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Myeloablative Chemoradiotherapy and Autologous Bone Marrow Infusions for Treatment of Neuroblastoma: Factors Influencing Engraftment

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Bone marrow harvested from cancer patients for autologous bone marrow reinfusion (ABMR) after myeloablative treatment may be injured, in both its proliferating and stromal cell pools, by either previous treatment or manipulation at the time of harvest. We have examined the relative effects of seven covariates on hematologic recovery after ABMR in children with neuroblastoma (NBL) using univariate and step-up analysis. We measured recovery by times to achieve (1) white blood cell counts greater than 1,000/μL; (2) absolute neutrophil counts greater than 500/μL; and (3) platelet counts greater than 20,000/μL without transfusion. In univariate analysis, recovery was significantly associated with the amount of prior chemotherapy and the interval between last chemotherapy and marrow harvest. Patient sex, the number of granulocyte-macrophage colonies infused, harvest-to-freeze interval, and use of purging were marginally associated. After adjusting for potential confounders in a multivariate model, the amounts of chemotherapy and granulocyte-macrophage colonies infused were independently significant predictors of time to total white blood cell count recovery; chemotherapy courses and chemo-to-harvest interval were predictors of neutrophil count recovery; and sex, use of purging, and harvest-to-freeze interval were marginal predictors of platelet recovery. The speed of hematologic recovery after ABMR seems to depend mainly on pre-existing factors and marginally on manipulation of the marrow after harvest. These factors may affect both proliferating and stromal cell pools.

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AUTOLOGOUS bone marrow reinfusion (ABMR) after myeloablative cancer treatment avoids some limitations of allogeneic transplantation, notably donor unavailability and graft-host reactions. But ABMR is potentially restricted by the presence of occult neoplastic cells, prior injury by chemotherapy to the marrow stroma and stem cell pool, and freezing, purging, and thawing procedures. Surmounting these obstacles could increase the successful use of ABMR as a hematologic support for cancer patients.

This risk of injury to hematopoietic and stromal cells means that factors associated with the rate and completeness of hematologic recovery must be defined. We have analyzed possible factors in a large group of children who underwent ABMR for disseminated neuroblastoma (NBL). We have reported the clinical results elsewhere.[1,2]

MATERIALS AND METHODS

Treatment of Patients

One hundred and twenty-three patients with metastatic NBL who received myeloablative treatment and ABMR at Pediatric Oncology Group (POG) centers were available for study (see Appendix). Their average age was 4.56 years (standard deviation, 2.48). Just over 95% of the patients were less than 8 years old. They were not all entered on POG protocols and some data were unavailable. All were treated from diagnosis with chemotherapy combinations including cyclophosphamide, doxorubicin, cisplatinum, and teniposide or etoposide, according to POG or institutional protocols. Cyclophosphamide, ifosphamide, cisplatinum, vincristine, and/or etoposide were used for reinducing patients after relapse. Some patients received irradiation to residual disease before marrow harvesting.

After marrow harvest and just before ABMR, patients received myeloablative chemoradiotherapy including high-dose melphalan (60 mg/m^2 intravenously [IV] daily for 3 days) and total body irradiation (TBI) (1.5 Gy to 2.0 Gy twice daily for 3 days). Some patients also received irradiation of local lesions. Central venous catheters were used for blood drawing, blood and antibiotic administration, and parenteral nutrition. Blood products were irradiated to 15 Gy to prevent graft-versus-host disease (GVHD) from transfused lymphocytes. During recovery all patients were nursed in isolation to reduce microbial contamination. Systemic antibiotics were administered for fever during the neutropenic phase and amphotericin was added if fever persisted. Patients were discharged when clinically stable with adequate blood counts.

Marrow Harvesting, Purging, and Freezing

Marrows were harvested for freezing in liquid nitrogen after induction when restaging showed patients were in clinical remission with normal aspirates and biopsies, defined as greater than 75% of normal cellularity without microscopic evidence of persisting NBL cells. Fifteen to 25 mL/kg of marrow was aspirated under general anesthesia from the posterior iliac crests using syringes rinsed with phenol red-free Medium 199 (GIBCO BRL Laboratories, Grand Island, NY) containing 20 U/μL of preservative-free heparin. We tried to collect a minimum of 10^8 nucleated cells/kg patient weight. The marrow was transferred to 600-mL blood bags after filtering through 400-μ and 100-μ steel-mesh screens.

One hundred and seven (87%) of the 123 marrows underwent immunomagnetic purging at the University of Florida (UF) before cryopreservation, as described elsewhere.[1,2] Marrows were flown from other centers on wet-ice packs within 4 hours of harvesting, after sampling for cell count and cultures. They were returned in

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containers with enough liquid nitrogen to keep an internal temperature of $-196^{\circ}C$ for at least 7 days.

For purging, marrow aliquots were mixed with 6% Hetastarch (American McGaw, Wellington, DE) in a ratio of four parts to one with and incubated at ambient temperature for 30 to 60 minutes to sediment red blood cells (RBCs). The supernatant was washed three times before adding antineuroblastoma monoclonal antibodies (MoAbs). Six MoAbs were used for purging (UJ13A, 223.8, 181.4, H11, Thy 1, and 127.11; provided by Dr John Kemshead, Imperial Cancer Research Fund, London, UK) all of which bind selectively to NBL cells.[3] They were purified using immobilized protein A or fast-performance liquid chromatography and titrated by indirect immunofluorescence on tissue-cultured NBL cell lines.

We adjusted the final hematocrit to 20% to minimize loss of hematopoietic cells,[1] incubated the marrow with MoAbs on ice for 30 minutes, washed it three times, and resuspended it in medium 199/PPF. Magnetic microspheres (Dynabeads; Dynal AS, Oslo, Norway) coated with sheep antimurine Ig antibodies were added and the mixture was rotated on ice for 30 minutes, transferred to a 300 mL blood bag, and pumped through the separation chamber into a transfer pack on wet ice.

Thirty-milliliter aliquots were mixed with equal volumes of 20% medium 199/PPF and 20% dimethyl sulfoxide (Cryoserve Research Industries Corp, Salt Lake City, UT) in 120-mL cryopreservation bags (Stericon Inc, Deerfield, IL), cooled in aluminum canisters in a programmable freezer to $-90^{\circ}C$ with eutectic point compensation, and transferred to liquid nitrogen in the liquid phase until needed. Before and after purging we performed nucleated cell counts and colony-forming unit granulocyte-macrophage (CFU-GM) assays by the method of Iscove et al.[4] Processing the marrow always took less than 8 hours, but because some marrows were transported for purging the interval from harvest to freezing sometimes exceeded 24 hours. The marrow was thawed rapidly in a 37°C bath at the patient's bedside for reinfusion.

Statistical Methods

Measuring recovery. Our three recovery parameters were days to achieve (1) total white blood cell (WBC) counts for two consecutive days above 1,000/μL (WBC >1,000); (2) absolute neutrophil counts (ANC) for 2 consecutive days above 500/μL (ANC >500); and (3) platelet counts for 3 consecutive days above 20,000/μL without transfusion (PL >20,000). Time to recovery was censored if a patient died before reaching any of these levels, and we also censored recovery times greater than 100 days at 100 days to avoid imprecise analyses due to infrequent measurements. This censoring had no impact on WBC recovery because only one patient had not recovered by day 100 and the impact on ANC and platelet recovery was slight. Because of this censoring we have restricted our analyses to determinants of recovery during the first 100 days after ABMR.

We examined the following seven covariates: Pre-ABMR: *sex*, indicator of patient sex; *chemo*, cumulative number of chemotherapy doses before marrow harvest; ABMR-specific: *chemo-to-harv*, interval in days between the last course of chemotherapy and harvesting the marrow; *harv-to-freeze*, interval in hours between completing marrow harvest and completing cryopreservation; *purge*, use or not of immunomagnetic purging; *cells*, number ($\times 10^8$/kg body weight) of viable nucleated cells infused; *CFUs*, number ($\times 10^5$/kg body weight) of granulocyte-macrophage colonies infused. Not all covariates were measured for all patients. Most notably, all nonpurged patient marrows were missing data for the covariates *harv-to-freeze, cells,* and *CFUs*.

We analyzed the data for covariates affecting recovery using the log rank test to test for univariate effects and estimated crude recovery curves with the product limit estimate.[5] For description we produced Kaplan-Meier curves by categorizing continuous covariates into two groups divided arbitrarily to give about equal numbers of recoveries in each. We adjusted for potential confounders using the proportional hazards model,[6] and estimated the proportion not recovered adjusted for covariates by maximum likelihood in the proportional hazards model.[7] We assessed the adequacy of proportional hazards by graphical means and residual analysis.[8]

Analysis of the data. Table 1 lists the numbers of subjects available for analyzing the seven covariates and three recovery parameters. We excluded cases from an analysis only when we were missing data for a covariate in that analysis. In Table 2 we provide estimates of the hazard ratio for individuals differing by a single unit for each covariate. The hazard is the instantaneous probability of hematologic recovery; a hazard ratio estimate greater than 1 suggests an increased chance of recovery with increasing values of the corresponding covariate. A hazard ratio estimate less than 1 suggests a decreased chance as the corresponding covariate increases. A statistically significant effect at the .05 level is synonymous with a 95% confidence interval for the hazard ratio excluding 1.

The covariate *chemo-to-harv* seemed to have a threshold effect in that the main difference in recovery time was between 1 to 30 days and 31 to 60 days. There was a minimal difference between 31 to 60 and 60+ days and so we dichotomized this covariate as *chemo-to-harv 30.* We computed univariate hazard ratio estimates for each recovery parameter for each covariate being considered (*sex, chemo, chemo-to-harv 30, purge, harv-to-freeze, cells,* and *CFUs*). We then explored multivariate models for evidence of confounding among the covariates. For each recovery parameter we present the univariate estimates, as well as estimates adjusted for potential

Table 1. Descriptive Statistics

Covariate	Available Cases	Frequency (%)	Median	Mean (SD)
Sex	123			
Female		45.5		
Male		54.5		
*Chemo**	89		28.0	30.1 (11.9)
Prior drug doses				
Chemo-to-harv†	77		37.0	44.9 (28.7)
1 to 30 d		20.8		
More than 30 d		79.2		
Harv-to-freeze‡	102		8.8	14.3 (8.7)
0 to 16 h		68.6		
More than 16 h		31.4		
Purge	123			
Purged		87.0		
Not purged		13.0		
Cells ($\times 10^8$/kg)	105		1.8	2.0 (1.0)
CFUs ($\times 10^5$/kg)	89		0.6	0.7 (0.5)
WBC >1,000	98			
Censored		8.2		
Recovered		91.8		
ANC >500	89			
Censored		11.2		
Recovered		88.8		
PL >20,000	87			
Censored		24.1		
Recovered		75.9		

*Total number of doses of all chemotherapy agents administered before marrow harvest.

†Time in days from last course of chemotherapy to marrow harvest.

‡Time in hours from completing marrow harvest to completing cryopreservation.

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Table 2. Model for BC, ANC, and PL Recovery

	Unadjusted					Adjusted*				
		Hazard	95% CI				Hazard	95% CI		
	n	Ratio	Lower	Upper	*P* Value	n	Ratio	Lower	Upper	*P* Value
WBC										
Chemo†	88	0.978	0.957	0.999	.046	88	0.976	0.954	0.999	.043
CFUs	75	1.517	0.916	2.513	.105	69	1.672	1.010	2.770	.046
Sex	98	1.504	0.985	2.295	.059	88	1.562	0.999	2.443	.051
ANC										
Chemo-to-harv‡	68	0.554	0.310	0.990	.046	67	0.486	0.269	0.878	.017
Chemo†	79	0.976	0.952	1.002	.068	67	0.970	0.944	0.998	.033
CFUs	67	1.666	0.976	2.844	.061	51	1.510	0.824	2.766	.182
PL										
Purge	87	0.567	0.307	1.046	.069					
Harv-to-freeze§	70	1.040	0.997	1.084	.069					
Sex	87	1.576	0.962	2.580	.071					

Abbreviation: CI, confidence interval.

*Adjusted for *sex, chemo* (WBC); *chemo, chemo-to-harv* (ANC).

†Total number of chemotherapy doses administered before marrow harvest.

‡Time in days from last chemotherapy course to marrow harvest.

§Time in hours from completing marrow harvest to completing cryopreservation.

confounders. The choice of variables included in the multivariate models was dictated in part by strength of association with the recovery parameter, associations with other predictor variables, and patterns of missing data. We could not adjust all covariates for *harv-to-freeze, cells,* or *CFUs* because of missing data from non-purged patients. The proportional hazards model fit the data well in almost all cases and this agreement was confirmed by residual analysis.

RESULTS

Figure 1 shows the patient distribution by hematologic recovery times for *WBC,* those who died before recovery, and those alive at last follow-up without recovery. Most reached WBC >1,000 between 10 and 40 days after ABMR. Kaplan-Meier estimates of cumulative recovery for all three parameters (Fig 2) show it was fastest for WBC, then ANC, and then PL recovery.

Table 2 contains univariate hazard estimates for models of WBC >1,000. Kaplan-Meier estimates of the proportion recovered at days 20, 40, 60, 80, and 100 are .218, .660, .840, .920, and .990, respectively. Stepwise model building identified *sex* and *chemo* as the most significant covariates and Table 2 also contains hazard ratio estimates adjusted for these two. As an example, we see the hazard ratio estimate for *chemo* is .976; so for two patients of the same sex, one more dose of chemotherapy produces a 2.4% lower chance of WBC recovery at any time-point. A patient having 10 additional chemotherapy doses would have a WBC recovery probability of $.976^{10}$, equal to 78.4% of that of a same-sex patient at the same time-point.

Figure 3A and B illustrates cumulative WBC recovery according to *sex* and *chemo,* showing it was slower for females and patients receiving more prior chemotherapy.

Table 2 also contains univariate hazard estimates for models of ANC >500. Kaplan-Meier estimates of the

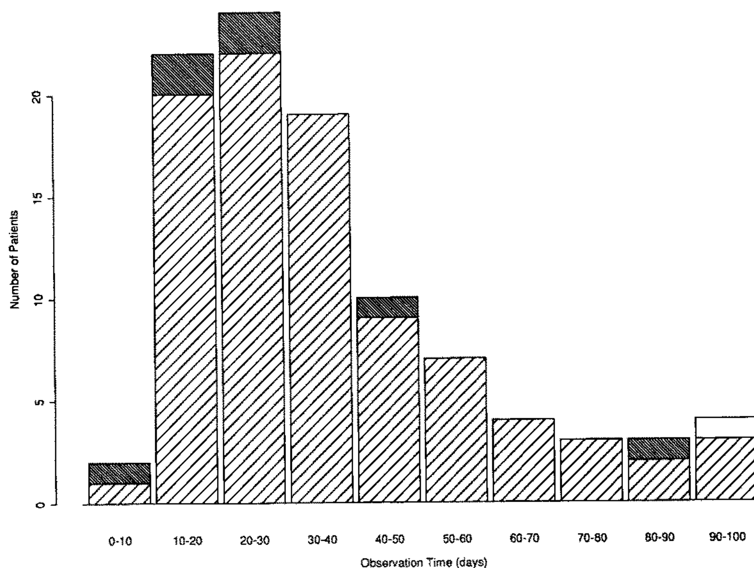

Fig 1. Distribution of times to WBC >1,000 or death or last follow-up. (▨) Engraftment; (■) death before engraftment; (□) alive at last follow-up, no engraftment.

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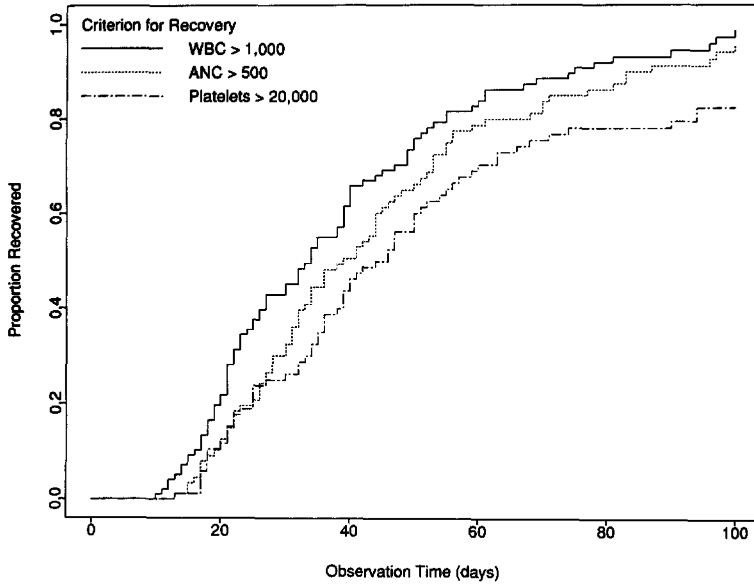

Fig 2. Proportion achieving hematologic recovery (WBC >1,000; ANC >500; PL >20,000).

proportion recovered at days 20, 40, 60, 80, and 100 are .126, .506, .788, .863, and .956, respectively. A stepwise model identified *chemo* and *chemo-to-harv 30* as most significant and Table 2 also contains hazard ratio estimates adjusted for these two.

Figure 4A through C illustrates cumulative neutrophil recovery according to *chemo, chemo-to-harv* interval, and *CFUs,* showing it is slower with higher *chemo* and lower *CFUs.* Although a 30- to 60-day interval between last chemotherapy and harvest seems associated with slower recovery than either shorter or longer intervals, in proportionate hazards modelling there was a threshold effect at 30 days.

Table 2 also contains univariate hazard estimates for models of PL >20,000. Kaplan-Meier estimates of the proportion recovered at days 20, 40, 60, 80, and 100 are .117, .462, .704, .781, and .825, respectively. No covariate was found to be significantly associated with platelet recovery time.

Figure 5A through C illustrates cumulative PL recovery according to *sex, purge,* and *harv-to-freeze* interval, again showing it was slower for females, with marginal apparent effects of *purge* and *harv-to-freeze* interval.

Examining results across analyses we find unadjusted hazard ratios related to number of colonies infused of

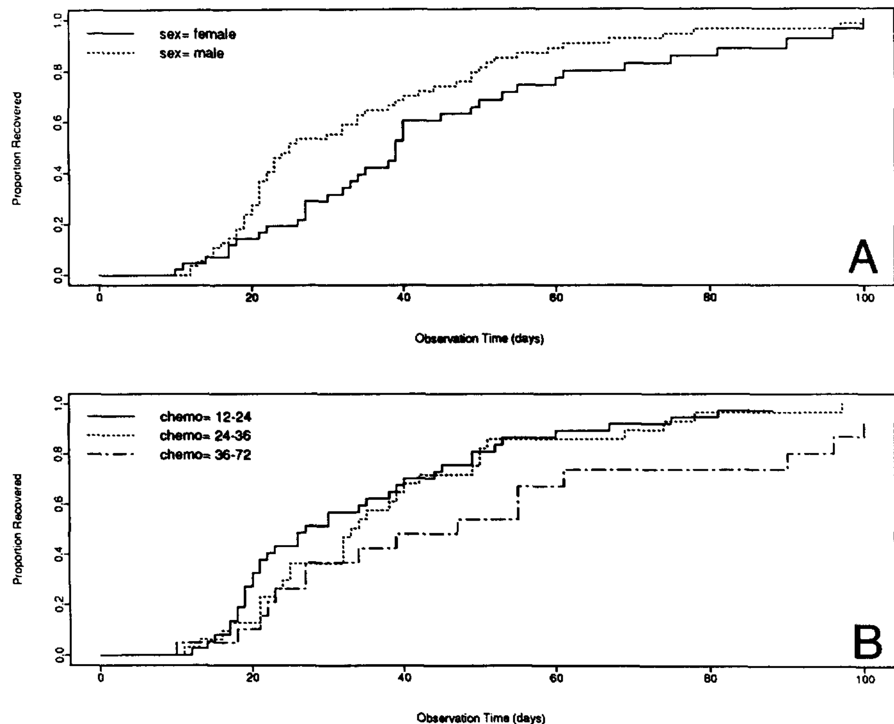

Fig 3. Recovery (WBC >1,000) by (A) sex and (B) amount of prior chemotherapy.

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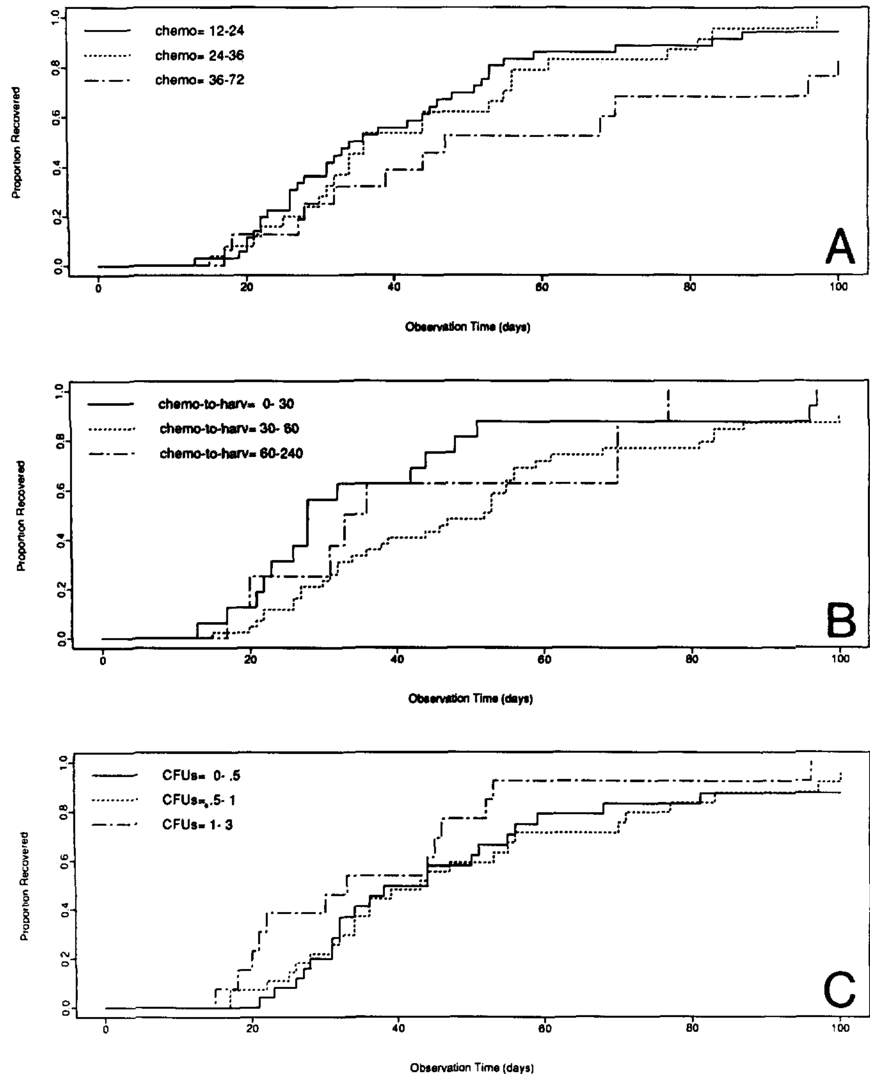

Fig 4. Recovery (ANC > 500) by amount of (A) prior chemotherapy, (B) *chemo-to-harv* interval, and (C) granulocyte-macrophage colonies infused.

1.517, 1.666, and 1.14 for WBC, ANC, and PL recovery, respectively. Although we did not see statistical significance, in each case an increase of 10^5 colonies/kg infused is associated with a 14% to 67% higher probability of recovery at any time point.

DISCUSSION

Information about factors affecting hematologic recovery after ABMR has come mostly from small series of patients with different diagnoses who received different myeloablative regimens.[9-15] We have studied a large group of patients close in age with the same diagnosis who received similar treatment both before marrow harvest and as myeloablation before ABMR. Marrow purging was also uniform. Our conclusions must still be tentative because of missing data and the study's retrospective nature.

Our findings highlight a limitation of ABMR, that of slow hematologic recovery, uncommon after HLA-matched allogeneic transplantation. Recovery rates varied in our patients according to the cell type we used as an endpoint, but the three different measures give a broadly similar picture. Manipulating the marrow after harvest has a less apparent effect than pre-existing factors, notably patient sex, prior chemotherapy, and the interval between last chemotherapy and harvest, which seem to be independent predictors. Although these covariates were not all significantly associated with recovery time by all three measures, the hazard ratio estimates were consistent.

Others have implicated the amount of chemotherapy before harvest as the prime factor affecting hematologic recovery after ABMR.[10,11,14] The very myelosuppressive induction administered to patients with acute myeloblastic leukemia may explain their slower recovery after subsequent ABMR compared with patients with lymphoblastic leukemia or lymphoma, although direct involvement of the myeloid line by the disease may contribute. Chemotherapy administered before harvesting probably produces a persistent reduction in the number of pluripotential progenitor cells available for proliferation.

Although patient sex has not been reported before to affect the rate of recovery after ABMR, Hellenglass et al[16] noted slower recovery after allogeneic transplants from

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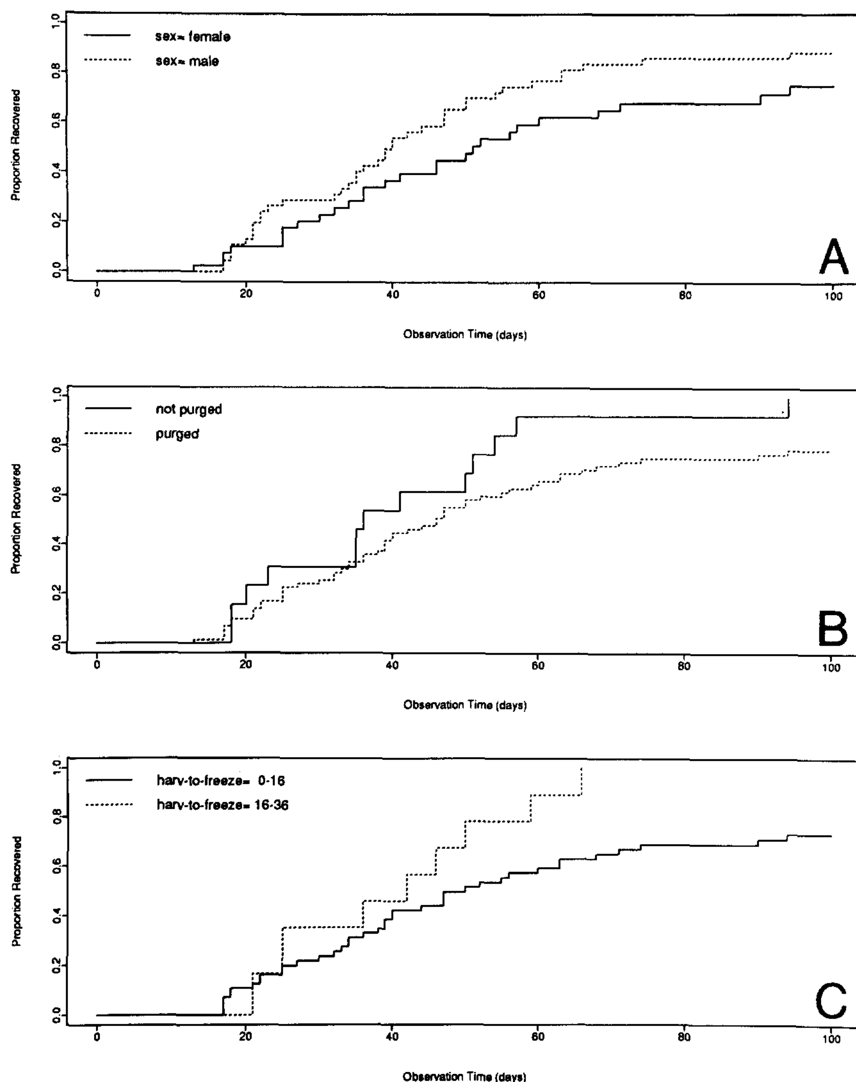

Fig 5. Recovery (PL >20,000) by (A) sex, (B) use of purging, and (C) harvest-to-freeze interval.

female than from male donors, therefore, there may be an inherent difference in the proliferative capacity of male and female marrows.

We found total WBC and neutrophil recovery time to be associated with the number of granulocyte-macrophage colonies but not the number of nucleated cells infused. The number of colonies infused was significantly associated with total WBC recovery after adjusting for amount and timing of prior chemotherapy and patient sex. This finding may reflect both pre-existing factors reducing the number of proliferative cells harvested and their further depletion by purging, freezing, and thawing, because immunomagnetic purging decreases by about 50% the number of nucleated cells and colonies available for reinfusion.[1] The marginal effect we found between purging and slow platelet recovery suggests it may reduce early progenitor cells, but the small number of nonpurged marrows in this study makes this a tentative claim.

Others have found assays of progenitor cell colonies more useful than nucleated cell numbers for predicting neutrophil recovery rates after autologous marrow infusions, although they are less helpful for reticulocyte and platelet recovery.[9,12,15,17,18] The dynamics of recovery may depend on how the marrow is treated after harvest and correlations may be less clearcut above a certain threshold number of progenitor colonies. When a small number (less than 10^4/kg) is infused, as after purging with 4-hydroperoxycyclophosphamide, recovery time of all three lines correlates directly with granulocyte-macrophage numbers infused.[12] Immunologic methods of purging probably do not injure progenitor cells and so conserve a larger number, which may be why we find no correlation between cell number infused and recovery rate. Assays of pluripotent hematopoietic progenitors[18] in marrows to be reinfused may prove more precise predictors.

Marrow stromal elements as well as proliferative cells are injured by chemotherapy, which would not be reflected in cell or colony yield at harvest. The stroma plays an active role in hematopoiesis although the critical cell is undefined.[19-23] Chemotherapy and radiation in mice[24,25] and humans[22] deplete both hematopoietic and stromal progenitors. Although we know little about their relative sensitivity,

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murine stromal cells recover from radiation slower than hematopoietic colonies,[26] and prior treatment with cyclophosphamide causes more later radiation injury to stromal cells than proliferative cells.[27] All our patients received large amounts of cyclophosphamide before marrow harvest. On the other hand, stromal cell numbers return to normal faster than hematopoietic progenitors after allogeneic marrow transplantation.[28,29] It is controversial as to whether stromal cells are transplantable or if hematologic reconstitution depends on residual recipient stroma in the recipient.[23,29-32]

It is hard to explain the marginal inverse relationship between *harv-to-freeze* interval and time for platelet recovery in our patients. We think this relationship is explained by a trend to more rapid platelet recovery times in the three centers, although such a center effect was not statistically significant.

A complex of factors governs the recovery of normal hematopoiesis when autologous marrow is used to redeem myeloablative chemoradiotherapy, particularly when the marrow has been injured by earlier treatment. Clearer definition of these factors has important implications for the ability of ABMR to reconstitute hematopoiesis quickly and permanently. That some patients recover only after many months or not at all is unacceptable, but this is the current state of affairs. To define the timing and minimal progenitor cell content of autologous marrow infusions that will produce timely recovery in all cases requires prospective studies with large patient numbers in different diseases. Given the popularity of this treatment such trials seem essential.

APPENDIX

Principal Investigators Participating On This Study

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