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THE ROLE OF TOTAL BODY IRRADIATION IN BONE MARROW TRANSPLANTATION FOR LEUKEMIA*

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OVER the last 30 years rapid progress has been made in the development of techniques for bone-marrow transplantation as a curative measure in leukemia patients. From the first laboratory work in animals, total body irradiation has played a central role in these procedures. This

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paper, after a brief review of the historical background, rationale, and some of the problems involved, will describe our present program at Memorial Hospital, with an emphasis on our techniques. The radiobiological rationale for our fractionation schedule and partial lung-shielding technique will be described, and our current results will be presented. Although radiotherapy treatment planning for these patients is somewhat complex, treatment *per se* has proved relatively simple, and we believe that our promising results justify such complex planning.

Background

In 1982, in spite of great strides in the treatment of leukemia by multiagent chemotherapy regimens, 16,000 deaths annually are still estimated to occur in the United States from leukemia and 23,500 new cases are diagnosed.[1] In New York State alone, 1,400 deaths are estimated to occur from leukemia.[1] Clearly, in the vast majority of cases, leukemia is not being cured. One attempt to improve this cure rate has been bone-marrow transplantation in eligible patients, a treatment that is in itself not without risk.

Since some patients will actually be cured by multiagent chemotherapy regimens, one has to ask which patients would be most likely to benefit from transplantation? The answer to this question has been continually evolving as procedures themselves improve and risk decreases, and as the success rate for chemotherapy alone also increases.

At present, median remission duration for patients with newly diagnosed acute lymphocytic leukemia is greater than two years with significant percentage of "cures", so it is not appropriate today to consider transplanting this group, although with further definition of high risk factors, subsets may emerge which would benefit from such an approach. Acute lymphocytic leukemia patients who have relapsed, however, have a remission duration of less than one year, and patients with newly diagnosed acute nonlymphocytic leukemia have a remission duration of about 1.5 years in the best studies. These two groups, therefore, are now considered reasonable candidates for bone marrow transplantation, and continually improving results from various centers justify this approach.

Chronic myelocytic leukemia patients have also been transplanted successfully, but the risks appear to be greater in this group for unknown reasons. Most patients were treated during blast crisis in the initial studies; more recent results indicate that results will be better in patients trans-

planted at an earlier stage, i.e., during remission or very early relapse.

Historically, bone marrow transplantation may be considered to have begun with animal studies in 1951, when "lethally irradiated" mice and guinea pigs were protected by bone marrow infusion with observed recolonization of their marrow.[2] In 1957 E. Donnall Thomas infused bone marrow safely into man, achieving a transient engraftment.[3] An excellent review of this historical background was made by Thomas et al.[4] in 1975.

In 1967 graft-versus-host disease was described,[5] which basically involves the reaction of donor lymphocytes against host tissues, especially skin, liver, and gastrointestinal tract. This led to the study of the complex histocompatibility system in man, which governs graft rejection as well as the reverse reaction, the graft-versus-host phenomenon. Through study of this system, many answers have been found and as many new questions have arisen. Because the major histocompatibility complex of genes is inherited in a block on one chromosome from each patient, it can be expected that one sibling in four would be perfectly matched, so marrow transplantation is further limited to a subgroup of the otherwise eligible leukemic population. Much research is going on in this area, especially in terms of removing from the marrow graft the mature T-lymphocytes responsible for graft-versus-host disease.

Why were the initial marrow grafts only transient? As indicated above, the answer lies in the immune system: host lymphocytes simply reacted against donor marrow cells, even when the known tissue antigens had been carefully analyzed and matched between host and donor. For this reason, various "cytoreduction" regimens were developed, which would hopefully destroy the host immune system sufficiently to allow permanent engraftment. In addition, these regimens could serve a dual purpose in leukemia patients by also destroying abnormal leukemic cells. At present, it is felt that cytoreduction may aid in a third area, namely, destruction of the host's natural killer cells which may stimulate the graft-versus-host response.[6] A fourth benefit may simply be a physical destruction of marrow to allow physical space for donor marrow repopulation, as suggested in marrow analysis in animal studies involving total lymphoid irradiation, in which marrow repopulation occurs preferentially in the areas of marrow which were in the radiation fields.[7]

Cytoreductive regimens have involved chemotherapy alone, e.g., cyclophosphamide or multiple agents, total body irradiation alone, or, most successfully, cyclophosphamide and total body irradiation together. In most studies, cyclophosphamide was given first (generally 60 mg./kg.

each day for two days), followed by total body irradiation given in a single fraction (1,000 rad). Lower radiation doses have been tried, as well as daily fractionation schedules. All regimens have had problems, however, and one can be sure that experimentation with radiotherapy time, dose, and fractionation schedules, as well as chemotherapy agents and schedules, will continue in attempts to optimize this cytoreduction.

Problems have included the following: 1) nonengraftment, 2) infection, especially viral, 3) graft-versus-host disease, 4) interstitial pneumonitis, and 5) relapse. Nonengraftment is usually no longer a problem with current combined chemotherapy-total body irradiation regimens, but viral infections in immunosuppressed transplant patients and graft-versus-host disease, even in "perfectly matched" donor-patient situations, remain serious problems awaiting new drugs or alternative solutions. Interstitial pneumonitis in most single fraction total body irradiation series was unacceptably high, occurring in 50 to 70% of the patients, with 2/3 of these dying as a result.[8,9,10] Relapse of leukemia could still occur, and, surprisingly, could even occur solely in donor cells, 2 of 110 patients in one series.[11] In acute lymphocytic leukemia patients who were cytoreduced while in remission, the probability of remaining in remission after two years was about 50%, while the probability of being in remission this long for patients cytoreduced during relapse was only 25%.[12]

With this background, the Memorial Hospital group undertook to design a cytoreductive regimen which could theoretically address two problems, namely, interstitial pneumonitis and relapse: we shall describe the rationale, design, and results of our approach.

Rationale

Interstitial pneumonitis is a complex phenomenon, which may have many contributing factors, including 1) chemotherapy (e.g., cyclophosphamide, methotrexate), 2) lung irradiation, 3) viruses (e.g., cytomegalovirus, Herpes), 4) *Pneumocystis carinii*, 5) graft-versus-host disease, and even 6) age of the patient. One factor we could manipulate was the total body irradiation portion of the regimen.

Ideally, one would like to be able to increase the total dose given so as to increase leukemic cell kill (and thereby decrease the relapse rate) while delivering it in such a way as to reduce its effect on normal lung parenchyma. One way to do this, theoretically, is to increase the number of fractions while decreasing the dose/fraction, so that the dose delivered in each fraction is still within the shoulder of the cell-survival curve for

normal tissues. For most normal human cells, this is in the range of 100-150 rad/fraction. Given daily, however, this would protract the irradiation over a one and one-half to two week period, which could allow leukemic repopulation to become significant and also prolong the period of immunosuppression, which would increase the risk of infection.

Because the shoulder of the cell survival curve represents repair processes, generally complete in five hours, we designed a "hyperfractionation" regimen, in which the patient is treated three times/day, five hours apart, with only 120 rad/fraction.[10,13] With this scheme one can calculate, for a variety of total doses, the theoretical cell kill for the type of normal tissue described above, as well as for leukemic cells which have only a miniscule shoulder to their survival curves. In short, for essentially the same normal cell kill as with 1,000 rad in a single dose (1,320 rad total dose), one could anticipate a 100-fold increase in leukemic cell kill if one were to give 120 rad in each of 11 "hyperfractions."

Although this would be expected to impact favorably on the problem of relapse, it was felt that since the same normal tissue effects would be expected with this increased dose, the lungs would have to be further protected. For this reason we also added partial lung shielding during each treatment in an attempt to reduce the dose to approximately half that of the rest of the body.

One additional possible benefit of five-hour intervals between total body irradiation fractions is a cell-cycle effect, predicted from a variety of studies, including the work on leukemic cells at Hammersmith,[14] in which split doses given five to six hours apart produced a greater cell kill than if the same total dose were given at one time. Presumably, this was because cells partially synchronized by the first dose moved into a more radiosensitive phase of the cell cycle by the time the second dose was given.

Materials and Methods

Our program, initiated in May 1979, has continued to the present with only minor alterations, and involves a hyperfractionated regimen which begins on day −7 prior to transplant. From day −7 through day −4 the patient is treated with 10 MV photons, 120 rad/treatment, 3 fractions/day (7:30 A.M., 12:30 P.M., and 5:30 P.M.), with the exception of the last day, when only two fractions are given, for a total of 1,320 rad. Treatments are five hours apart during the day and dose rate varies between 6 and 19 rad/min, depending upon the source-axis-distance required to encompass the patient's entire standing height. With small dose fractions in the shoulder

of the survival curve it was felt that dose rate would not be an essential variable, so we have tried to keep treatment time as short as feasible because the patient is in the standing position.

Treatments are alternately anterior and posterior, with one half-value-layer lung blocks strapped directly on the patient each time. Because each treatment may take from eight to eighteen minutes, the patient stands on a specially-designed stand, which has several support straps and tissue-equivalent support handles as well as an adjustable pole for patients who require intravenous therapy. A 1 cm. thick Lexan screen is placed in front of the patient on each treatment for dose build-up so that the dose will be homogeneous to the skin surface.

During the last two days of treatment, at the morning fraction, the chest wall is "boosted" with electrons in the areas of previous lung shielding so that marrow in the ribs will get the same dose as the rest of the body. Each of these two electron treatments is prescribed to give an additional 300 rad to the inner chest wall. We now also give a single "boost" treatment to the testes in male leukemia patients utilizing the appropriate electron energy and bolus, if necessary, to give 400 rad to the posterior surface of the testes because we initially had four testicular relapses in our first 33 male patients.

To plan for this course of total body irradiation, the patient is seen in consultation at least one week prior to treatment, during which time measurements of patient height and thickness at various levels are taken. The patient is simulated in the treatment position with anterior and posterior chest radiographs so that lung outlines may be obtained for shield construction, a CAT scan level may be chosen, and tattoos may be made anteriorly and posteriorly, corresponding to the top of the lung blocks, midway between them. With this reference point, lung blocks can be placed consistently on each treatment. The same tattoo is used for placing the electron shields, in which we have cut out a small hole in the tattoo position for ease of alignment; a small plug fills this hole when alignment is achieved. On the first anterior and posterior treatments, verification films are taken so that any small variations from ideal block placement due to patient posture, etc. may be corrected on subsequent treatments.

The CAT scan is utilized for computerized electron beam treatment planning on an Ohio Nuclear Deltaplan system for the chest wall "boost" treatments, so that the appropriate electron energies and, if necessary, thicknesses of polystyrene bolus material are chosen to insure 90% of the

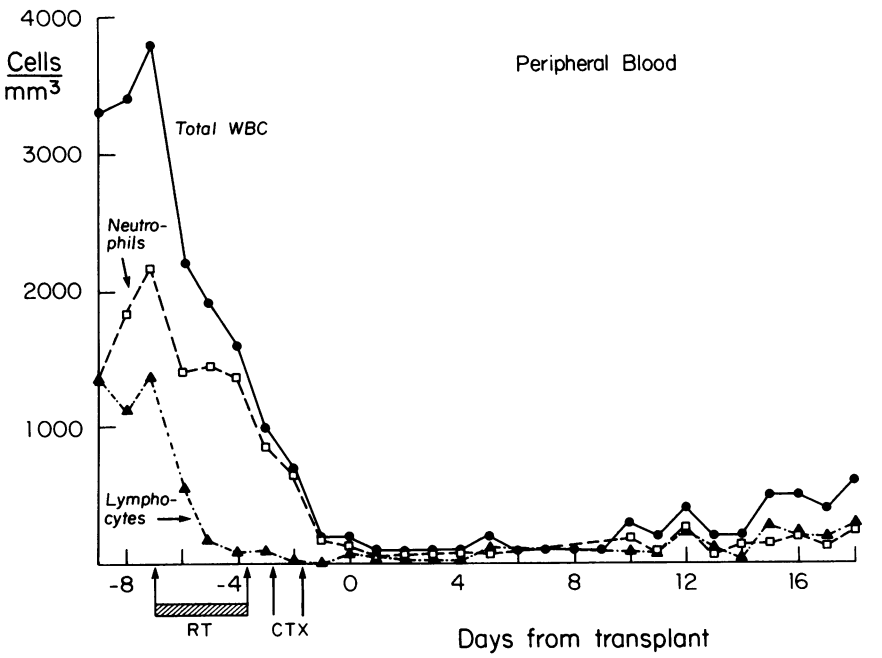

Fig. 1. Typical pattern of blood count changes during cytoreduction and beginning of engraftment. RT = hyperfractionated total body irradiation; CTX = cyclophosphamide; WBC = white blood cells.

dose at the inner chest wall and 10% or less at the midline of the lungs. The actual cumulative dose, with photons and electrons added together, at the midline of the lungs, is approximately 900 rad total, verified by thin lithium dosimetry in phantoms.[15]

The day after completion of total body irradiation, cyclophosphamide infusion is begun, with 60 mg./kg. being given on days −3 and −2. Then, after one day (or two) of rest, the bone marrow transplant is done (day 0). Methotrexate, 15 mg./kg., is given on day 1, and repeated at a smaller dose (10 mg./kg.) on days 3 and 6, and weekly thereafter for at least two weeks. Transfusion support (platelets, granulocytes, and packed erythrocytes) are given as needed. Approximately half the patients are in reverse isolation on the bone marrow transplant unit (usually the patients at greater risk), while the other half may be hospitalized in private rooms on the regular hospital floors.

Mean age of our patient population was 18 years, with a range from 10 months to 42 years. Male:female patient ratio was 1.1:1. There were 41

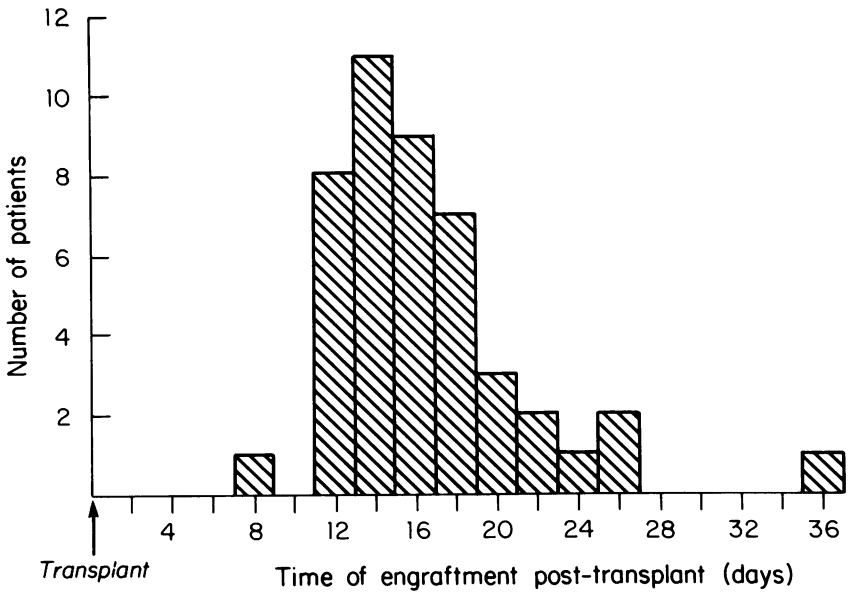

Fig. 2. Distribution of time of engraftment.

acute nonlymphocytic leukemia, 31 acute lymphocytic leukemia, and four chronic myelocytic leukemia patients.

Results

Cytoreduction during the course of total body irradiation and cyclophosphamide treatment is illustrated in Figure 1. Clearly, it is rapid, and peripheral lymphocytes decrease most rapidly. Engraftment, as manifested by the slow rise in total white blood count and neutrophils, is generally seen in about two weeks. The patient population analyzed here consists of 76 patients treated from May 1979 to March 1981, who were reviewed for this publication in May 1982, so that the minimum follow-up was 14 months from the time of transplant. No monozygous twin transplants are included in this group.

All patients who lived longer than three weeks engrafted with the use of our regimen. The pattern of engraftment with time analyzed in the first 42 patients is shown in Figure 2, and it is seen that the mode is two weeks, the latest occurring at 36 days as defined by a white count consistently greater than 500 cells/mm.^{3} We have found that engraftment is dependent on bone marrow cell dose given, as one might expect, although no simple

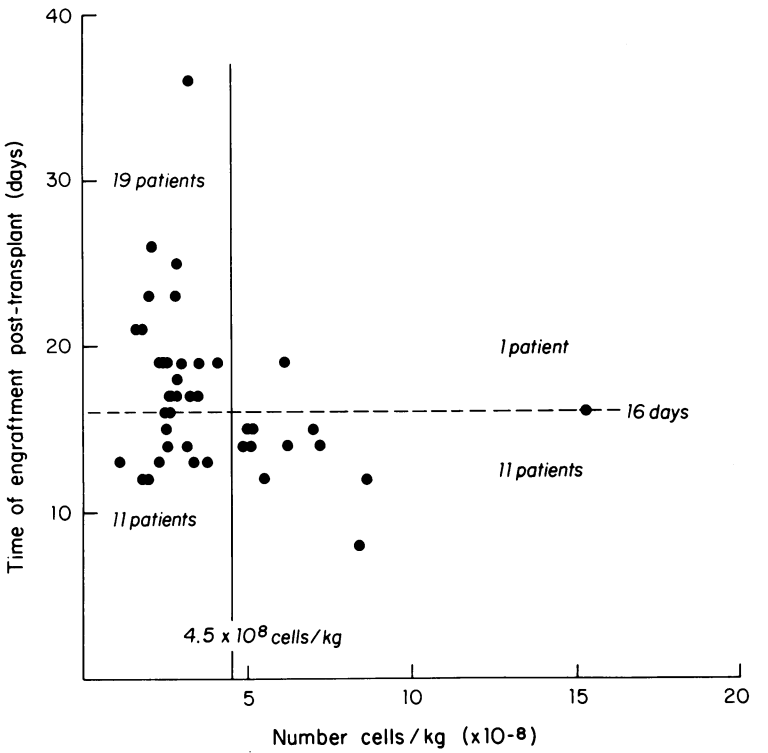

Fig. 3. Time of engraftment as a function of marrow dose per body weight of the host.

straight line curve is seen when time of engraftment is plotted against cell dose (Figure 3). If more than 4.5×10^8 cells/mm.^{3} is infused into the patient, only 1 of 12 patients (8%) required greater than 16 days to engraft, whereas when less than this amount was infused, 19 of 30 patients (64%) required more than 16 days to engraft.

Overall acute nonlymphocytic and acute lymphocytic leukemia patient status is shown in Table I. Initial sites of relapse are listed in Table II. Of interest is the high rate of testicular relapse (four of 33 males or 12%), which led us to add our present testicular "boost" dose of 400 rad. Since the institution of this additional dose, for a total minimum testicular dose of 1,720 rad, we have seen no testicular relapses. Factors contributing to death are shown in Table III. The obvious point is that generally multiple factors contribute to early deaths, with sepsis, interstitial pneumonitis, graft-versus-host disease, and relapse all playing important roles.

We have, however, made significant gains in reducing the incidence of

TABLE I. PATIENT STATUS ON HYPERFRACTIONATED REGIMEN IN 72 ACUTE NONLYMPHOCYTIC AND ACUTE LYMPHOCYTIC LEUKEMIA PATIENTS

Status	*No.*
Alive, no evidence of disease	33
Alive, relapsed	4
Dead	35

TABLE II. INITIAL SITES OF RELAPSE WITH HYPERFRACTIONATED REGIMEN IN 72 ACUTE NONLYMPHOCYTIC AND ACUTE LYMPHOCYTIC LEUKEMIA PATIENTS

Site	*No.*
Testis only	2
Testis and marrow	1
Testis, marrow, paraaortic nodes	1
Central nervous system	2
Marrow only	14
Total	20

interstitial pneumonitis, and, as a result, deaths resulting from this problem. We now have an incidence of 24%, with a fatal outcome in 18% of the initial population. For the most part, when we have observed interstitial pneumonitis, we have been able to pinpoint a specific cause, and viruses are the most prominent cause.

Survival, of course, is the most important analysis of the success of a given procedure. We have found that gender does not appear to play a role in survival, but that age is an extremely important variable.[10] The mean age of the patients who died early deaths (within six months of transplant) was 25 years, compared with a mean age of 18 years for the entire transplanted group. The incidence of interstitial pneumonitis parallels this age relationship and the mean age of the group developing interstitial pneumonitis was also 25 years.

Our four chronic myelocytic leukemia patients in this study, all of whom were in blast crisis, fared dismally, and each died an early death, two with interstitial pneumonitis and two with sepsis and graft-versus-host disease. This is consistent with the difficulty encountered in this group by the Seattle transplant team also.[16]

Turning now to our patients with acute lymphocytic leukemia, of whom 17 of 31 (55%) were treated in relapse as defined by >5% blasts in the

TABLE III. FACTORS CONTRIBUTING TO DEATH IN HYPERFRACTIONATION REGIMEN (76 ACUTE NONLYMPHOCYTIC, ACUTE LYMPHOCYTIC AND CHRONIC MYELOCYTIC LEUKEMIA PATIENTS)

	Factors	*No.*	
	Sepsis	3	
	Sepsis + GVHD*	5	
			13 (Sepsis)
	Sepsis + IP†	4	
14 (IP)	Sepsis + GVHD + IP	1	
	IP	8	
	IP + GVHD	1	
	Hemorrhage	1	
	Relapse	16	
	Total	39	

*GVHD = Graft-versus-host disease
†IP = Interstitial pneumonitis

marrow prior to cytoreduction (for purposes of comparison with the Seattle data), 11 of 31 (35%) have relapsed, with one in testis only and one in the central nervous system only initially.

There was no difference in overall survival or relapse-free survival between our acute lymphocytic leukemia patients treated during relapse or remission, when relapse and remission are defined as above, contrary to the results from Seattle.[12] Overall survival and relapse-free survival for the entire group of acute lymphocytic leukemia patients is shown in Figure 4, with 61% and 50% overall survival at one and one and one-half years respectively, and 45% and 41% relapse-free survival at one and one and one-half years. Breakdown by remission status (Table IV) shows no difference in survival between patients in relapse or remission at the time of cytoreduction.

However, if one looks at the nine patients with >10% blasts in the marrow (most of whom had >20% blasts), there was only a 22% (2 patients) relapse-free survival at 1½ years, indicating that when the tumor burden is very large, present cytoreduction methods are insufficient to eradicate all leukemic cells.

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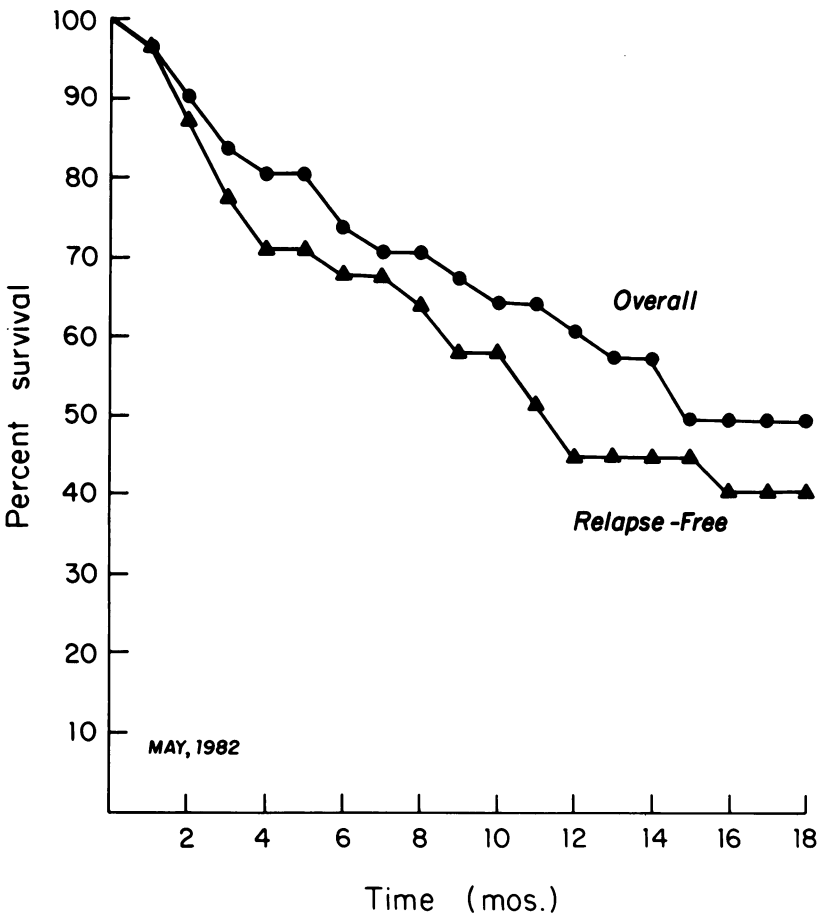

Fig. 4. Overall and relapse-free actuarial survival for all 31 patients with acute lymphocytic leukemia.

In the 41 acute nonlymphocytic leukemia patients, there is a difference in survival (Figure 5) between those patients who began cytoreduction while in remission, compared with those who were in relapse (defined as those who have >10% blasts in their marrow at that time). Although not plotted beyond 1½ years, there is no further drop in survival or relapse-free survival out to two years. One patient who was in remission at cytoreduction has, however, relapsed at 25+ months. Those in remission have 60% relapse-free (and overall) two-year survival, compared with only a 35% overall and 30% relapse-free two-year survival in those who were treated during relapse. We have previously compared our original single dose total body irradiation regimen with our current

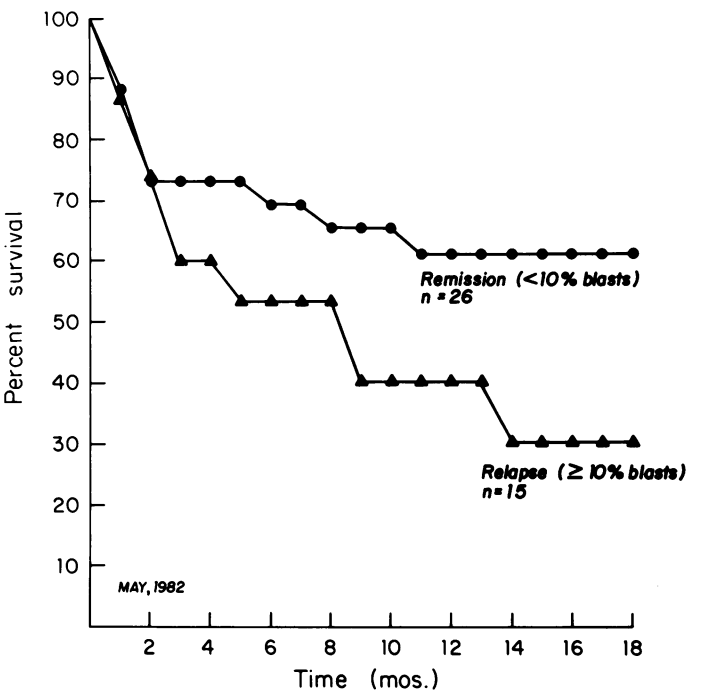

Fig. 5. Relapse-free actuarial survival for patients with acute nonlymphocytic leukemia in remission or in relapse at the time of cytoreduction.

hyperfractionated regimen,[10] and found that in the acute nonlymphocytic leukemia patients (the only group that was large enough in the single dose regimen for comparison), that overall survival and relapse-free survival were significantly greater than could be explained by their remission status alone. This advantage has been maintained with time, with 51% overall two-year survival in the hyperfractionated group compared with only 8% (one of 12 patients) in the single dose group. Relapse-free two-year survival, similarly, is 50% in the hyperfractionated group compared with only 8% (one of 12) in the single dose group. This increase in survival is primarily due to the decrease in early deaths related in part to interstitial pneumonitis.

Discussion

In our hyperfractionation regimen at Memorial Hospital, initiated with the goals of reducing fatal interstitial pneumonitis while concomitantly decreasing the risk of leukemic relapse, we have begun to see the possible realization of our aims. Interstitial pneumonitis, which was considered to

TABLE IV. OVERALL AND RELAPSE-FREE SURVIVAL AT ONE AND ONE-HALF YEARS FOR PATIENTS WITH ACUTE LYMPHOCYTIC LEUKEMIA IN RELAPSE OR REMISSION AT CYTOREDUCTION

Status	*Overall survival*	*Relapse-free survival*
≤ 5% blasts	46%	43%
>5% blasts	52%	40%

be substantially attributable to the lung irradiation in patients treated with single fraction high dose (1,000 rad) total body irradiation, contributed to death in anywhere from 37 to 100% of patients in various studies.[10] With our present regimen, we have only an 18% incidence of fatal interstitial pneumonitis, compared with our previous experience of 50% fatal interstitial pneumonitis.

With regard to the question of relapse, we appear to have gained an advantage in acute lymphocytic leukemia patients in relapse at the time of cytoreduction. Thomas et al. in Seattle[12] has a considerably lower survival at one and one-half years in relapse (>5% blasts) acute lymphocytic leukemia patients (15% overall and relapse-free survival) compared with those in remission (50% overall and 41% relapse-free survival). Our survival curves for *both* patients in relapse and remission, defined in the same manner, parallel the Seattle remission curve (see Table IV). It is of interest also, that our median time to relapse for patients done in remission (11 months) is four months longer than the seven months observed in the Seattle remission group, and that, similarly, our median time to relapse for patients done in relapse (seven months) is two months longer than the five months observed in the Seattle group, which may suggest that, on the average, the leukemic cell population may be reduced by a greater fraction with our higher total dose (1,320 rad).

It is of interest that we have had no testicular relapses since we instituted our additional testicular "boost" dose of 400 rad, for a total of 1,720 rad to the testes. This may, ultimately, increase survival, because four of our first 33 male patients who did *not* have this "boost" treament failed in the testes, and two had this as the only site of relapse evident initially.

It is clear that there is still a long way to go in transplant technology, since many problems still exist, the most vexing being graft-versus-host

disease and viral infections. Although inroads are being made in the problems of leukemic relapse and interstitial pneumonitis as described above, bone-marrow transplantation for leukemia will still be considered a risky procedure as long as any interstitial pneumonitis, graft-versus-host disease or other problems occur. In leukemias with high risk of relapse, however, it may be the best option for a patient with a suitable donor.

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