CORRESPONDENCE

Busulfan Alone as Cytoreduction Before Autografting for Chronic Myelogenous Leukemia

To the Editor:

A number of prospective randomized studies have recently been designed to address the question of whether autografting prolongs survival for patients with chronic myelogenous leukemia (CML) in chronic phase,[1,2] but there is no general agreement as to the optimal approach to cytoreduction before transfusion of autologous stem cells.

Table 1. Clinical Data on 37 Patients Autografted for CML With Busulfan Only as Cytoreduction

A		No. of Patients (%)
Disease status at autograft		
CP		28 (76)
CP2		2 (5)
AP		6 (16)
BC		1 (3)
Autograft method		
BM		5 (14)
PBSC		8 (22)
Mobilized PBSC		11 (30)
MYB antisense*		4 (11)
Vancouver†		9 (24)
B	**Median**	**Range**
Age at autograft (yr)	45.3	(20.8-56.7)
Duration of disease at autograft (mos)	30.2	(7.2-105.0)
Nucleated cell dose ($\times 10^8$/kg)	3.8	(0.7-12.3)
Duration of neutropenia (d)	12.5	(2-110)
Duration of platelet support (d)	23	(0-158)
Hospital stay (days)	35	(13-124)
Interval from autograft to restarting anti-leukemic therapy (mos)	4.5	(0.8-19.8)
C	**Median**	**95% CI**
Survival from 1st autograft (yr)	3.4	(1.7-5.9)
Survival from diagnosis (yr)	6.3	(5.7-6.9)

A: Disease status and autograft method; B: Age, duration of disease, and autograft details; C: Survival.

Abbreviations: CP, chronic phase; CP2, second chronic phase after blastic transformation; AP, accelerated phase; BT, blastic transformation; BM, bone marrow; PBSC, peripheral blood stem cells.

*Autograft performed with marrow cells incubated in vitro with a MYB antisense oligomer.

†Autograft performed with marrow cells incubated for 10 days in liquid culture.

We believe that the use of high-dose busulfan alone, as used in patients subjected to second allograft procedures,[3] may be a good compromise between maximal cytoreduction and minimal regimen-related toxicity.

A heterogeneous group of 37 patients with CML in different phases of CML were autografted at the Hammersmith Hospital in London over a 5-year period by using busulfan alone as cytoreduction (Table 1). The regimen consisted of 4 mg/kg/d busulfan orally for 4 consecutive days (total, 16 mg/kg). A loading dose of 1,000 mg oral phenytoin was administered 1 day before the start of chemotherapy and phenytoin was continued at a dose of 300 mg/d for 7 days to prevent epileptic seizures. Neither busulfan nor phenytoin levels were monitored. Autologous cells were infused 48 hours after the last dose of busulfan. All patients had some degree of stomatitis, but no other major toxicities[4] were encountered (Table 2). Specifically, no patient had busulfan-related pulmonary toxicity, hepatic veno-occlusive disease, or epileptic seizures, and no patient experienced persisting alopecia.

We did not formally compare the use of busulfan alone with that of other more intensive cytoreduction regimens. However, the complete/major cytogenetic response rate at 3 months postautograft was 20% (6 patients) and the median survival postautograft was 3.4 years (95% confidence interval [CI]: 1.7 to 5.9) (Table 1). Thus, we can be reasonably confident that the use of this cytoreduction regimen produced results at least as good as those achieved with the combinations of busulfan plus cyclophosphamide or cyclophosphamide plus total body irradiation.

The principal reason why busulfan alone might be preferable to more intensive regimens is simply the fact that it may achieve the same level of cytoreduction with less toxicity. Conversely, the fact that the cells used for the autograft usually contain at least some Ph^+ progenitor cells such that relapse must originate at least partly from the autografted material[5] might mean that the attempt at complete marrow ablation with maximal chemotherapy or chemoradiotherapy was not justified. Moreover, busulfan alone is relatively easy to administer and administration will become even more straightforward when the intravenous preparations now being developed become available for routine use.

We conclude that if one chooses to autograft a patient with CML, then busulfan alone is a reasonable cytoreduction regimen associated with minimal toxicity which should still permit the possibility of a subsequent allograft or second autograft procedure.

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Table 2. Toxicity After Cytoreduction With Busulfan Alone in 37 Patients Autografted for CML

	Cardiac	Bladder	Renal	Respiratory	Hepatic	CNS	Stomatitis	Gastrointestinal
Grade III or less	0	0	1 (3%)	0	0	0	0	0
Grade II or less	0	0	2 (5%)	0	1 (3%)	0	28 (76%)	0
Grade I only	0	0	3 (8%)	0	2 (5%)	0	9 (24%)	5 (14%)
Total with any degree of toxicity	0	0	6 (16%)	0	3 (8%)	0	37 (100%)	5 (14%)

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The Prothrombin Gene 3′-Untranslated Region Mutation Is Frequently Associated With Factor V Leiden in Thrombophilic Patients and Shows Ethnic-Specific Variation in Allele Frequency

To the Editor:

As data accumulate on the recently identified genetic variant in the 3′-untranslated region of the prothrombin (factor II) gene (G20210A), it is apparent that this mutation confers a moderate risk for venous thrombosis.[1-3] Data from several abstracts presented at the 1997 ISTH meeting in Florence, Italy and a recent manuscript from Dr Rosendaal and coworkers, which revealed an association of this genetic variant with an increased risk of myocardial infarction in young women, suggest that an ethnic-specific variability in the frequency of the prothrombin gene mutation exists in healthy controls from European populations, analogous to that reported for factor V Leiden.[3-5] The ethnic distribution frequency of the G20210A mutation in Americans has not yet been reported. In addition, as pointed out in a recent letter to *BLOOD* summarizing results from a moderate size study of French families, an increased cosegregation frequency of heterozygosity for the prothrombin gene mutation and carriership for factor V Leiden in families with hereditary thrombophilia has not unequivocally been shown. In contrast to data obtained from the Dutch population,[1] the French study showed that the prothrombin gene A20210 allele is not frequently found in their thrombophilic families carrying the Leiden allele of the factor V gene.[6] In fact, none of the probands or family members had the prothrombin gene mutation. Therefore, the hypothesis that cosegregation of the prothrombin gene mutation and heterozygosity for activated protein C resistance results in increased expressivity of hypercoagulability and thrombophilia within these families remains unproved.

We investigated the frequency of the prothrombin gene mutation in consecutive thrombosis patients at Emory Hospital (Atlanta, GA). Seventy-two out of 477 thrombosis patients were found to be heterozygous for factor V Leiden (15.1%) and 4 were homozygous (0.84%). Genomic DNA samples were available for 48 of these 76 thrombosis patients that were either heterozygous or homozygous for factor V Leiden. The factor II gene mutation was identified in 5 of these 48 patients (10.4%). Out of 278 apparently healthy subjects, we identified the prothrombin gene variant in 7 (2.5%). These data are comparable to that found in the Dutch population (2.3% in a population-based case/control study and 1% in healthy controls). Although not representing a family study, our data does suggest that the coexistence of these two prothrombotic genetic variants may increase the clinical expressivity of thrombophilia and thus provides further validation of the ''double hit'' theory as a mechanism of thrombophilia in the younger patient. Interestingly, as reported for the factor V Leiden mutation, the frequency of the G20210A mutation was very rare in African Americans. In fact, none of the 52 healthy African Americans in our study carried the prothrombin mutation and none of the 5 thrombosis patients who were double heterozygotes for the factor II and V variants were of African ancestry.

We conclude that in our population, the G20210A prothrombin allele is frequently associated with activated protein C resistance and most likely confers an increased thrombosis risk for these individuals. In addition, a better understanding of the apparent ethnic-specific variability of the factor II gene mutation should help to provide better diagnostic algorithms that optimize cost-effective laboratory evaluation of the thrombophilic patient.

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