Autologous Bone Marrow Transplantation in Acute Leukemia: A Phase I Study of In Vitro Treatment of Marrow With 4-Hydroperoxycyclophosphamide to Purge Tumor Cells


This phase I study was conducted to determine the maximal safe concentration of 4-hydroperoxycyclophosphamide (4HC) that could be used for in vitro treatment of bone marrow from patients with acute leukemia undergoing autologous bone marrow transplantation. Concentrations of 40 to 120 μg/mL of 4HC were used in 30 patients with relapsed or high-risk acute leukemia and in six patients with nonleukemic malignancies. All patients received marrow-lethal cytoreductive therapy followed by infusion of the 4HC-treated marrow. Complete inhibition of granulocyte and macrophage colony-forming cells was obtained at 80 μg/mL. Nevertheless, only one transplant-related death and otherwise full hematologic recovery was observed at concentrations of 4HC up to 100 μg/mL. At 120 μg/mL, there were three transplant-related deaths, including two of the three patients who required the infusion of reserve marrow. Among the acute leukemia patients, three remain in complete remission at 1,337, 1,017, and 967 days after transplant. Among the nonleukemic patients, two remain in complete remission at 1,081 and 1,017 days after transplant. At the maximum safe concentration of 4HC (100 μg/mL), satisfactory hematologic recovery can be obtained, despite elimination of detectable hematopoietic progenitors.

© 1985 by Grune & Stratton, Inc.

THE LONG-TERM relapse-free survival (RFS) of a significant fraction of patients with relapsing or refractory acute leukemia who receive bone marrow transplants (BMT) from identical twins indicates that cure of this disease may be achieved by a supralethal pulse of chemoradiotherapy in the absence of graft-v-tumor effects. Although few patients with acute leukemia possess a monozygotic twin, their autologous remission marrow is a source of syngeneic stem cells. The problem that prevents the more general use of cryopreserved autologous marrow is the presence of occult leukemic cells in remission marrow. The feasibility of using in vitro immunologic or pharmacologic treatment of remission marrow to eliminate all occult leukemic cells has been shown in animal systems. One such method involves the use of a congener of cyclophosphamide, 4-hydroperoxycyclophosphamide (4HC), which is cytotoxic in vitro. A drug dose-dependent clearing of tumor cells from a mixture of normal marrow and tumor cells was first demonstrated in a model of acute myelogenous leukemia in the Lewis-Brown Norway hybrid rat. Further increases of drug concentration resulted in increasing death rates due to marrow failure.

We have begun a two-phase clinical study for patients with acute lymphoblastic and nonlymphoblastic leukemia (ALL and ANLL) using marrow-lethal chemoradiotherapy followed by rescue with cryopreserved autologous remission marrow treated in vitro with 4HC. This report details the results of the first phase of this clinical study, the goal of which has been to determine the maximal concentration of 4HC that can be used without significantly interfering with hematologic recovery.

MATERIALS AND METHODS

Clinical Study Design

The study was designed to escalate the concentration of 4HC used for in vitro treatment of marrow by increments of 20 μg/mL. Marrow collected from each patient was aliquoted into a treated and reserve fraction. Initially, the treated fraction was incubated with 40 μg/mL of 4HC, and the reserve marrow was untreated. In subsequent groups, the treated marrow was incubated at 60, 80, 100, and 120 μg/mL, and the reserve fraction was treated at 40 or 60 μg/mL. The treated marrows were infused after the patients received marrow-lethal doses of cytoreductive therapy. By three weeks after marrow infusion, if the peripheral blood counts showed no evidence of a rising leukocyte, platelet, or reticulocyte count and the marrow aspirates and biopsies showed no evidence of clones of newly developing hematopoietic cells, the reserve marrow was infused. The trial was to terminate when three patients met the criteria for infusing reserve marrow.

Patient Selection and Characteristics

A total of 36 patients are included in the study; 21 with ALL, nine with ANLL, five with non-Hodgkin's lymphoma (NHL), and one with neuroblastoma (NB). Thirty-three of the patients were referred...
to the Johns Hopkins Oncology Center, where the autologous BMT was carried out. Three patients designated by unique patient numbers (UPN) A001, A002, and A003 were referred to the University of Pittsburgh and received their autologous BMT at Montefiore Hospital in Pittsburgh. Criteria for inclusion in the study generally included the following: (1) an expected two-year RFS of less than 5% and (2) multiple samples of bone marrow prior to harvesting had to be microscopically free of tumor (a differential cell count of <5% blasts on marrow aspirate and/or the absence of focal collections of tumor cells on marrow biopsy) and had to have 60% of normal cellularity.

Table 1 indicates the status of each patient at the time of marrow harvesting and immediately before their preparative regimen. Two patients with acute leukemia had marrow collected and were transplanted in initial remission, UPN 267 and 269. The former patient was referred because his physicians had to discontinue maintenance chemotherapy after less than a year of treatment due to progressive toxicity. The latter patient failed on primary and secondary remission induction therapy before achieving an initial complete remission (CR) about four months after diagnosis. Twelve patients began the transplant preparative regimen not in complete remission. Eight of the patients with acute leukemia (UPN 242, 253, 272, 344, 373, A001, A002, A003) exhibited a partial relapse, with between 7% and 20% leukemic blasts in the marrow during the two-to-six-week interval between marrow harvesting and the start of their pretransplant preparative regimen.

**Informed Consent**

The protocols were reviewed and approved by the Joint Committee on Clinical Investigations of the Johns Hopkins Medical Instit-

---

**Table 1. Post-transplant Clinical Course and Status of Patients as of Nov 1, 1984**

<table>
<thead>
<tr>
<th>Concentration of 4HC</th>
<th>UPN</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Preparative Regimen**</th>
<th>Status at BMH**</th>
<th>Status at BMH†</th>
<th>Infection</th>
<th>Other Severe Organ Toxicity†</th>
<th>Hematologic Recovery</th>
<th>Days Post-BMT</th>
<th>Remission Duration</th>
<th>Days Post-BMT</th>
<th>Survival†</th>
<th>Current Status and Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 μg/mL</td>
<td>214</td>
<td>14/M</td>
<td>ALL</td>
<td>III</td>
<td>CR3</td>
<td>PR</td>
<td>B</td>
<td>28 31 41 68+</td>
<td>1032+</td>
<td>0</td>
<td>1032+</td>
<td>0</td>
<td>ACCR</td>
<td></td>
</tr>
<tr>
<td>60 μg/mL</td>
<td>253</td>
<td>14/M</td>
<td>ALL</td>
<td>III</td>
<td>CR3</td>
<td>PR</td>
<td>B</td>
<td>34 34 33 31</td>
<td>116 204</td>
<td>0</td>
<td>116 204</td>
<td>0</td>
<td>ACCR</td>
<td></td>
</tr>
<tr>
<td>80 μg/mL</td>
<td>258</td>
<td>6/F</td>
<td>ALLLL</td>
<td>II</td>
<td>CR2</td>
<td>CR2</td>
<td>B</td>
<td>21 20 25 35</td>
<td>165 1,373+</td>
<td>36</td>
<td>1,373+</td>
<td>36</td>
<td>36</td>
<td>DTX</td>
</tr>
<tr>
<td>100 μg/mL</td>
<td>267</td>
<td>12/M</td>
<td>ALLLL</td>
<td>II</td>
<td>CR1</td>
<td>CR1</td>
<td>L</td>
<td>84 25 66 224</td>
<td>1,337+</td>
<td>0</td>
<td>1,337+</td>
<td>0</td>
<td>1,337+</td>
<td>DTX</td>
</tr>
<tr>
<td>120 μg/mL</td>
<td>269</td>
<td>18/M</td>
<td>ALLLL</td>
<td>II</td>
<td>CR3</td>
<td>CR3</td>
<td>B</td>
<td>25 19 14 21</td>
<td>777 1,331+</td>
<td>36</td>
<td>1,331+</td>
<td>36</td>
<td>1,331+</td>
<td>DTX</td>
</tr>
<tr>
<td>120 μg/mL</td>
<td>282</td>
<td>15/M</td>
<td>NHLL</td>
<td>III</td>
<td>CR5</td>
<td>CR5</td>
<td>B</td>
<td>24 22 21 41+</td>
<td>33 384</td>
<td>36</td>
<td>384</td>
<td>36</td>
<td>384</td>
<td>DTX**</td>
</tr>
<tr>
<td>120 μg/mL</td>
<td>305</td>
<td>14/F</td>
<td>NHLL</td>
<td>II</td>
<td>CR2</td>
<td>PR</td>
<td>B</td>
<td>24 21 17 47</td>
<td>60 85</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>85</td>
<td>DTX</td>
</tr>
<tr>
<td>120 μg/mL</td>
<td>306</td>
<td>3/M</td>
<td>NHLL</td>
<td>III</td>
<td>CR2</td>
<td>CR3</td>
<td>L</td>
<td>12 13 17 35</td>
<td>1,081+</td>
<td>1,081+</td>
<td>1,081+</td>
<td>1,081+</td>
<td>1,081+</td>
<td>DTX</td>
</tr>
</tbody>
</table>

* BMH, bone marrow harvest; B, positive blood culture; L, localized infection; GI, mucositis and/or bleeding; L, liver toxicity; Retic, reticulocytes; PLTs, platelets; DT, died with progressive tumor; DTX, died of transplant toxicity; ACCR, alive, continuous remission, off therapy; AREL, alive after relapse.
* See text on preparative regimen for details or modifications.
* At the time of bone marrow harvest.
* Immediately prior to the transplant preparative regimen.
* 0, no infection.
* 0, no toxicity.
* # is equivalent to ≥.
* **This patient had residual leukemia at postmortem exam.
tions and the Protection of Human Subjects Committee of Montefiore Hospital, University of Pittsburgh. The procedures, potential risks and benefits, and possible alternative therapies were explained to the patients and/or appropriate family members, and informed consent was obtained.

**Bone Marrow Harvesting, Processing, and Reinfusion**

Harvesting of marrow from the iliac crest under general anesthesia and preparation of a single-cell suspension was carried out as described by Thomas and Storb. All blood transfusions given during the procedure or in the prior week were first irradiated with 1,500 to 3,000 rad. Every attempt was made to obtain 4 x 10^9 nucleated cells per kilogram of patient body weight for the treated marrow along with 2 x 10^9 nucleated cells per kilogram as the reserve marrow. In one instance (UPN 364), the entire yield (4.2 x 10^9 cells per kilogram) was treated with 120 μg/mL of 4HC, because a marrow had been obtained and cryopreserved without 4HC treatment during the patient’s initial remission, four years earlier.

The nucleated cells in the blood–marrow mixture were separated by centrifugation in blood transfer bags (Fenwall 4R2023, Deerfield, Ill.) on a Sorvall RC-3B (Wilmington, Del) centrifuge at 2,900 rpm (HG-4L head) for ten minutes. The residual red cell pellet and plasma were remixed in order to extract a second buffy coat. The buffy coat fractions were pooled and the volume adjusted with autologous plasma and tissue culture medium (TC199), so that the final concentration of nucleated cells was 2 x 10^9 cells per milliliter in 80% TC199 and 20% plasma. A volume of a freshly prepared stock solution of 10 mg/mL of 4HC in phosphate-buffered saline was then added to the cell suspension to achieve the desired drug concentration. The cells were incubated at 37 °C for 30 minutes, cooled to 4 °C, and centrifuged at 2,900 rpm for ten minutes. The cell pellet was resuspended at a concentration of 4 x 10^9 cells per milliliter in 45% TC199, 45% autologous plasma, and 10% dimethyl sulfoxide (DMSO). Fifty-milliliter aliquots were transferred to polyolefin bags (2030-2; Del-Med Corp, Holbrook, Mass) and frozen in a Cryo-Med Model 100 freezer (Cryo-Med Corp, St Clemens, Minn) at 1 °C/min to -50 °C and then at 10 °C/min to -70 °C. The bags were stored in the liquid phase of a liquid nitrogen freezer. At the time of transplant, each bag was thawed rapidly in a 37 °C water bath and infused rapidly without further processing or removal of DMSO.

**Pretransplant Preparative Regimens**

The day of autologous marrow infusion is designated as day 0. All patients with ANLL received oral busulfan, 1 mg/kg for 16 doses on days -9 through -6, and cyclophosphamide, 50 mg/kg for four doses on days -5 through -2. All but two of the ALL patients received 50 mg/kg cyclophosphamide for four doses on day -8 through -5, followed by fractionated total body irradiation (TBI) at 300 rad/d for four doses on days -4 through -1. Because of concerns about toxicity, one patient with ALL (UPN 228) and one with NHL (UPN 305) received a modified cyclophosphamide–TBI regimen with 60 mg/kg cyclophosphamide on day -6 and -5, followed by fractionated TBI. Three patients with NHL, one patient with Burkitt’s cell ALL, and the patient with NB received a modified chemotherapy protocol, which included Adriamycin (Adria, Dublin, Ohio), 30 mg/m² for three doses on days -7 through -5 and 60 mg/kg cyclophosphamide on days -6 and -5. This was followed by fractionated TBI on days -4 through -1.

**Supportive Care**

All patients were hospitalized in single rooms that were ventilated with 32 nonlaminar air exchanges per hour through high-efficiency filters. Conventional reverse-isolation procedures were instituted when the granulocyte levels fell below 500 cells per microliter. All patients had central venous catheters—most having double-lumen Hickman catheters—through which intravenous fluids, antibiotics, blood products, and parenteral nutrition solutions were administered. During the post-transplant aplasia, platelet transfusions were administered to maintain the platelet count above 20,000 platelets per microliter, and packed red blood cells were administered to maintain a hematocrit above 30%. All blood products were irradiated with 1,500 to 3,000 rad to prevent possible graft-versus-host reactions. Fears during the post-transplant aplasia were treated with broad-spectrum antibiotics. Amphotericin B was used empirically if fevers persisted for more than six days. Once begun, antimicrobial therapy was continued until the patients were afebrile and their granulocyte counts exceeded 500 cells per microliter.

**Hematopoietic Progenitor Cell Measurements**

For each patient, aliquots of the harvested marrow before and after 4HC treatment were reserved for soft-agar assay of the frequency of granulocyte-macrophage progenitors (CFU-Cs). Mononuclear cells prepared by Ficoll-Hypaque (Sigma, St Louis) density gradient centrifugation from the marrow buffy coat were cultured in McCoy’s 5A medium with 15% fetal calf serum and 0.3% agar, using human placental-conditioned medium as a source of colony-stimulating factor. Colonies (>40 cells) were scored after ten to 12 days incubation at 37 °C, 7.5% CO₂, and high humidity. Assay results were used to calculate the total CFU-Cs for each patient.

**Analysis of Hematologic Recovery**

The analysis of hematologic recovery is based on the time to reach the following peripheral blood end points on two successive observations: an absolute granulocyte count (AGN) over 0.5 x 10^9 per microliter, a total leukocyte count (WBC) over 1.0 x 10^9 per microliter, a reticulocyte count over 1%, and a platelet count over 50 x 10^9 per microliter. These data were used to calculate Kaplan-Meier estimates of the probability of meeting a given end point by a given post-transplant day. For each end point, separate Kaplan-Meier curves were calculated for each group of patients receiving marrows treated at the different concentrations of 4HC. A natural grouping of the data revealed by these calculations was to pool patients into low (40 μg/mL), intermediate (60, 80, and 100 μg/mL), and high (120 μg/mL) 4HC concentration groups.

**RESULTS**

**Post-transplant Clinical Course**

All patients experienced severe, life-threatening hematologic toxicity. WBC nadirs of less than ten cells per microliter occurred within three to five days of completing the pretransplant therapy, and all patients required transfusions with platelets and red blood cells for median durations of 26 and 30 days, respectively. Associated with the severe hematologic toxicity, all patients exhibited post-transplant fever of variable duration (median, 16 days) and severity. Infections were documented in 28 patients, including 23 patients with one or more positive blood cultures (Table 1). It is noteworthy that 17 of the 23 patients with bacteremia cultured out gram-positive organisms, predominantly *Staphylococcus aureus* and *Staphylococcus epider-*
midis and Streptococcus viridans. Among these 23 patients, 11 were blood culture-positive within three days of the onset of fever, suggesting that the cultured agent was the primary infection. The remaining 12 patients were blood culture-positive seven to 30 days after the onset of fever, suggesting superinfection. Five patients had localized infections without bacteremia.

Some patients exhibited other life-threatening complications, five with severe mucositis and/or GI bleeds and four with severe liver toxicity (Table 1). Two of these latter patients (UPN 294, 355) died with liver failure. Other post-transplant complications included mild to moderate gastrointestinal (nausea, vomiting, diarrhea, and mucositis) and liver (serum transaminases transiently in the range of 1.5 to 3.0 times the upper limit of normal) toxicities.

Despite the severity and multiplicity of the complications, only one of the first 26 patients (marrows incubated with concentrations of 4HC ranging from 40 to 100 μg/mL) had a transplant-related death. This patient, UPN 294, died of liver failure secondary to venoocclusive disease. Among the ten patients whose marrows were incubated with 120 μg/mL of 4HC, there were three transplant-related deaths. UPN 355 developed polymicrobial sepsis, despite evidence of early hematologic recovery, and died with progressive pulmonary and hepatic failure. Three patients (UPN 364, 373, 380) whose marrows were incubated at 120 μg/mL failed to show evidence of marrow recovery by day 21 and had their reserve marrows infused. Two of these patients died (UPN 373 of cytomegalovirus pneumonia and UPN 380 of disseminated aspergillosis), and at postmortem, neither showed histologic evidence of significant hematologic recovery. UPN 364 received an untreated reserve marrow obtained in his initial remission and showed evidence of rapid hematologic recovery. He had a subsequent benign course until he relapsed 260 days after transplant. Among the 32 remaining patients, the median duration of their post-transplant hospitalization was 37 days. Except for patients who exhibited early tumor relapse, the discharged patients were able to resume normal activity.

Hematologic Recovery

Figure 1 shows the effect of 4HC treatment on CFU-Cs. In addition to the values obtained for the patients transplanted in this study, the graph includes data on marrows obtained from patients who have not been transplanted. A concentration-dependent inhibition of CFU-C growth is seen, with virtually complete inhibition at concentrations of 80 μg/mL of 4HC or greater.

We have already noted that three patients whose marrows were incubated at 120 μg/mL of 4HC failed to show evidence of hematologic recovery by 21 days after BMT and, therefore, received their reserve marrows. The number of days to each criterion for hematologic recovery (eg, AGN >500 cells per microliter) is shown for each patient in Table 1. A more general characterization of hematologic recovery is provided by the Kaplan-Meier recovery curves for each hematologic end point, with patients grouped according to the concentration of 4HC used to treat marrow, ie, low, intermediate, or high (Fig 2). These curves suggest a dose–response relationship between 4HC concentration and granulocyte and reticulocyte recovery but not total leukocyte or platelet recovery.

Therapeutic Efficacy

Although a phase I study is not expected to answer questions of therapeutic efficacy, data on post-transplant remission duration, survival, and current status of the patients are of obvious interest. These values are calculated as of Nov 1, 1984, and shown in Table 1. The post-transplant remission durations of patients dying of transplant-related complications are censored at the day of death, except for UPN 373, who had evidence of leukemia at postmortem. Five patients remain in continuous complete remission; two with NHL, one with ALL, and two with ANLL. Although most patients who relapsed died shortly thereafter with progressive disease, there are five who remain alive at 340 to 1,208 days after their post-transplant relapse. UPN 258 is particularly noteworthy, because she has been in continuous CR (CCR) for over 36 months since her post-transplant reinduction and has been off of all chemotherapy for over 12 months. We have previously noted that eight of the 30 acute leukemia patients exhibited evidence of partial relapse in the interval of time between bone marrow harvesting and transplant. All of these eight patients have relapsed, with a median remission duration of 95 days as compared to 170 days in the remaining 22 patients.
DISCUSSION

Post-transplant Clinical Course

Although autologous bone marrow transplantation is not likely to have as high a complication rate as allogeneic bone marrow transplantation, this series illustrates the need for maximal supportive care, even in the context of autologous transplantation. Of particular note in the current series is the high rate of primary and secondary bacteremia. The high relative rate of gram-positive bacteremia is consistent with the recent experience of other institutions caring for patients with prolonged severe neutropenia.11

From the perspective of the phase I question posed by this study, the key observation is that three of the four early deaths occurred in the group of patients receiving marrow treated with 120 µg/mL of 4HC. This fact, coupled with the requirement for infusion of reserve marrow in three patients in the 120 µg/mL group, indicates that a concentration of 4HC over 100 µg/mL—under the conditions of in vitro incubation used in this study—is associated with an unacceptable risk for the patient.

Hematologic Recovery

The interpretation of the data on hematologic recovery depends on the assumption that the observed recovery was a function of the infused 4HC-treated marrow cells. The preparative regimens used in this study contained what is generally accepted as a marrow-lethal dose of TBI or what we consider to be equally marrow-lethal doses of busulfan. Direct evidence for the marrow-lethal dose of busulfan in man is not available, but this drug is one of the few cytotoxic agents that can produce fatal aplasia in experimental animals.12 In rats an LD100 dose of 30 mg/kg can be reversed by syngeneic BMT.13 Based on published conversion factors, this would be equivalent to a dose of about 6 mg/kg in man,14 ie, less than half the dose used in the busulfan—cyclophosphamide regimen.

The effect of 4HC incubation on measurable hematologic progenitor cells depends on the conditions of incubation.15 In particular, variations in nucleated cell concentration, red cell contamination, and serum or protein concentration can result in as much as a fivefold shift in the degree of CFU-C inhibition. Since the red cell concentrations of the buffy coat preparations of marrow used in these studies vary considerably, the degree of variability in CFU-C inhibition at lower drug concentrations is not surprising, despite the use of constant nucleated cell and serum concentrations.

The pluripotent lymphohematopoietic stem cell cannot currently be measured in human bone marrow. Most clinical investigations of autologous BMT have, therefore, used measurements of CFU-Cs to assess the
quality of the marrow cells infused. This use of CFU-Cs suffers from a number of problems. First, the CFU-C is several stages further along the differentiation pathway than the pluripotent stem cell. Second, most clinical studies of autologous BMT have shown that the correlation between the number of CFU-Cs infused and the rate of recovery is minimal at best. Finally, this study has shown that satisfactory hematologic recovery can be obtained, despite inhibition of all measurable CFU-Cs. Thus, even if there is normally a strong correlation between pluripotent and committed stem cells, this correlation can be uncoupled by drug treatment. It would appear, based on this observation, that there is a considerable difference in the cytotoxic effect of 4HC on pluripotent stem cells as compared with the effect on committed progenitor cells. The mechanism responsible for this apparent differential sensitivity is an interesting but unresolved question. No matter what the underlying mechanism, the strong differential effect of 4HC on committed progenitor cells may help account for the observation that the dose–response relationship between 4HC concentration and hematologic recovery appears to hold principally for early measures of hematologic recovery, ie, AGN >500 and reticulocytes >1%.

**Therapeutic Efficacy**

As already noted, a phase I study is not expected to provide statistically valid conclusions regarding therapeutic efficacy. Thus, while the long-term post-transplant RFS in two of five NHL patients is encouraging, their possible cure cannot be attributed to the 4HC treatment of marrow, since it is possible for patients with relapsed NHL to have a marrow that is free of clonogenic tumor. One potentially important observation relating to the efficacy of 4HC treatment is the 100% relapse rate and shortened remission duration of the eight patients who exhibited a partial relapse between harvesting and transplant. This suggests that the degree of subclinical disease will influence the efficacy of 4HC treatment. Finally, among the patients with acute leukemia, three remain in complete remission. Since one of these was transplanted in initial remission, the role of the BMT in his subsequent course cannot be evaluated. Two patients may have benefited from the autologous BMT; UPN 309 with a 34-month post-transplant CCR was in third remission at the time of transplant, with a second complete remission of only four months' duration, and UPN 339 with a 32-month post-transplant CCR was in second remission at the time of transplant, with an initial remission duration of about 23 months. Obviously, clear assessment of the therapeutic efficacy of in vitro incubation of marrow with 4HC must await completion of the phase II trial currently underway.

**ACKNOWLEDGMENT**

The authors are grateful to the many referring physicians and the nurses on the Transplant Service. Special thanks are due to Denise Carter, Transplantation Coordinator, for her assistance; Shirley Quaskey for data processing; Jean-Pierre Cote and Michael Hayden for their technical assistance in marrow processing and cryopreservation; and Connie Rutter for preparing the manuscript.

**REFERENCES**


14. Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE:


Autologous bone marrow transplantation in acute leukemia: a phase I study of in vitro treatment of marrow with 4-hydroperoxycyclophosphamide to purge tumor cells

H Kaizer, RK Stuart, R Brookmeyer, WE Beschormer, HG Braine, WH Burns, DJ Fuller, M Korbling, KF Mangan and R Saral