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Toxicity associated with high-dose cytosine arabinoside and total body irradiation as conditioning for allogeneic bone marrow transplantation

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Summary:

Seventy-three patients with hematological cancers undergoing allogeneic bone marrow transplantation (BMT) were evaluated for event-free survival (EFS) and toxicity. All received 36 g/m^2 cytosine arabinoside (HDA) and 1200 cGy fractionated total body irradiation (TBI). We assessed the association of EFS and toxicities with the following risk factors: age, gender, diagnosis, initial relapse risk and patient–donor histocompatibility. The EFS probability is 33% at 800 days post-BMT. Twenty-six patients (36%) died of toxicity within 100 days and 14 (19%) have relapsed. EFS was inversely associated with age ($P < 0.0001$) and initial relapse risk ($P = 0.007$). The risk of pulmonary ($P = 0.023$) and hepatic toxicity ($P = 0.011$) increased with age. Diagnosis other than acute lymphoblastic leukemia (ALL) was a risk factor ($P = 0.015$) for graft-versus-host disease (GVHD); and fewer ALL patients died from toxicity ($P = 0.014$). The probability of sepsis within 100 days post-BMT correlated ($P = 0.007$) with initial relapse risk. We conclude: (1) the lower EFS and greater pulmonary and hepatic toxicity associated with increasing age indicate a need for less toxic regimens that maintain high antileukemic efficacy for older patients; (2) the high GVHD and sepsis rates seen in certain categories of patients indicate a need for careful definition of eligibility criteria for this still highly toxic treatment.

Keywords: toxicity; transplantation; allogeneic; cytosine; total body irradiation

Myeloablative chemoradiotherapy supported by allogeneic BMT is often used to try to cure patients with hematological diseases.[1,2] The ideal outcome is a low subsequent relapse rate with an extent of toxicity acceptable to both patient and caregiver. Over the past two decades several conditioning regimens have been tested that have included high doses of cyclophosphamide, busulphan, cytosine arabinoside (HDA) and etoposide, often combined with total body irradiation (TBI).[3–6] The anti-leukemic activity of HDA in patients refractory to standard therapy was first demonstrated by Herzig *et al*[7] in 1983. Over a 9-year period from September 1983 to October 1992, we transplanted 73 patients with hematologic disease at the University of Florida using a uniform regimen of HDA and fractionated TBI. This paper reports the results of a retrospective analysis of these patients in terms of their survival and major organ toxicity. We make proposals for further clinical research.

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Materials and methods

Conditioning regimen and nursing care

Seventy-three patients aged 2–55 years received a conditioning regimen of HDA 3 g/m^2 intravenously over 1 h every 12 h on days −10 to −5 (total 36 g/m^2), plus TBI in twice-daily 200 cGy fractions on days −4 to −2. Male patients also received testicular irradiation (200 cGy/day for 5 days). Bone marrow was infused on day 0. All patients were nursed in laminar air-flow rooms during the neutropenic phase, and received intravenous broad-spectrum antibiotics and antifungal drugs for fever spikes. Corticosteroid eye drops were used to lessen conjunctivitis, as well as hyperalimentation and irradiated blood products as clinically indicated.

GVHD prophylaxis: Varying regimens were used. In general, prior to 1987, prednisone only or prednisone and methotrexate (MTX) were used. After 1987, MTX and cyclosporine prophylaxis was used. Three syngeneic patient transplants did not receive any GVHD prophylaxis. Pan T cell purging of marrow was also used as GVHD prophylaxis in four or five of six antigen-matched donor transplants. Because of lack of consistency and a general trend of change in prophylaxis over the years it was difficult to assess the significance of this factor.

Demographic data

Table 1 shows demographic data. There were 46 males and 27 females. Fifty patients had ALL and 23 other diagnoses (acute non-lymphocytic leukemia (ANLL) 12, myelodysplasia three, Hodgkin's disease (HD) two, chronic myelogenous leukemia (CML) three, acute undifferentiated leuke-

Table 1 Demographic details of the 73 patients

Category	*No.*	*(%)*
Sex		
Male	46	(63)
Female	27	(37)
Diagnosis		
ALL	50	(68)
Other[a]	23	(32)
Risk of relapse[b]		
High	29	(40)
Low	43	(60)
Match		
Matched	50	(68)
Mismatched[c]/MUD	23	(32)
Overall	73	(100)

[a]Other diagnoses detailed were acute non-lymphocytic leukemia (ANLL), myelodysplastic syndrome (MDS), Hodgkin's disease (HD) or chronic myelogenous leukemia (CML).
[b]Risk of relapse was not available for one patient.
[c]Mismatched. At least one of the six major histocompatibility (HLA) antigens mismatched between donor and recipient.
MUD = matched unrelated donor.

mia one and myelofibrosis two. Fifty patients were fully HLA-matched including five syngeneic BMT, 21 mismatched, and two had unrelated donors phenotypically matched. Mismatched donors included those mismatched for up to three histocompatibility loci (7, 10 and 4 respectively). The latter 23 patients were grouped together for this analysis. Twenty-nine patients were considered to be at higher initial relapse risk, namely those with ALL in later than second remission, ANLL in later than first remission, or CML in blast crisis or relapse at the time of BMT. One of these 29 patients had HD but was considered at high risk because it was his second malignancy.

Toxicity criteria

Organ toxicity was graded per standard NCI common toxicity scoring criteria from 0 to IV for lung, liver, kidney and gastrointestinal (GI) tract. Also, Herzig *et al*[7] have described organ toxicity for the liver and GI tract in patients on similar doses of Ara-C. Toxicity of grade III or higher was analyzed for possible associations with patient age, gender, diagnosis, initial relapse risk and matching status. Toxic death was defined as death within 100 days of BMT irrespective of cause. For this analysis patients were considered to have graft-versus-host disease (GVHD) if they required treatment for it. Patients with positive blood cultures for bacteria, viruses or fungi and/or histopathological proof of infection were considered to have sepsis.

Statistical methods

Patients were grouped according to age, gender, diagnosis, initial relapse risk, and HLA matching status. These covariates were analyzed for their association with EFS probability, organ toxicity, sepsis and GVHD. EFS was defined as survival without either relapse or death. Kaplan–Meier EFS curves were developed and compared using the log-rank test.[8] The Cox proportional hazards model[8] was used to assess the association of the covariates with post-BMT EFS probability. The appropriateness of the Cox model was assessed by graphical methods.[8] A stepwise procedure was used to select the covariates significantly ($P < 0.05$) associated with EFS probability. Selected covariates were used in a proportional hazards model to estimate the adjusted relative risk and the associated 95% CI with respect to each covariate in the model. Logistic regression analysis[9,10] was used to assess the association of the covariates with the development of major organ toxicity, sepsis and GVHD. A stepwise selection procedure determined the covariates to be included in the logistic model.

Results

Figure 1 shows the overall EFS probability, estimated to be 33% at 800 days post-BMT. The median EFS time was less than 1 year from BMT. Most failures during the first year were from toxic deaths within 100 days (38 (86%) *vs* 6 (14%) due to relapse).

Table 2 shows the risk factors for EFS, toxic death, organ toxicity, sepsis, and GVHD. The probability of EFS decreased significantly ($P = <0.0001$) with age. The relative risk (RR) of failure was estimated as 1.07 (CI: 1.04, 1.09) per year of age. That is, for every 1 year increase in age, the risk of an event (relapse or death) increased by a factor of 1.07. Figure 2 shows a plot of the RR as a function of age, using the risk for an 11-year-old as baseline (ie RR = 1 for age = 11).

Probability of EFS was also significantly ($P = 0.007$) lower for patients with a high initial relapse risk (RR = 2.23, CI: 1.22, 4.04). Of the 29 high-risk patients, 12 (41%) died of toxicity and seven (24%) have relapsed, compared with 13 (30%) toxic deaths and seven (16%) relapses among the 43 standard-risk patients.

Increasing age was also associated with higher risks of pulmonary ($P = 0.023$, RR = 1.06 per year, CI: 1.01, 1.11) and hepatic ($P = 0.011$, RR = 1.07 per year, CI: 1.01, 1.12)

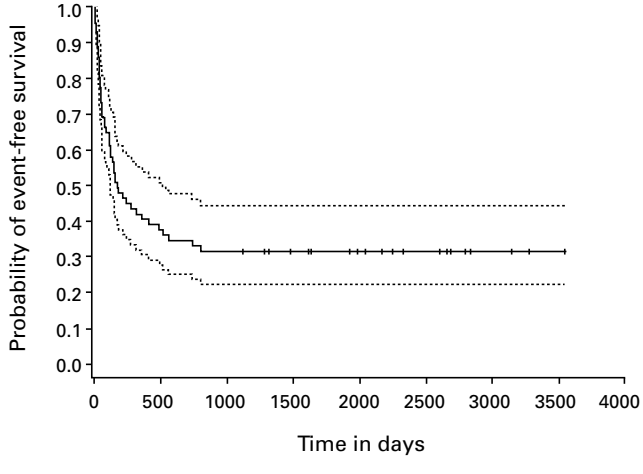

Figure 1 Event-free survival for all patients ($n = 73$). (——) Probability of EFS; (-----) 95% CI.

Table 2 Summary of results

Outcome	*Risk factor*	*RR[a] or PT[b]*	*CI[c]*	*P value*
Event-free survival	Age	RR = 1.07 (age +1 *vs* age)	1.04, 1.09	<0.0001
	Risk of relapse	RR = 2.23 (high *vs* low)	1.22, 4.04	0.007
Sepsis	Risk of relapse	RR = 4.40 (high *vs* low)	1.50, 12.98	0.007
Pulmonary toxicity	Age	RR = 1.06 (age +1 *vs* age)	1.01, 1.11	0.023
Hepatic toxicity	Age	RR = 1.07 (age +1 *vs* age)	1.01, 1.12	0.011
Genitourinary toxicity	None	PT = 0.28	0.19, 0.39	NS
Gastrointestinal toxicity	None	PT = 0.22	0.14, 0.34	NS
Toxic death	Diagnosis	RR = 3.70 (other *vs* ALL)	1.31, 10.46	0.014
GVHD	Diagnosis	RR = 3.64 (other *vs* ALL)	1.29, 10.28	0.015

[a]RR (relative risk of failure) is the risk of failure for risk group 1 divided by the risk of failure of risk group 2.
[b]PT is the probability of developing toxicity.
[c]CI is the 95% confidence interval.
NS = $P > 0.05$.

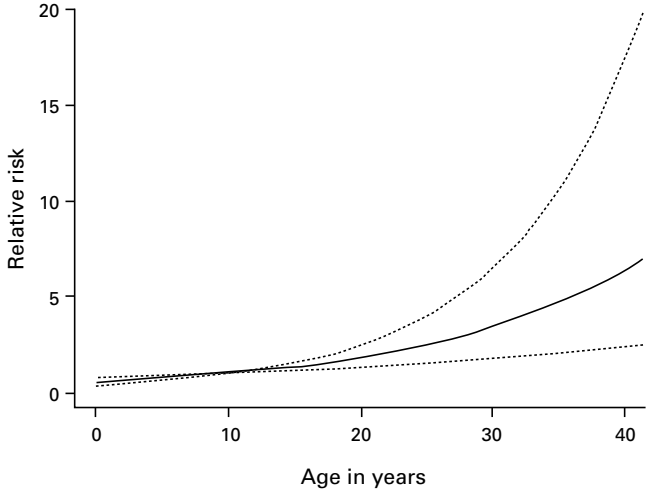

Figure 2 Relative risk of death or relapse. (——) RR (baseline age = 11 years); (-----) 95% CI. RR for age 11 is 1.

toxicities, while GU and GI toxicities were not associated with any of the covariates tested in this study.

Lastly, patients with diagnoses other than ALL had a higher risk of both toxic death ($P = 0.014$, RR = 3.70, CI: 1.31, 10.46) and of GVHD requiring treatment ($P = 0.015$, RR = 3.64, CI: 1.29, 10.28). Also a high initial relapse risk was a significant risk factor for sepsis (RR = 4.40, CI: 1.50, 12.98) ($P = 0.007$). We identified no specific organ toxicity associated with the use of HDA as a conditioning agent. Major pulmonary complications included interstitial pneumonitis (11%), pulmonary hemorrhage (4%) and adult respiratory distress syndrome (19%), all occurring at the expected rate.[11–13] Veno-occlusive disease (8%) and hemorrhagic cystitis (10%) also occurred in the frequencies seen in other series.[11,14] The minor side-effects of acral erythema and conjunctivitis were observed in similar frequencies to that described following HDA in other series.[4,14,15] Causes of toxic death are depicted in Table 3.

Table 3 Causes[a] of toxic death in 26/73 patients

ARDS 8 (including 2 with pulmonary hemorrhage)
DIP 2
GVHD or GVHD and sepsis 5
CMV pneumonitis 3
Hepatic 4 (including one patient who bled after a liver biopsy)
Fungemia 4
CNS hemorrhage 1
Renal failure 1

[a]Some patients had more than one cause listed for 'cause of death'.
ARDS = adult respiratory distress syndrome; DIP = diffuse interstitial pneumonitis; GVHD = graft-versus-host disease; CMV = cytomegalovirus; CNS = central nervous system.

Discussion

The overall EFS probability of approximately 33% is comparable to that reported in other studies of similar patients.[11,15,16] We found increasing age to be a significant risk factor for low EFS probability. Data from other studies of similar patients conditioned with HDA-TBI or cytoxan-TBI report mixed age effects. Riddell *et al*,[11] in a series of 29 patients, and Woods *et al*,[15] in a series of 16 patients receiving allogeneic BMT for leukemia, reported no age effect. Gale *et al*[17] and Weisdorf *et al*[18] also reported no age effects in larger cohorts of patients treated with cytoxan-TBI. In a large multicenter analysis of 14 institutions that used HDA-TBI and included the patients reported here, Weyman *et al*[16] did find age to be a significant risk factor for EFS.

We also found age to be a significant risk factor for lung and liver toxicity. Patients 20 years old and older had at least a 38% risk of severe lung toxicity and at least a 55% risk of severe hepatic toxicity, higher than the 10–20% toxicity reported in other series. Initial relapse risk was also positively associated with sepsis and negatively associated with EFS probability.

This high-risk group was comprised of multiply relapsed

patients who had received a lot of prior chemotherapy. The poor tolerance of this regimen by older patients emphasizes the need to define closely selection criteria for allogeneic BMT. Irrespective of conditioning regimen,[19] older age may be correlated with not only greater toxicity, because of greater immunocompromise, but also more resistant disease, because of atypical immunophenotypes and diagnoses other than ALL.

A poor outcome among such high-risk patients has also been a consistent finding in other studies, irrespective of the conditioning regimen used.[15,17,20,21] It seems important to reach consensus, particularly when comparing results across series, about eligibility criteria for patients with refractory hematological cancer to receive a treatment that remains very toxic and still fails to cure most patients.

Patients with diagnoses other than ALL were at significantly higher risk for acute GVHD requiring treatment, as well as a higher risk of toxic death. This association was independent of age of patients or matching status of donor. The patient number in the non-ALL group is small (23) and therefore such a conclusion may be skewed. Also, other factors like year of transplant and changes in GVHD prophylaxis, nursing care, sepsis rates over 10 years which can affect GVHD outcome as well as toxicity, were not analyzed and could have affected this result.

Based on this series of 73 patients treated uniformly at a single institution, we recommend that alternative conditioning regimens be explored, particularly for older patients with refractory hematological cancers. We should also seek global consensus about eligibility criteria for allogeneic BMT, perhaps using the resources of the International BMT Registry and cooperative clinical trial groups.

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