Deleterious Effects of Irradiation and Bone Marrow Transplantation Therapy in the Genetically Anemic an/an Mouse

By Janan T. Eppig and Jane E. Barker

The efficacy and outcome of bone marrow transplantation therapy following lethal irradiation were examined in syngeneic mice that had a hereditary macrocytic anemia (an/an) or were genotypically normal (+/ +). Successful RBC and WBC replacement, based on blood cell parameters and donor genetic markers, were observed in all combinations of transplant therapy. Nevertheless, the an/an mice died prematurely several months after treatment, whether they received +/+ or an/an marrow cells.

The MOUSE has been used extensively as a model system for bone marrow replacement therapy because it is well defined genetically, and the availability of syngeneic animals allows study of stem cell replacement without the complication of graft-vs-host disease (GVHD). In the mouse, some genetically determined diseases of the hematopoietic system and immune system can be cured by supplanting the host bone marrow with bone marrow from a normal donor mouse.1,2

A single gene mutation known to cause hereditary macrocytic anemia in the mouse is Hertwig’s anemia (an). Homozygous an/an mice have a phenotypically milder macrocytic anemia than do homozygotes of either the S1 or W genes. Homozygous an/an mice cannot be cured of their anemia without bone marrow ablation treatment. Cures of the macrocytic anemia have been reported in an/an mice that were lethally irradiated and reconstituted with normal bone marrow from syngeneic mice.3

We report the long-term results of lethal irradiation and bone marrow transplantation therapy in an/an mice. Our results show that while the an/an mice initially were cured by this treatment, these mice underwent a rapid decline and died 2 to 8 months after the irradiation and bone marrow replacement therapy. Such results cannot be explained by differences in lethal irradiation dose sensitivity between +/+ and an/an mice.4 We thus sought to discover the cause of death in the irradiated and bone marrow-transplanted an/an mice that were dying prematurely after successful replacement of their hematopoietic system with syngeneic donor bone marrow. Our results suggest that in these an/an mice, some long-lived somatic cell type may fail to recover after irradiation or some stem cell type may fail to be replaced by the donor marrow cells.

MATERIALS AND METHODS

Donor and recipient mice. All mice used in these experiments were 2- to 5-month-old F1 hybrids from crosses between C57BL/6J and WB/ReJ mice in which the an gene was segregating. A closely linked coat color marker gene, Bb (brown light), was present on the chromosome carrying the an allele and was used to distinguish an/an, +/an, and +/- littermates. The Hertwig’s anemia phenotype was confirmed by determining RBC parameters of all mice that were genotypically BB/Bb and presumed an/an homozygotes. Genotypically, these mice were also Gpi-1a/Gpi-1a Hbb'/Hbb' (glucose phosphate isomerase-1 and hemoglobin β-chain, respectively).

Mice used as donors for bone marrow transplantation were either C57BL/6J mice, genotypically +/+ or an/an and Gpi-1a/Gpi-1a Hbb'/Hbb', or B6.CAST/Ei-Gpi-1a mice, genotypically +/+ and Gpi-1a/Gpi-1a Hbb'/Hbb'. To obtain marrow cells for transplantation, the marrow was flushed from the femurs into physiologic saline. Cells were centrifuged, resuspended in 1 mL saline, counted using a hemocytometer, and diluted appropriately. Recipient mice were injected through the tail vein with 0.1 mL saline containing 1 to 2 × 10^6 cells.

Necropsy. Mice were killed by cervical dislocation and necropsied when moribund to determine whether there were any abnormal lesions or tumors present.

Irradiation. Mice were whole-body irradiated by placing them in a plexiglass container on a rotating table within a 137Cs irradiator. Dosages used for the lethal irradiation and marrow transplantation experiments were 750 or 1,000 rad. Because no differences in outcome were detected using the two doses, results are combined.

Blood parameter determinations. One hematocrit tube of blood was obtained from the retroorbital sinus of each mouse. RBC and WBC number was determined using a model ZBI Coulter Counter. Hematocrit tubes were sealed and centrifuged, and the percentage of RBCs was measured. Mean cell volume was calculated by dividing the hematocrit value by the RBC number.

Cell separation. Lymphocytes and RBCs were separated from whole blood using a modification of the technique of Van Zant et al.6 Whole blood, 150 mL, was added to 10 mL phosphate-buffered saline (PBS) and centrifuged at 670 g. The pellet was eluted in 1 mL Percoll (1.07 g/mL density), underlaid with 2 mL Percoll (1.09 g/mL) and overlaid with 1 mL PBS. The gradient was centrifuged at 1,000 g for ten minutes. Lymphocytes were collected at the PBS-Percoll interface and RBCs from the pellet. This procedure produces a lymphocyte fraction that is occasionally contaminated with a few RBCs and an RBC fraction that is virtually free of nucleated cells.

Gpi-1 and Hbb determinations. Gpi-1 and Hbb genotypes were determined by electrophoresis on Titan III cellulose acetate plates. Packed RBCs were sampled for Hbb, and percentage of Hbb1 was

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determined by scanning the Ponceau S-stained and cleared Titan III cellulose acetate plate on a Helena Densitometer (Helena Laboratories, Beaumont, TX). Samples for Gpi-I were either packed RBCs or WBCs separated as described above. The methods used for electrophoresis were those of Eicher and Washburn7 for Gpi-I and those of Whitney8 for Hbb. The sensitivity of these electrophoretic assays has been reported to be 5%.9,10

Determination of WBC types. A smear of whole blood was made on a precleaned microscope slide, air-dried, and stained with Wright’s-Giemsa (Harleco, Gibbstown, NJ) for two minutes. Slides were rinsed under tap water, air-dried, and examined microscopically to determine the distribution of WBC types.

RESULTS

Lifespan of lethally irradiated and bone marrow-transplanted mice. To determine the efficacy of bone marrow replacement therapy in anemic (an/an) mice, long-term bone marrow transplantation studies were undertaken to compare an/an mice and +/+ mice that were lethally irradiated and marrow transplanted with either an/an or +/+ marrow cells. A dramatic difference in survival time was noted between the lethally irradiated an/an and +/+ mice regardless of the source of the donor marrow cells (Fig 1). The irradiated and reconstituted an/an mice survived a maximum of 7 months when injected with +/+ cells. One an/an mouse receiving +/+ marrow survived for 9 months after treatment. The irradiated and reconstituted +/+ mice survived a maximum of 23 months when injected with +/+ cells. One +/+ mouse injected with an/an cells survived for 24 months. At 9 months, after all an/an mice had died, 90% of the +/+ mice that received an/an marrow cell replacement and 100% of the +/+ mice that received +/+ marrow cell replacement were still alive.

Proof of donor marrow implantation. The premature deaths of irradiated an/an marrow recipients were unexpected. One explanation for the observation was that donor cells were unable to implant. To test this hypothesis, RBCs from recipient mice were evaluated every 8 weeks for at least 64 weeks for RBC parameters, Hbb, and Gpi-I phenotypes (Table 1). RBCs were demonstrated to be donor type by 8 weeks after transplantation. The anemia of an/an mice injected with an/an cells was more severe than in untreated an/an mice. This indicates that the combination of irradiation and anemic marrow transplantation was deleterious, as might be expected. The genetic markers Gpi-I and Hbb are more accurate indicators of donor cell replacement and were used to measure and compare erythrocyte-lymphocyte or erythrocyte replacement, respectively. Both the circulating RBCs (Table 1) and lymphocytes (data not shown) were fully donor type within 8 weeks. Results show that the mice not only attained but also retained the RBC phenotype of the donor bone marrow cells throughout the experiment. Thus, the premature death of an/an mice was not caused by lack or reversal of marrow implantation.

RBC values decreased sharply just before death in all of these mice. The impact of this decrease cannot be seen in Table 1 because composite values for all mice in the experiment are presented. Figure 2 illustrates RBC counts over time for three representative mice in each group of lethally irradiated and bone marrow-transplanted mice (+/+ mice receiving +/+ marrow cells, +/+ mice receiving an/an marrow cells, an/an mice receiving +/+ marrow cells, and +/+ mice receiving +/+ marrow cells. The +/+ mice survived 12 to 23 months after treatment as contrasted to the identically treated an/an mice that survived 2 to 9 months after treatment. The genotype of the donor cells (+/+ or an/an) was not a survival factor. All mice were fully repopulated with donor-type cells as shown by the circulating RBC parameters and genotypes. Symbols x → y indicate that marrow cells from mice of genotype x were transplanted into lethally irradiated mice of genotype y.

![Fig 1. Survival of lethally irradiated bone marrow-transplanted mice. The +/+ mice survived 12 to 23 months after treatment as contrasted to the identically treated an/an mice that survived 2 to 9 months after treatment. The genotype of the donor cells (+/+ or an/an) was not a survival factor. All mice were fully repopulated with donor-type cells as shown by the circulating RBC parameters and genotypes. Symbols x → y indicate that marrow cells from mice of genotype x were transplanted into lethally irradiated mice of genotype y.](image-url)
### Table 1. Blood Parameters of Irradiated Bone Marrow-Transplanted Mice

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<td>RBCs (× 10^{12}/L)</td>
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<td>Hematocrit (%)</td>
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<td>9.20 ± 0.18</td>
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<td>Mean cell volume (μm³)</td>
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<td>Hematocrit (%)</td>
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<td>28.4 ± 3.1</td>
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<td>an/an</td>
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All values are mean ± SE.

* RBC genetic markers were Gpi-1 or Hbb.

† All an/an mice receiving +/+ marrow died before the 32-week test.

‡ All an/an mice receiving an/an marrow died before the 24-week test.
Fig 2. RBC counts for three representative mice from each group. All mice were lethally irradiated and bone marrow transplanted. Individual panels indicate donor and recipient genotype. The RBC counts decreased dramatically in all cases as the mice neared death.

an/an mice receiving an/an marrow cells). From these results and the fact that the phenotype of the RBCs remained donor type, we conclude that the implanted bone marrow cells failed to generate sufficient RBCs.

WBCs of lethally irradiated marrow-transplanted +/+ and an/an mice. One effect of homozygosity for the an mutation is depressed WBC count. To determine whether the WBC compartment was being replaced appropriately, we monitored WBC counts at 4-week intervals in lethally irradiated +/+ or an/an mice transplanted with +/+ marrow cells. RBC parameters and Hbb phenotype determined at each time confirmed complete and continuous RBC replacement by donor cells (data not shown). The irradiated and reconstituted +/+ mice showed an increase, followed by a leveling in their WBC counts. The irradiated and reconstituted an/an mice showed an increase, followed by a decrease in their WBC counts. WBC numbers in 3-month-old untreated an/an mice were previously reported to be 16.0 x 10^9/L, decreasing by age 24 months to 11.8 to 16.4 x 10^9/L.

In the +/+ mice injected with +/+ cells, the WBC values attained and maintained over the 24 weeks of the experiment were less than expected for untreated +/+ mice. In the an/an mice injected with +/+ cells, the WBC values peaked 12 weeks posttreatment at a level higher than those of treated or untreated +/+ mice, then decreased sharply through the 24-week measurement (Fig 3). These data suggest that WBCs in an/an mice that have received irradiation and bone marrow transplantation therapy are replaced but not maintained at normal levels.

To evaluate further the relative contributions of lymphocytes and granulocytes to the WBC population in transplanted mice, we examined the composition of nucleated cells in the peripheral blood over time. Lethally irradiated +/+ or an/an mice transplanted with syngeneic +/+ or an/an bone marrow cells were monitored every 2 weeks for RBC parameters and appropriate genetic markers (Gpi-I or Hbb) to assure that the marrow transplantation was successful (data not shown). Determination of WBC Gpi-I phenotype
showed that WBCs were repopulated by donor cells by 6 weeks. Whole blood smears were made and stained with Giemsa, and WBC types were evaluated microscopically. No significant differences were observed between the four experimental groups. As with the RBC counts, there was a decrease in lymphocyte counts when individual mice were moribund (data not shown).

Pathologic examination of moribund animals. Pathological analysis was performed on irradiated and bone marrow-transplanted an/an mice as they became moribund. Grossly, the an/an mice became thin, hunched, and were suffering respiratory distress. Many of the an/an mice had pneumonialike symptoms or a scaly irritated region around their neck. The most frequently noted abnormalities in autopsied an/an mice were enlarged and/or granular kidneys, fluid in the chest cavity or abdomen, and hemorrhagic foci in the lung. None of these findings was universal among the an/an mice.

In three paired autopsies, moribund an/an mice that had received irradiation and +/+ bone marrow transplants were autopsied and compared with +/+ mice that had received identical irradiation and transplant treatment at the same interval after treatment. All an/an mice had fluid in the chest cavity; lungs were pale, lungs and kidneys appeared pitted, and spleens were enlarged. All +/+ mice had normal-appearing organs, and no fluid was present in the chest cavity.

Figures 4A and B show hematoxylin and eosin-stained sections of lungs from such an/an and +/+ mice. The histologic appearance of the an/an lung was suggestive of pneumonitis. Silver staining did not reveal Pneumocystis carinii. Antibodies to other pathogenic organisms such as pneumonia virus of mouse, reovirus, Sendai, and minute virus of the mouse were not detected in the serum. Similar but very much less extensive lung damage was observed in irradiated and transplanted +/+ mice when they became moribund ~1 year later.

Figures 5A and B show hematoxylin and eosin-stained
longitudinal sections of bone marrow from irradiated and marrow transplanted an/an and +/+ mice. The marrow of both genotypes was very active and many RBC precursors were present. The marrow of the an/an mouse, however, was considerably paler than marrow of the +/+ mouse, although this is not easily discernible in the photographs. The +/+ mouse marrow contained many more megakaryocytes and hemosiderin-filled macrophages than did the an/an bone marrow.

**DISCUSSION**

Previous reports indicated that the anemia of an/an mice could be cured by lethal irradiation and bone marrow transplantation with congenic +/+ bone marrow. Those studies, however, did not follow the long-term outcome of such therapeutic treatment in an/an mice. Our studies demonstrate a severe reduction in life expectancy in an/an mice receiving lethal irradiation and bone marrow transplantation therapy. Untreated +/+ mice live ~4 months longer than their an/an siblings, with mean lifespans of 25.3 (SD = 5.7) months for +/+ mice (n = 203) and mean lifespan of 21.7 (SD = 3.8) months for an/an mice (n = 276). (J.T. Eppig, J.E. Barker, unpublished observations, December 1986). Our results demonstrate that although irradiation and bone marrow transplantation was successful and replacement of the blood system was observed, an/an mice die prematurely as a result of this therapy within 8 months after treatment. The treatment therefore is ultimately worse than the disease.

These results clearly show that observation of hematopoietic replacement in a disease state is not equivalent to observation of a cure. Furthermore, they suggest that in any treatment deemed successful, the very long-term outcome should be carefully evaluated. In this instance a cure is attained for up to 8 months, but the treated and “cured” an/an mice are dying prematurely as compared with untreated an/an mice. Such long-term experiments are not routinely performed to determine whether bone marrow stem cells will cure a genetic lesion or disease state. More frequently, animals are monitored for 2 to 4 months to establish that the donor cells have replaced the recipient cells and cured the animal.\(^3\)

Hematopoietic replacement with cells donated by marrow transplant was monitored in these experiments in several ways. RBC parameters were used to distinguish normal \(\nu\) anemic RBC phenotype. Although this is the most common way to measure "cure," the use of genetic markers, \(Hbb\) and \(Gpi-1\), is a more sensitive measure of donor cell contribution (sensitivity is reported at 5\%\(^9\)\(^{11}\)). In all experiments, blood cell values decreased in mice that were declining in health regardless of whether they received normal or anemic marrow. However, we showed that these same mice continue to display fully donor-type blood cells based on genetic analysis of \(Hbb\) and \(Gpi-1\) phenotypes. Thus, the differentiated hematopoietic cells continue to be derived from the marrow implants, and the lower blood values cannot be attributed to competition with native stem cells. Furthermore, the marrow of these mice continue to show active production of hematopoietic cells (Fig 5).

One possible explanation for the early death of irradiated marrow-transplanted an/an mice was that the WBC compartment was not being repopulated from the donor stem cell precursors at a sufficient rate or in the appropriate proportions. No difference was observed when WBC subpopulations were counted over time in smears from the treated mice. No differences were observed between any of the combinations of genotypic recipients–donors. That is, normal (+/+ or anemic (an/an) mice receiving either +/+ or an/an marrow showed the same distribution of WBC types in the circulation. There was more variability between individuals than between groups. However, the maintenance of WBC numbers was not sustained in the irradiated and reconstituted an/an mice (Fig 3). Donor WBC appeared, peaked at a level higher than normal +/+ mice at ~12 weeks posttreatment, and decreased throughout the remainder of the experi-
mend. Thus, the short-term repopulation of the WBCs was successful in the an/an mice, but long-term maintenance was not.

The premature death in lethally irradiated and bone marrow transplanted and cured an/an mice does not result from donor marrow failure based on genetic analysis of circulating blood cells over time and histologic observations on the marrow from moribund mice. Neither do we believe that it results from the acute effects of irradiation, since an/an homozygotes are near normal in their LD_{50} lethal irradiation dose (695 rad for an/an mice v 795 rad for +/+ mice). Radiation effects on the lungs were observed: an/an mice sustained more overt lung damage and scarring than did +/+ mice (Fig 4). We hypothesize that chronic radiation damage results in the long-term recurrence of anemia in +/+ mice. Further experiments should help resolve these questions.

ACKNOWLEDGMENT

We thank Eleanor McFarland-Starr, Sheila Compton, and Trey McPherson for excellent technical assistance. Part of the work on the differential WBC counts was performed by summer student Alison Lehman.

REFERENCES

4. Bernstein SE: Personal communication, January 1972
10. Harrison DE, Astle CM, Lerner C: Number and continuous bone marrow replacement therapy. Possible mechanisms that result in chronic radiation damage include the failure of some long-lived somatic cell type to recover in irradiated an/an mice or the failure of some cell type to be replaced by the donor marrow cells. One such affected cell type may be necessary for continued maintenance and differentiation of RBCs and WBCs. Alternatively, an autoimmune phenomenon may be triggered in irradiated marrow-transplanted an/an mice. Further experiments should help resolve these questions.
Deleterious effects of irradiation and bone marrow transplantation therapy in the genetically anemic an/an mouse

JT Eppig and JE Barker