Rapidly Cycled Courses of High-Dose Alkylating Agents Supported by Filgrastim and Peripheral Blood Progenitor Cells in Patients with Metastatic Breast Cancer

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ABSTRACT

Our purpose was to determine the feasibility of a regimen of multiple, rapidly cycled courses of high-dose alkylating agents, including paired courses of escalating doses of thiotepa, supported by peripheral blood progenitor cells and filgrastim, in patients with responding stage IV breast cancer.

The regimen consisted of two courses of cyclophosphamide (3.0 g/m²/course) followed by two courses of thiotepa (500–700 mg/m²/course). All courses were supported by filgrastim. Leukaphereses were performed after each cyclophosphamide course to harvest peripheral blood progenitors (PBPs) for use as rescue following thiotepa administration. The planned interval for all courses was 14 days.

Forty-two patients were enrolled. Thirty-eight received all four courses, and four did not receive the second thiotepa cycle due to poor PBP mobilization. The maximum dose of thiotepa that was administered was 700 mg/m² × 2. At this dose, one patient developed encephalopathy, which resolved over several weeks. The median number of days to an absolute neutrophil count of 0.5 × 10⁹/liter after PBP reinfusion for cycles 1 and 2 of thiotepa were 9 (range, 7–16) and 9 (range, 8–13) days, respectively. The corresponding values for platelet recovery to >20 × 10⁹/liter were 11 (range, 8–39) and 12 (range, 10–28) days, respectively. There were no treatment-related deaths. Hospitalization was required following 28 of 84 cyclophosphamide courses and 76 of 80 thiotepa courses. Four patients developed grade III-IV mucositis. The median interval between courses of treatment was 15 (range, 13–29) days. Of 19 patients who entered the protocol with measurable disease in partial response from prior therapy, 8 (42%) achieved complete response following the high-dose therapy. Nine (21%) of 42 remain progression free at a median follow-up of 28 (range, 20–32) months.

Therefore, we concluded that the administration of multiple, rapidly cycled courses of high-dose alkylating agents is feasible.

INTRODUCTION

When used as initial chemotherapy for breast cancer patients with newly diagnosed metastases (1–3) or as consolidation for patients whose disease had responded to prior conventionally dosed chemotherapy (4–9), HDC/ABM² support produces CR rates of approximately 50%. Eddy (10) has documented that this CR rate is more than four times higher than those reported for regimens using lower doses. The majority of these CRs are, however, transient. As a result, the median survival of patients on HDC/ABM regimens has not been demonstrated to be prolonged compared to patients receiving more “conventionally dosed” therapy (11).

It is possible that these relapses from CR are invariably due to the presence of clones of highly drug-resistant cancer cells. In this case, it would require novel therapies after HDC (12). However, another possibility, derives from the successful chemotherapy of germ cell cancer and Hodkgin’s disease. Here, cure resulted from the identification of highly active regimens and the application of a minimum number of cycles of those regimens. For example, the median number of cycles of nitrogen mustard-vincristine-procarbazine-prednisone chemotherapy required to produce a CR in patients with Hodgkin’s disease is three, suggesting that many patients would not have been cured had they received only a single course (13). Although it can be argued that these data might not be extrapolatable across disease types, similar data do in fact exist for stage II breast cancer, where a single perioperative course of chemotherapy has been shown to be inferior to a traditional multicycle regimen as adjuvant therapy (14). Is it not also possible that the high-dose regimens, which are used in the therapy of metastatic breast cancer, might be more efficacious if applied in multiple courses?

The interval between courses of multicycle regimens might also influence the outcome. The Gompertizian model predicts that a phase of rapid subclinical regrowth could occur following a massive but noneradicated cell kill. Such regrowth would tend to undermine much of the advantage of multiple treatments, particularly if the intertreatment interval was unduly prolonged (15).

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² The abbreviations used are: HDC/ABM, high-dose chemotherapy with autologous bone marrow; CR, complete response; PBP, peripheral blood progenitor; CSF, colony-stimulating factor.
The prominent toxicity of HDC/ABM, which in early studies, resulted in treatment-related mortality rates of as high as 20% (16) obviously complicated attempts to deliver multiple timely courses. While “tandem transplants” have been accomplished, the interval between treatments is usually at least 1 month (1, 4, 17). For other regimens, prohibitive toxicity has precluded successful “double transplant” (18). Another strategy involved administering a “split course” of very high-dose therapy supported by a single administration of autologous marrow (2).

Advances in hematopoietic support have reduced the toxicity of high-dose therapy, and, hence, have facilitated repetitive treatments. The current trial was designed to test the hypothesis that filgrastim and PBP could facilitate the rapid (approximately biweekly) delivery of four courses of high-dose alkylating agents, including tandem courses of high-dose thiopeta.

**MATERIALS AND METHODS**

The protocol was approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board. All patients were informed of the potential risks and benefits of participation in the protocol and gave written consent to participate.

Eligibility criteria included: histologically proven metastatic breast cancer in the process of response to a phase of prior conventionally dosed induction chemotherapy (or following definitive surgery or radiotherapy of localized metastases); Karnofsky performance status >70%; life expectancy >6 months; absolute neutrophil count > 1.5 × 10^9/liter; platelet count >10^9/liter; bilirubin <1.5 x upper limit normal; normal serum creatinine; negative pregnancy test in premenopausal patients; caloric intake of at least 1000 calories/day; <450 mg/m^2 of prior anthracycline exposure, gated blood pool cardiac ejection fraction >50%, with normal myocardial wall motion; absence of any serious co-morbid disease or prior history of malignancy; absence of brain metastases; and prior radiotherapy to <50% of the bone marrow. Because of the risks of infection and liver toxicity, patients with HIV infection or active hepatitis to <50% of the bone marrow. Because of the risks of infection and liver toxicity, patients with HIV infection or active hepatitis were excluded.

Patients had an initial bone marrow harvest performed from the posterior iliac crest under general anesthesia in an ambulatory surgical facility. A double lumen Hickman dialysis catheter was inserted during the same anesthesia. Approximately 2 days later, patients were admitted to the hospital for the first course of chemotherapy with cyclophosphamide at a dose of 3.0 g/m^2. Patients received intensive hydration commencing on the night before treatment, which continued for 24 h after treatment, at which point they were discharged from the hospital. Ondansetron, dexamethasone, and lorazepam were administered as anti-nausea medication. Filgrastim (granulocyte colony-stimulating factor), 5 μg/kg/day, was given as s.c. injections and was started on the second day following the administration of cyclophosphamide (Fig. 1). Patients received p.o. ciprofloxacin at a dose of 500 mg p.o. twice a day as antibacterial prophylaxis during periods of neutropenia. All catheter flushes were performed with a dilute vancomycin-heparin solution.

Leukapheresis was begun when the leukocyte count had recovered to 1.0 × 10^9/liter during early hematological recovery from each cyclophosphamide-induced period of myelosuppression. Four procedures were performed using a Fenwal CS 3000 cell separator. Ten liters were processed using continuous flow centrifugation, a flow rate of 70 ml/min, a small volume insert, and an interface of 125.

We planned to administer the second cyclophosphamide course approximately 14 days after the first course. Details of supportive care, hydration, leukapheresis, and so forth were identical to those for the first cyclophosphamide course.

Patients were then treated with two courses of thiopeta starting 14 days after the second cyclophosphamide dose. Hematopoietic rescue was attempted by reinfusion of the previously leukapheresed PBPs. Successive cohorts of patients received escalating doses of thiopeta (without intrapatient dose escalation). Patients at dose level I received 500 mg/m^2/course, at level II 600 mg/m^2/course, and at level III 700 mg/m^2/course. Each course was administered in two divided doses on consecutive days. The previously harvested PBPs were administered 48 h after completion of the thiopeta infusion. The PBPs that had been collected following the first course of cyclophosphamide were used as rescue following the first thiopeta course, and the cells from the second cyclophosphamide course were used for the second thiopeta course. We attempted to administer thiopeta No. 2 14 days following thiopeta No. 1. Prophylactic antibiotics and filgrastim were again administered. At least five patients were to be treated per dose level. In the event of any patient developing grade IV nonhematological toxicity, we planned to treat an additional three patients at that level, and if another grade IV toxicity occurred, dose escalation was to stop, and the level below the toxic level was to be considered the maximum tolerated dose.

Mental status examinations were carried out before and after protocol therapy. These examinations consisted of 30 standardized questions designed to test orientation, recall, attention, calculation, language, reading, writing, and copying.

**RESULTS**

Forty-two patients were accrued to the study, including eight at level I and six at level II. Eight patients were initially accrued to level III, and this level was subsequently expanded by a protocol amendment to include an additional 20 patients...
(vide infra). Their pretreatment characteristics are outlined in Table 1. Two patients were found to have progressive cancer after registration in the study, but prior to the institution of protocol chemotherapy. They were continued on protocol.

The bone marrow harvests yielded a median of 1.7 × 10⁸ mononuclear cells (range, 0.45–3.2 × 10⁸)/kg body weight. The median numbers of peripheral blood CD34⁺ cells/kg body weight infused for the thiotepa courses were 2.1 × 10⁶ (range, 0.26–10.5 × 10⁶) and 1.53 × 10⁶ (0.29–8.99 × 10⁶), respectively.

Of the 42 patients enrolled in the study, 38 received all four courses of therapy. One patient had failure of engraftment following thiotepa No. 1 administration. Three subsequent patients were considered to have inadequate numbers of CD34⁺ cells to sustain two courses of thiotepa (vide infra), and each received single courses supported by the entire available PBP collection. The median interval between all chemotherapy courses on the protocol was 15 (range, 13–29) days. The median interval between thiotepa courses was 16 (range, 14–27) days. The median number of days of inpatient hospitalization from the date of protocol entry until recovery from the last course of chemotherapy was 32 (range, 22–71) days for patients receiving all four courses of treatment.

**Toxicity.** There were no therapy-related deaths. No patient required transfer to the intensive care unit.

Grade III-IV myelosuppression occurred following every course of cyclophosphamide. Neutropenic fever complicated 28 of 84 cyclophosphamide courses. Two patients had documented bacteremia after cyclophosphamide therapy, another had pneumonia. Grade IV myelosuppression occurred following every course of thiotepa. Neutropenic fever complicated 76 of 80 courses of thiotepa. Five of these patients developed bacteremia, another three had radiological evidence of pneumonia. Two patients developed clinical cholecystitis and proceeded to cholecystectomy following completion of protocol therapy.

Hematological recovery data following thiotepa treatments are depicted in Table 2. Four patients were prospectively identified as being at risk for delayed engraftment after thiotepa therapy on the basis of low CD34⁺ cells counts in the leukapheresis collections. One of these patients had failure of engraftment following the first dose of thiotepa at 500 mg/m², and required reinfusion of the back-up bone marrow on day 36 after PBP infusion. Hematological recovery was still incomplete following this autologous marrow rescue, and the patient had persistent thrombocytopenia at 6 months. Three subsequent patients with total CD34⁺ counts of 0.29, 0.63, and 0.32 × 10⁹/kg, respectively, were each treated with one course of thiotepa, which was rescued with all of the PBPs. Two of these patients had prompt engraftment, the third had persistent thrombocytopenia at 125 days, and the autologous marrow was administered. The median number of platelet transfusion events was 7 (range, 2–29). The median number of units of RBCs transfused was 10 (range, 4–16).

Thirty-five patients had paired mental status examinations carried out before and after protocol therapy. In 34 there was no decline in score. One patient had evidence of profound neurotoxicity following the second course of thiotepa at the 700-mg/m² dose level. This was manifested by somnolence, inattention, and memory loss. This toxicity recovered completely over the succeeding 3 weeks. As per the protocol, additional patients were accrued at this level. No additional clinical episodes of neurotoxicity occurred. Because the incidence of this toxicity had been reported to rise steeply with thiotepa doses greater than 1000 mg/m² (19, 20), and because our patients were now receiving 1400 mg/m², the principal investigators elected not to proceed to a higher dose level. The protocol was amended to allow additional accrual at this level, and a total of 28 patients were treated at this dose.

One patient developed disseminated varicella infection at 1 month after completion of protocol therapy. Another patient developed dermatomal zoster. Both were treated with acyclovir and recovered completely. One patient developed bilateral retinal hemorrhages while profoundly thrombocytopenic. This patient suffered severe visual loss, which is slowly resolving over 24 months. Clinical features of veno-occlusive disease of the liver occurred in two patients following the second course of thiotepa (maximum bilirubin elevations were 4.2 and 1.5, re-

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**Table 1** Patient characteristics

| Total no. | 42
| Median age, yr (range) | 42 (28–55)
| Median yr disease free (range) | 2.1 (0–4.8)
| Hormone receptor positive | 21
| Hormone receptor negative | 15
| Hormone receptor unknown | 6
| No. of prior chemotherapy regimens | 2 (1–3)
| Sites of metastases | 
| Lung | 6
| Liver | 7
| Bone | 17
| Soft tissue/local | 12
| Lymph nodal | 21
| Disease status on entry to protocol | 
| Complete response | 7
| Measurable partial response | 19
| Surgical/radiation metastatectomy | 3
| Progressive cancer | 2
| Bone-only metastases | 10
| Invaluable for response* | 1
| Median Karnofsky performance status | 90

* Patient had bone marrow-only metastases.

**Table 2** Hematological recovery after thiotepa course

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Median (range) days* to absolute neutrophil count &gt;0.5 × 10⁹/liter</th>
<th>Median (range) days* to platelets &gt;20 × 10⁹/liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg/m²</td>
<td>Cycle 1 8.5 (8–16) 11 (9–13)</td>
<td>Cycle 2 10 (8–11) 14 (12–15)</td>
</tr>
<tr>
<td>600 mg/m²</td>
<td>Cycle 1 9 (8–10) 10.5 (8–12)</td>
<td>Cycle 2 9.5 (8–11) 12 (10–12)</td>
</tr>
<tr>
<td>700 mg/m²</td>
<td>Cycle 1 9 (7–11) 11 (8–39)</td>
<td>Cycle 2 9 (7–13) 13 (10–28)</td>
</tr>
<tr>
<td>Total</td>
<td>Cycle 1 9 (7–16) 11 (8–39)</td>
<td>Cycle 2 9 (8–13) 12 (10–28)</td>
</tr>
</tbody>
</table>

* Measured from the day of PBP infusion, day 0.
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disease with complete resection or irradiation of metastases; PD, progressive cancer.

Table 3 Number of patients with grade 3–4 National Cancer Institute Common Toxicity Criteria) nonhematological toxicity after thiopeta course

<table>
<thead>
<tr>
<th>Dose level patients</th>
<th>Neurological</th>
<th>Hepatic</th>
<th>Diarrhea</th>
<th>Mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4 Response data

<table>
<thead>
<tr>
<th>Status on study entry</th>
<th>Status on study completion</th>
<th>No. of progression free (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>2 (31+, 29+)</td>
</tr>
<tr>
<td>Measurable PR</td>
<td>CR</td>
<td>8 (29+, 27+)</td>
</tr>
<tr>
<td>Measurable PR</td>
<td>PR</td>
<td>2 (27+, 24+)</td>
</tr>
<tr>
<td>Measurable PR</td>
<td>Stable/PR</td>
<td>4</td>
</tr>
<tr>
<td>Bone only</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Stage IV NED</td>
<td>NED</td>
<td>10</td>
</tr>
<tr>
<td>Progression</td>
<td>PR</td>
<td>2</td>
</tr>
<tr>
<td>Inevaluable</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>42</td>
</tr>
</tbody>
</table>

**Table 5** Characteristics of long-term progression-free survivors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hormone receptor</th>
<th>Metastatic site</th>
<th>Adjuvant therapy</th>
<th>Therapy for metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Lung</td>
<td>CAF</td>
<td>MFL, taxol</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Lymph node</td>
<td>CAF</td>
<td>Taxotere</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>Bone, lung</td>
<td>AT</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>Bone</td>
<td>CAF</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>Lymph node</td>
<td>CMF</td>
<td>Taxol</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>Lymph node</td>
<td>Tam</td>
<td>CMF, A</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>Bone</td>
<td>AFM, PE</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>Lymph node</td>
<td>CAF</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>Lymph node</td>
<td>Tam</td>
<td>CMFVA</td>
</tr>
</tbody>
</table>

* C, cyclophosphamide; M, methotrexate; F, fluorouracil; A, doxorubicin, P, cisplatin, E, etoposide; Tam, tamoxifen; L, levocovorin; T, thiopeta; V, vincristine.

Progrfess free at 31+, 29+, 29+, and 22+ months, respectively.

Two patients entered the protocol with progressive cancer. One achieved a temporary partial response.

Ten patients received consolidative radiotherapy to sites of bulk disease following recovery from HDC. Seven patients underwent surgery following completion of HDC. In four cases this was to the breast. Seventeen patients were started on hormone therapy following completion of high-dose therapy.

With a median follow-up of 31 months for all enrolled patients, 9 (21%) of 42 patients are documented to be free of progressive cancer (Table 5).

**DISCUSSION**

These results demonstrate that a program consisting of multiple, rapidly cycled courses of high-dose alkylating agents is feasible in patients with metastatic breast cancer. The safety profile compares favorably with more traditional, single-course regimens supported by autologous bone marrow transplantation. In keeping with the emerging trend in HDC, our patients were managed on general oncology floors without the requirement for isolation units. Although the median number of days of inpatient care for patients in the study is likely longer than would be expected from a single high-dose course with PBP support, most patients did not require a lengthy period of continuous hospitalization.

Recent advances in hematopoietic support technology have facilitated the administration of multiple HDC courses. For some agents, e.g., cyclophosphamide (21, 22), etoposide (23), and doxorubicin (24) and for some combinations (25), CSFs factors facilitate multiple HDC courses. For other, more myelosuppressive therapies, e.g., thiopeta (26) and carboplatin (27), CSFs alone do not provide adequate rescue. However, substantial dose escalation can be effected here through the use of bone marrow autografting (19, 20, 28). The use of CSFs has also been demonstrated to accelerate leukocyte recovery following autografting (29). In addition, the CSFs administered at steady state or following myelosuppressive chemotherapy can mobilize hematopoietic progenitors into the peripheral blood stream (30), from where they can be harvested by leukapheresis and used as a supplement, or as an alternative to autologous bone marrow (31, 32). Thus, the Milan group and our group have

spectively). In both cases, spontaneous recovery occurred. Although mild to moderate mucositis was common, National Cancer Institute grade III-IV mucositis was noted in only four patients. A total of four patients required total parenteral nutrition. Grade III-IV diarrhea affected four patients. Skin hyperpigmentation was universal (Table 3).

Disease Response. Response details are outlined in Table 4. Nineteen patients entered the study in a state of ongoing measurable partial response following induction chemotherapy. Eight of these were “converted” to complete response following protocol therapy (dominant sites: liver, two; pleural/mediastinal, two; lymph nodal, two; soft tissue mass, one; bone marrow/lymph nodes, one). Two of these eight remain progression free at 29+ and 27+ months of follow-up. The six others developed relapsed cancer at 3, 4, 8, 10, 16, and 18 months. Seven of the 19 patients in initial partial response achieved further partial response, and 3 of these had complete resection of residual metastases. Two of these patients remain free of progressive cancer at 27+ and 24+ months. Four patients did not achieve an objective response.

Ten patients entered the study with metastases confined to bony sites. One of these achieved complete response and remains progression free at 27+ months. The other nine developed progressive disease at 18, 17, 16, 15, 12, 12, 11, 10, and 3 months, respectively.

Ten patients entered the protocol without evidence of disease, seven following prior chemotherapy, and three following surgical resection of all known metastatic sites. One of the surgically treated patients and five of the patients enrolled while in complete remission have developed relapsed cancer at 8, 8, 11, 12, 12, and 19 months, respectively. Four patients remain

The Milan group and our group have
devised multicourse HDC regimens in which patients are treated initially with one or more courses of high-dose cyclophosphamide supported by CSFs. Each dose is followed by multiple peripheral blood leukaphereses to harvest PBPs. These are then used to support a subsequent course of melphalan (33) or carboplatin-based combination chemotherapy (34). Other investigators have demonstrated the feasibility of using PBPs to support the administration of multiple courses of HDC administered at standard treatment intervals (35–37). Our group has shown that multiple cycles of PBP-supported high-dose carboplatin-containing regimens could be administered at approximately 14–15-day intervals (38, 39).

We included thiopeta in the current program because it is active as both a single agent and in combination in patients with metastatic breast cancer (40). O’Dwyer et al. (41) determined that the maximum tolerated dose of this drug was 75 mg/m² with dose-limiting myelosuppression. Granulocyte-macrophage colony-stimulating factor did not provide sufficient hematopoietic support to allow for major dose intensification of this agent (26). However, the use of ABM facilitates an approximately 10–15-fold dose escalation, limited by severe mucosal and central nervous system toxicities (19, 20). Such high doses have been reported to produce frequent complete remissions in patients with metastatic breast cancer (42, 43).

Although only 1 of 28 patients who received two courses of thiopeta at 700 mg/m²/course developed severe neurotoxicity, the substantial incidence of this complication at higher single-course doses (19, 20) led us to suspend further dose escalation following consultation with the Institutional Review Board. The incidence of other nonhematological toxicities appears to be similar to that reported for other conventional single-cycle autograft-based approaches and for stem cell requiring multicyle regimens (35).

Although our response and survival data and the characteristics of our long-term progression-free survivors appear to be similar to those reported for single-course multiagent regimens, these high-dose combinations may have higher intrinsic anticancer activity than any of the individual components of our program, particularly the paired courses of cyclophosphamide (44, 45). Thus, this regimen does not provide a test of our hypothesis that multiple, timely courses of HDC might improve the outcome for patients with metastatic breast cancer, and as a result, limited significance should be attached to the response rates that are quoted here. At the time that our study was designed, it was uncertain how many PBPs would be required to support two courses of thiopeta, and, hence, the paired cyclophosphamide courses were included to maximize the number of leukaphereses. With increasing experience and validation of the CD34⁺ assay as a real time index of the adequacy of PBP collections (46), we attempted to intensify our program further in a subsequent study.

In this study, a single course of PBP-supported high-dose melphalan (180 mg/m²) was administered instead of the second cyclophosphamide course, and all of the leukaphereses were performed following a single course of higher dose cyclophosphamide (5.0 g/m²). Results of this pilot experience will be performed following a single course of higher dose cyclophosphamide (5.0 g/m²). Results of this pilot experience will be reported separately, but the regimen produced a very high rate of complete response at the cost of substantial pulmonary toxicity which was fatal in 3 of 17 patients (47). These regimens are being refined in ongoing studies, in an attempt to limit the occurrence of severe nonhematological dose-limiting toxicity.

Precise quantitation of the risks and benefits of HDC in metastatic breast cancer will require prospective random-assignment trials. These trials should use state of the art hematopoietic support technology to ensure that drug-related morbidity is minimized and that dose and dose intensity are maximized, preferably in multidose regimens.

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