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/m² 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.¹² 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 al⁷ 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.

Materials and methods

Conditioning regimen and nursing care

Seventy-three patients aged 2–55 years received a conditioning regimen of HDA 3 g/m² intravenously over 1 h every 12 h on days −10 to −5 (total 36 g/m²), 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*           | 23  | (32)|
| Risk of relapse* |     |     |
| High             | 29  | (40)|
| Low              | 43  | (60)|
| Match            |     |     |
| Matched          | 50  | (68)|
| Mismatched/MUD   | 23  | (32)|
| Overall          | 73  | (100)|

*aOther diagnoses detailed were acute non-lymphocytic leukemia (ANLL), myelodysplastic syndrome (MDS), Hodgkin’s disease (HD) or chronic myelogenous leukemia (CML).

*bRisk of relapse was not available for one patient.

**Mismatched. At least one of the six major histocompatibility (HLA) antigens mismatched between donor and recipient.

MUD = matched unrelated donor.

5a, 5b

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)
Table 2  Summary of results

| Outcome                  | Risk factor       | RR* or PT*                  | CI          | 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         |

*RR (relative risk of failure) is the risk of failure for risk group 1 divided by the risk of failure of risk group 2.

PT is the probability of developing toxicity.

CI is the 95% confidence interval.

NS = P > 0.05.

Table 3  Causes of toxic death in 26/73 patients

| Causes* 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 |

*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.\textsuperscript{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 reported mixed age effects. Riddell et al.\textsuperscript{11}, in a series of 29 patients, and Woods et al.\textsuperscript{15}, in a series of 16 patients receiving allogeneic BMT for leukemia, reported no age effect. Gale et al.\textsuperscript{17} and Weisdorf et al.\textsuperscript{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.\textsuperscript{19} 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 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.\textsuperscript{11–13} Veno-occlusive disease (8%) and hemorrhagic cystitis (10%) also occurred in the frequencies seen in other series.\textsuperscript{11,14} The minor side-effects of acral erythema and conjunctivitis were observed in similar frequencies to that described following HDA in other series.\textsuperscript{3,14,15} Causes of toxic death are depicted in Table 3.
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, 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. 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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