cell Transplantation: Determining Its Role in Multiple Myeloma

To the Editor: The data reported by Badros et al[1] regarding nonmyeloablative allogeneic transplantation provide some scope for optimism in the development of treatment strategies for multiple myeloma. They need, however, to be interpreted in the context of the follow-up provided. The nonchemosensitive group represents an update and extension of earlier data.[2] The high response rate provided a central message to this previous report, but an important aspect of the data on overall survival/progression-free survival provided in the current article was the lack of durability of these responses in this group. In the Badros et al[1] article, Fig 3 demonstrates that of those patients treated with progressive disease (n = 17) only two remain alive and progression free at more than 15 months after nonmyeloablative allograft. Of the five with responsive disease and a history of two or more previous autografts, only one remains alive and progression free by 7 months after transplantation. The event-free survival for the group with responsive disease and one prior autograft looks promising, but close inspection of the survival curves in Fig 3 shows that only two patients have more than 12 months follow-up (and four have less than 6 months). The longest follow-up in this group is only about 21 months, with a median of less than 9 months. Because this group included six primary responders, the event-free survival would be expected to be better than for the other groups. Given the limited patient numbers and follow-up, it is difficult to assess how well a similar group receiving a second autologous high-dose procedure would have faired, and evidence that these responses can be maintained and hopefully translate into cure are required before these approaches can be generally recommended. Despite initial disease responsiveness, a lack of durability of the graft-versus-myeloma effect has been noted in many cases after donor lymphocyte infusion (DLI) for relapsed disease after conventional myeloablative allografting.[3,4] This has also has been our experience after DLI for residual/progressive disease after reduced intensity conditioning, even for those patients treated with primary responsive disease (Peggs K, manuscript in preparation). In addition, extramedullary relapse with a hypo/nonsecretory clone may also occur in this setting, which can cause some delay in diagnosis of progression.

The morbidity of graft-versus-host disease associated with DLI can also be significant and led to a change in treatment protocol during the time of the study. There are currently little data available to form decisions concerning the safety of given T-cell doses at particular time points after transplantation. Unfortunately, the authors do not provide data on the doses administered in either this or their previous publication.[1,2]

Decisions regarding the appropriate treatment of patients with advanced disease are made increasingly difficult by the development of newer treatment modalities, such as thalidomide derivatives (selected cytokine inhibitory drugs and immunomodulatory drugs) and proteasome inhibitors. Although the reduced intensity approach described by Badros et al showed a nonsignificant tendency to reduced overall mortality over 12 months compared with conventional myeloablative transplantation,[1] the role of the latter remains to some degree controversial in myeloma, particularly for those with more advanced disease. In many cases, survival curves for patients undergoing allogeneic transplantations take many years to demonstrate superior survival to less aggressive approaches.[5] The cost and morbidity associated with reduced intensity allografts, the possibility of patient selection bias, and the lack of sufficient follow-up requires that we must view with caution any claims that overall outcome is improved by such approaches, as indeed is recognized by the authors in their discussion. Entry of patients into controlled trials incorporating these new approaches in association with assessment of quality-of-life indices are an important next step in defining the place of these therapies in the overall management of patients with myeloma.

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In Reply: In our study,[1] high-risk multiple myeloma (MM) patients "as defined by chromosome 13 abnormalities in association with B-2 microglobulin level of 2.5 mg/L or higher" who received a planned tandem allogeneic transplantation early in the disease course after an autologous stem-cell transplantation (auto-SCT) has improved disease-free and overall survivals. The duration of follow-up is limited; however, the fact that none of these patients had relapsed at a median follow-up of 21 months (range, 17 to 37 months) is encouraging. The effect in these patients is clearly related to graft-versus-myeloma effect rather than a second cycle of high-dose melphalan, because median disease-free survival for high-risk MM patients after tandem auto-SCT is less than 9 months.[2]

Graft-versus-host disease (GVHD) continues to be a problem with nonmyeloablative allogeneic transplantations. In our study, all responses, especially in refractory patients, followed the development of GVHD. Actually, the development of chronic GVHD was an independent prognostic factor for better disease-free survival after allogeneic transplantation.[3] The importance of GVHD is re-emphasized by the high relapse rate seen in responding patients after adequate control of GVHD. Although it is presumed that T cells are the primary mediators of immune responses after allogeneic transplantations; the number of

CD3+ cells, in our study, did not correlate with the severity of GVHD or durability of graft-versus-myeloma responses in the small subset of patients who received donor lymphocyte infusion (unpublished data). In addition, the role of other effector cells (eg, NK and LAK) or the contributions of CD34+ cells that were infused with the granulocyte colony-stimulating factor mobilized CD3+ cells have not been fully evaluated. Whether pre-emptive donor lymphocyte infusion in the setting of persistent minimal residual disease can prevent relapse after allogeneic transplantation remains under investigation.

Until mature data are available on nonmyeloablative allogeneic transplantations, we believe that good-risk MM patients should receive a planned tandem auto-SCT upfront, even in presence of a matched sibling donor. These patients have an excellent quality of life and a complete remission rate of 40% to 50%, with a median survival of 9.5 years. Many of these patients are in continuous remissions more than 7 years after tandem auto-SCT.[4]

New therapies that target the bone marrow microenvironment, overcome drug resistance, or modify the immune responses should be integrated in future studies to further improve the outcome of allogeneic transplantations in MM.

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Unusual Pulmonary Lesions: Endobronchial Carcinoid of the Lung

To the Editor: In their article in the June 1, 2002, issue of the *Journal of Clinical Oncology*, Codrington et al[1] try to convince readers that simple endobronchial resection of an atypical carcinoid is reasonable. I think it is not.

There is only anecdotal published experience regarding simple endobronchial resection of a typical carcinoid. There are no data that actually define the survival and recurrence rates after such treatment. There are a great deal of data that patients with an atypical carcinoid have a much higher propensity for metastases and death than patients with a typical carcinoid. To extrapolate from anecdotal data in typical carcinoid to justify an approach in an atypical carcinoid is not reasonable. The authors question whether the classification of atypical carcinoid is appropriate in this patient. However, this argument is nothing more than speculation, because once again there are no data to corroborate their assertion.

It is crucial that we do not blindly accept established dogma, but continually question and search for new approaches in treating our patients. This is particularly true as new treatments and new technology become available. I fully support the authors in their interest in doing this. However, we must do this in a rational and progressive manner. A planned approach to endobronchial resection of typical carcinoids can be justified using newer technologies. Exploring new treatments cautiously is primarily appropriate in patients who have contraindications to the standard approach. However, the physicians caring for this patient have chosen to explore, all at once, a new treatment (endobronchial resection alone), new methods of surveillance (endobronchial ultrasound and high-resolution computed tomography), and a new definition of what should constitute an atypical carcinoid.

It is difficult to view the approach taken by Drs Codrington et al as a carefully considered, preoperatively planned-out approach when so many leaps of faith are involved. I find their arguments are not convincing, and I do not think the endobronchial resection of atypical carcinoid can be justified.

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In Reply: By asking if endobronchial resection should be the treatment of choice for an atypical carcinoid, Dr Detterbeck in fact questions whether the currently used classification[1] is appropriate for carcinoids presenting as endobronchial tumors. The reason for classifying the tumor in our patient[2] as atypical carcinoid is strictly based on the number of mitoses in 10 high-power fields (2-10/mm^2 instead of < 2/mm^2). In the previously used classification,[3] the cutoff point was at five mitoses. The new classification is based on a tumor tissue bank of 200 neuroendocrine pulmonary tumors. From the publication by Travis et al,[1] it is unclear how many, if any, tumors are included in this series that presented in the same way as our patient's did. Furthermore, in the univariate and multivariate analysis, the clinical presentation was not mentioned as a prognostic factor tested in this population; therefore, there remains uncertainty about whether the very strict cutoff point at two mitosis per 2 mm^3 is the only important criterion and as such more important than the clinical presentation in a patient like the one we described.

Based on our series, the clinical behavior of patients presenting with an endobronchially growing neuroendocrine tumor is much more like the behavior of a typical carcinoid, with no tendency to metastasize to regional lymph nodes or distant sites and no invasion of the surrounding tissue. In a series of 37 patients presenting with an endobronchial tumor, 19 patients were successfully treated with endobronchial resection; the mean follow-up of these patients was 5 years (range, 1 to 10 years). Of the remaining 18 resected patients, in 13 patients the invasion into the bronchial wall, measured using high-resolution computed tomography,[4] was to deep to make cure possible by this endobronchial technique. In four patients, resection was performed because of technical limitations of endobronchial treatment. In only one patient was there doubt about the diagnosis before treatment. Of these 18 patients, only one had a lymph node metastasis.

On the basis of these results, we still think that besides the histologic classification, the clinical presentation should also be taken into account before deciding what the appropriate treatment is for a patient with a neuroendocrine tumor presenting as an endobronchial tumor. Since the ability to evaluate local extension of a tumor is becoming more and more accurate, a local treatment, such as intraluminal therapy, should be taken into consideration for this tumor, with its rather benign behavior, as a possible alternative for the more dogmatic choice of immediate surgical bronchoplasty and bronchotomies.

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Cautious Arguments in Favor of Body Surface Area–Based Dosing

To the Editor: In the September 1, 2001 issue of the *Journal of Clinical Oncology*, de Jongh et al[1] put the following claim in the title of their article: "body-surface based dosing does not increase accuracy of predicting cisplatin exposure." I would like to criticize this article in two points. First, the article contains an obvious error at a sensitive point. On page 3,736 (second column) the authors state: "Furthermore, only a weak correlation was found between CL_{free} and BSA (CL_{free} = [1.54 ± 0.043] + [0.0055 ± 0.0007] × BSA; $r = 0.42$), with large variability in Cl_{free} across all studied BSA values in the 90 patients with three pharmacokinetically assessable courses (Fig 4)." However, the line defined by this equation does not even touch the data points in Fig 4, this raises doubts whether the reported value for *r* might be also incorrect.

The second criticism is of more principal nature. Obviously, the optimal studies that relate body-surface area (BSA)-based dosing to pharmacodynamic parameters are almost impossible to perform. Therefore, we have to content ourselves with studies that relate pharmacokinetic (PK) parameters with BSA. Plasma PK may not be the ideal compartment, which has been argued in a previous letter,[2] but usually, it is the only one accessible. Three parameters come to mind: area under the curve (AUC), volume of distribution (VD), and clearance. If the assumption is right, that BSA-based dosing should reduce variability, one should expect that AUC is less variable with BSA-based dosing and more variable with flat doses. Therefore, a study using only BSA-based dosing can hardly make direct assumptions about relations between BSA and AUC. In an indirect argument, one would expect that if BSA-based dosing makes sense, either VD or clearance (or both) should increase with BSA. A drug that shows virtually no positive correlation between VD and BSA is difficult to imagine. This alone would result in some sense in adjusting doses somehow to body size if one excludes for a moment the unlikely theoretical possibility that by increasing size a clearance could actually decrease. VD is sometimes difficult to determine reliably (situations of oral absorption, active metabolites, active free fractions, and so on), which does not invalidate the basic principle: "put a drug into a bigger volume and the concentration will decrease." Figure 4, in the study by de Jongh et al,[1] implies that at least some correlation between clearance and BSA exists. In terms of reducing the variability of AUC by BSA-based dosing, this adds to the meaningful adjustment to a larger VD. Therefore, the squared correlation coefficient (if $r = 0.42$, $r^2 = 0.176$) could be regarded as a minimum estimate of the proportion of variance in AUC that can be accounted for by knowing BSA. But how do we interpret this figure? My guess would be, that with flat dosing, the variance of the distribution of AUCs would be expected to increase by 17%, which is probably neither negligible nor of utmost importance. We have as yet no agreement how big an r^2 should be to warrant BSA-based dosing. The authors fail to provide arguments why $r = 0.42$ is not enough. Because BSA calculation is neither expensive nor dangerous for the patient, one could probably agree on a fairly small value. Flat dosing is a good means within a PK study to assess more objectively the relationship between BSA and AUC, but outside these studies, I would recommend using BSA-based dosing if "it is concluded that cisplatin CL is related to BSA"[1] as de Jongh et al do.

However, this should not reduce our efforts to explain the other admittedly more important factors contributing to the variance. Once we have them, we will think again.

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In Reply: We thank Dr Schuler for his interest and comments on our article that was published in the September 1, 2001 issue of the *Journal of Clinical Oncology*.[1] As pointed out, this article indeed contains an error in the equation that relates body-surface area (BSA) to the clearance (CL) of the unbound (free) fraction of cisplatin. Erroneously, the reported values for slope (a) and intercept (b) were derived from the same data with BSA as a function of CL [ie, BSA = (a × CL) + b]. The correct formula with the coefficients (± SE) from the linear-regression analysis is as follows (Fig 1): CL free (in L/h) = (31.80 ± 4.225) × BSA (in m^2) + (−1.985 ± 7.897).

The curvefit coefficients show 95% confidence limits of −17.53 to 13.56 ($P = .802$) for the intercept and 23.48 to 40.11 ($P < .0001$) for the slope, with an *r* value of 0.42 ($R^2 = 0.176$). In line with our original conclusions, this suggests that despite the significant slope, BSA accounts for only a small percentage of the observed kinetic variability.

We agree that there is no general consensus on optimal study designs to relate BSA-based dosing to pharmacodynamic outcome and that cutoff levels for significance and *r* still remain arbitrarily defined. Arguably, the best setting to test this relationship is a randomized comparative analysis with BSA-based

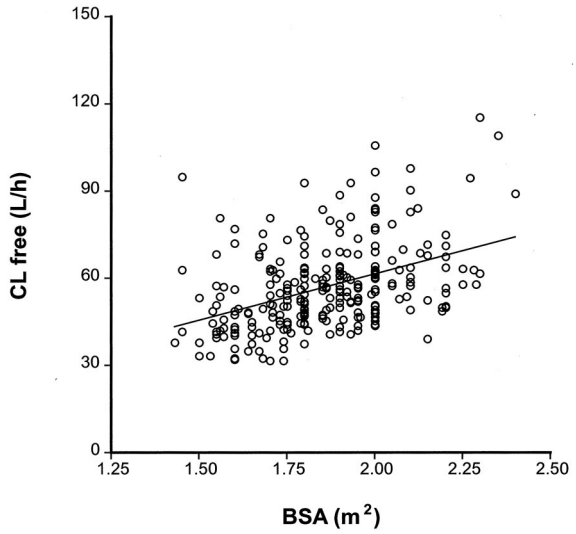

Fig 1. Relationship between BSA and the CL of unbound cisplatin (CL free) in a group of 268 adult cancer patients. The raw data are plotted with each symbol representing an individual patient, and the fitted line represents a linear-regression analysis.

versus flat-fixed dosing with appropriate attention to pharmacologic end points, as performed recently for paclitaxel.[2] Unfortunately, for the vast majority of agents used in today's clinical practice no data are available on the use of non-BSA–based dosing, with the exception of agents that do not induce any relevant degree of acute side effects (eg, bleomycin and novel target-based cytostatic drugs).[3] Therefore, the issue of whether non-BSA dosing might offer any improvement cannot be evaluated. However, it can be anticipated that implementation of such concepts as flat-fixed dosing would have significant economic implications. The ability to manufacture a unit dose has obvious benefits for the pharmaceutical company involved. Similarly, reconstituting a fixed dose without subsequent individualization for different patients is more efficient and cost-effective than preparing individualized doses, and would eliminate a significant source of error in attempting to obtain precise dosing.[4] In addition, and in contrast to the comment that BSA-based dosing is not dangerous, drug administration errors are very common in oncology and are usually the result of systematic error (eg, inaccuracy of the calculation algorithms) and inevitable convergence error (eg, use of inaccurate height and weight for BSA calculation).[5]

Although a large number of studies have appeared in the literature that clearly question the routine use of BSA in drug dose calculation, the message seems not to have been heard or understood, and many clinicians are still concerned. This concern is based on the intuitive belief that patients with a larger BSA necessarily require more drug to induce the same drug effects. In this context, the statement "put a drug into a bigger volume and the concentration will decrease" is a remarkable and unnecessary oversimplification. Furthermore, there is ample evidence that for some water-soluble agents (eg, doxorubicin and irinotecan) CL actually decreases with an increase in BSA, presumably as a result of poor distribution to adipose tissue.[6,7] A recent retrospective investigation involving 33 different drugs and 1,650 adult cancer patients shows that dosing strategies based on BSA may be relevant clinically only in very exceptional cases (Baher et al, manuscript submitted for publication). This is when drug disposition characteristics are confined to the central blood compartment (eg, temozolomide), and to a lesser extent, when renal function plays a principal role in drug elimination (eg, troxacitabine). This can be explained, in part, by known relationships between body size and blood volume and BSA and glomerular filtration rate, respectively.[8,9] In any event, we hope that performing exploratory analyses of BSA-CL relationships, such as that performed previously for cisplatin, will encourage investigators to adequately define and optimize dosing strategies for other agents.

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Hypersensitivity Pneumonitis Related to Imatinib Mesylate

To the Editor: Imatinib mesylate (imatinib, STI571, Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) has recently been proven to be an effective treatment of chronic myeloid leukemia and gastrointestinal stromal tumors.[1-3] Although follow-up of patients given this drug is still short term, it seemed that most patients had mild to moderate side effects, consisting mainly of nausea, diarrhea, myalgias, and edema.[1] We report the first case of hypersensitivity pneumonitis related to imatinib therapy.

A 41-year-old African woman, with a history of asthma since her childhood but no exacerbation in the last 5 years without any treatment, had chronic myeloid leukemia treated with hydroxyurea for 2 years beginning in October 1998. In March 2001, an accelerated phase was diagnosed. Treatment was changed to imatinib 600 mg/d (protocol CSTI5710114, Novartis Pharmaceuticals). A second chronic phase was obtained 7 months later, with no cytogenetic response. The patient showed good tolerance to imatinib, although self-limited conjunctivitis and mild bilateral ankle arthralgia were noted.

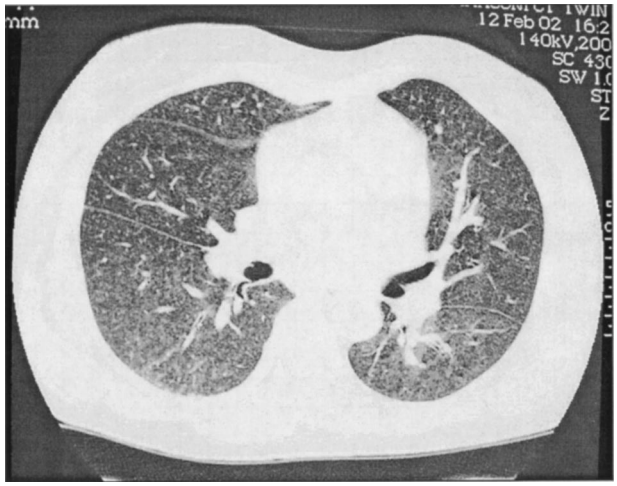

Fig 1. High-resolution lung CT showing bilateral and diffuse ground-glass opacities.

In December 2001, she experienced diffuse, extremely pruriginous skin lesions. Skin biopsy showed lichenoid dermatosis in favor of drug-induced toxicity. Imatinib was continued, and dermocorticoids permitted partial regression of these cutaneous lesions.

A genoidentical peripheral stem-cell transplantation was planned in February 2002. At admission to the transplant unit, chest x-rays revealed mild ground-glass opacities that were confirmed to be bilateral and diffuse by high-resolution lung computed tomography (CT) (Fig 1). The patient was afebrile and free of pulmonary symptoms. Results of the chest examination were strictly normal. Her WBC count was 5.7 $\times 10^9$/L, her hemoglobin level was 108 g/L, and her platelet count was 503×10^9/L. $CD4^+$ and $CD8^+$ cell counts were 484 cells/mm^3 and 182 cells/mm^3, respectively ($CD4^+$:$CD8^+$ ratio, 2.66). Her C-reactive protein level was 0.3 mg/L. Arterial blood gas measurement showed a pH of 7.40, arterial oxygen pressure of 88 mmHg, and carbon dioxide pressure of 35 mmHg. Fiberoptic bronchoscopy demonstrated normal airways, and analysis of bronchoalveolar lavage fluid showed 860,000 cells/mL with 37.5% foamy macrophages, 50.5% lymphocytes ($CD4^+$:$CD8^+$ ratio, 0.9), 8.5% neutrophils, and 3.5% eosinophils. No hemosiderin-laden macrophages were seen, and no proteinaceous material was noted. Stains and cultures for *Pneumocystis carinii*, *Toxoplasma gondii*, viruses (adenovirus, respiratory syncytial virus, influenza virus, parainfluenzae virus, herpes virus, and cytomegalovirus), fungi, and other microorganisms were negative. Bronchial biopsies showed no specific lesions. Her left ventricular ejection fraction, evaluated by gated acquisition scan, was in the normal range (69%). At that time, she was receiving no medication other than imatinib. Because drug-induced pneumonitis was highly suspected, imatinib was discontinued on February 21, 2002, without introduction of any other therapy. Eleven days later, the lung CT scan showed that her situation had normalized. It is noteworthy that, at that time, skin lesions had greatly improved. The patient finally underwent transplantation on March 12, 2002. Her conditioning regimen included busulfan and cyclophosphamide. No pulmonary complications were observed after transplantation.

Most of the lung complications reported during imatinib therapy are related to pulmonary edema, a rare manifestation of the fluid retention syndrome observed with this medication, with a reported incidence of 2.3% in the phase II study of late chronic phase patients.[3] In our observation, the foamy feature of the alveolar macrophages, the presence of a high number of lymphocytes with a low $CD4^+$:$CD8^+$ ratio in bronchoalveolar lavage fluid, and the diffuse ground-glass opacities on the CT scan associated with the cutaneous lesions were highly evocative of an immunoallergic mechanism and thus of hypersensitivity pneumonitis.[4,5] No cause other than imatinib was found. The disappearance of CT scan abnormalities after cessation of imatinib further supported this diagnosis. One case of allergic alveolitis had previously been described in a patient with a gastrointestinal stromal tumor who was receiving imatinib (Novartis, data on file).

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