Treatment of Chronic Lymphocytic Leukemia
by Extracorporeal Irradiation

By R. STORB, R. B. EPSTEIN, C. D. BUCKNER AND E. D. THOMAS*

THE SENSITIVITY OF LYMPHOCYTES to irradiation provides a rationale for the use of extracorporeal irradiation (ECI) of the circulating blood to destroy lymphocytes selectively. Since 1962, ECI has been used in various studies, including investigations of lymphocyte physiology and prolongation of allogeneic skin graft survival in calves. These studies1 established the basic feasibility and effectiveness of ECI in reducing the number of circulating lymphocytes and destroying immunologically competent cells. A logical extension of these studies was the application of ECI to treatment of hematologic disorders manifest by increased numbers of abnormal cells in the circulating blood. Theoretical considerations were discussed by Lajtha et al.,2 but their attempts to apply the method to two patients with myeloblastic leukemia were not encouraging. Thomas and co-workers3 reported initial favorable results in four patients with chronic lymphocytic leukemia. In one case of acute lymphoblastic leukemia, temporary reduction of the number of circulating leukemic cells was achieved. Schiffer and co-workers4 reported a similar reduction of the peripheral leukocyte counts in eight patients with acute myelocytic leukemia, two patients with chronic granulocytic leukemia and two patients with chronic lymphocytic leukemia.

The present article describes the effects of ECI in six patients with chronic lymphocytic leukemia. The initial course of four of these cases was given previously.3 The subsequent clinical events in these four cases are brought up to date, and two new cases are described.

METHODS

Three X-ray sources were used in these studies as described previously.3 Since May of 1965 the X-ray source has been a Philips Model MG-150B/15, 150 KVP, 15 MA, target-coil distances of 4 or 5 cm., half value layer 0.5 mm. of copper.

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Fig. 1.—Physical arrangement for ECI with rod-anode x-ray machine.

Teflon-silastic arteriovenous shunts were placed in the forearm of the patient.3 The arterial and venous cannulae were aseptically connected by a piece of silastic tubing 68-170 cm. long and 2.6 mm. internal diameter, which lead into the irradiation field. Flow rates through the shunt ranged from 75 to 124 ml. per minute and are listed in Table 1 for the various patients. The volume of blood in the irradiation field and the transit dose could be varied by altering the number of coils of silastic tubing and the distance from the X-ray tube. No external pump nor anticoagulation were employed. Details are illustrated in Figure 1.

Calculation of the mean dose and dose distribution by probability theory has been presented elsewhere. The calculation of the cumulative mean dose to the red blood cells applies only to those cells present in the blood throughout the period of ECI.

Immunoglobulins were determined by the method of Fahey and McKelvey.6 Normal values of the reference standard were IgG 1240 mg. percent, IgM 120 mg. percent and IgA 280 mg. percent.

CASE REPORTS

Case 1

In November of 1963, a 48-year-old man was found to have chronic lymphocytic leukemia with a white blood cell count of 225,000/mm.3 with 98 percent lymphocytes. Over the next 5 months he was treated with steroids, chlorambucil and vincristine sulfate with an unsatisfactory response. In May of 1964 he was treated with ECI for 2-4 hours daily for a period of 1 month (see Fig. 1).3 During ECI his white blood cell count fell to 30,000/mm.3, and over the next month the white blood cell count continued to fall to a value of 10,000/mm.3 The white blood cell count then rose slowly reaching 40,000/mm.3 by May of
Table 1.—Radiation Data

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*These data apply to the second course of ECI for cases 1 and 4. For additional data of cases 1 through 4, see Table 1 of reference 3.

†Applicable to red cells in circulation throughout period of ECI.

1965 when it rose more rapidly reaching values of 150,000–200,000/mm₃ by October of 1965. Prednisone was given during ECI and for 7 months thereafter. When prednisone was discontinued, the platelet count declined slowly from values of 100,000/mm₃ to 20,000/mm₃ by October of 1965. Prednisone, 20 mg. per day, was resumed at that time with a transient rise in platelet count.

Because of continued thrombocytopenia and a white blood cell count in the range of 150,000–200,000/mm₃, it was decided to treat him again with ECI. At that time, physical examination showed a minimal cervical, axillary and inguinal lymphadenopathy. The liver was palpable 2–3 cm. below the right costal margin and the spleen 3 cm. below the left costal margin. The white blood cell count was 175,000/mm₃, the platelet count 45,000/mm₃ and the hematocrit 44 percent. The bone marrow showed 864 lymphoid cells/1,000 nucleated cells. Immunoglobulin values were as follows: IgG 660 mg. percent, IgM 77 mg. percent and IgA 130 mg. percent.

The second course of treatment was started on June 10, 1966, and continued through July 10, 1966. Pertinent radiation data are listed in Table 1. Figure 2 shows the hematological changes during and following the second period of treatment. At the end of treatment the bone marrow showed 859 lymphoid cells/1,000 nucleated cells. Immunoglobulin values were as follows: IgG 600 mg. percent, IgM 160 mg. percent and IgA 110 mg. percent. Spleen scans before and after ECI showed no change in spleen size. The absolute granulocyte count remained within normal limits.
Prednisone, 15 mg. per day, was continued. The patient developed severe thrombocytopenia in August, 1966, with a platelet $T_{1/2}$ of 2 hours. Splenectomy was carried out with a prompt rise in the platelet level. On November 1 the platelet $T_{1/2}$ was 8 days. Prednisone was then discontinued. Profound thrombocytopenia recurred in December of 1966. There was a good response to prednisone, 80 mg. per day, which was tapered to 20 mg. per day over a two-week period. In March, 1967, prednisone was reduced to 15 mg. per day and to 12.5 mg. per day in May. On June 5, 1967, the white blood cell count was 23,100/mm$^3$ with 49 percent granulocytes, 48 percent lymphocytes and 3 percent monocytes. The platelet count was 371,000/mm$^3$ and the hematocrit 47.5 percent. Immunoglobulin values were as follows: IgG 800 mg. percent, IgM 210 mg. percent and IgA 220 mg. percent.

Comment. This patient was initially considered refractory to chlorambucil, steroids and vincristine but responded satisfactorily to a course of ECI. During the subsequent 12-month period, he had a relatively low white blood cell count and improved platelet count and hematocrit with a satisfactory clinical remission. A second course of ECI, two years after the first, again reduced the white blood cell count to below 30,000/mm$^3$ where it has remained for one year. There was no evidence of a change in the lymphoid tissue stores, but immunoglobulin values improved. Thrombocytopenia due to platelet destruction has been well controlled by splenectomy and prednisone.

Case 2

A 51-year-old man had had chronic lymphocytic leukemia since 1956. He had been treated with P$^{32}$ and with chlorambucil. Because of a rising white blood cell count despite increased doses of chlorambucil, it was decided to
treat him with ECI. Treatment was started on July 10, 1964, and continued for a period of one month (see Case 2). At the end of ECI, the white blood cell count was 17,000/mm.$^3$, and it fell to 10,000/mm.$^3$ over the following three weeks. The white blood cell count then rose reaching 197,000/mm.$^3$ five months after ECI. At that time, he was again treated with chlorambucil, and two months later the white blood cell count was 38,000/mm.$^3$ and seven months later it was 17,000/mm.$^3$. In August of 1965, the patient developed a right upper lobe pneumonia due to coagulase positive staphylococci, and he died four days later.

Comment. During ECI this patient's white blood cell count declined to a relatively low level while the lymphoid tissue stores remained unchanged as judged by organ size and bone marrow morphology. Following ECI, the white blood cell count increased to 197,000/mm.$^3$ within five months. The improvement in the hematocrit may have been due to discontinuation of the large dose of chlorambucil. A significant decline of the white blood cell count was then achieved with doses of chlorambucil which had given no response before ECI. Death resulted from a rapidly fatal staphylococcal pneumonia.

Case 3

A 64-year-old man had had chronic lymphocytic leukemia since 1960. He was maintained in good control with intermittent chlorambucil therapy until July of 1964, when the white blood cell count began to rise, and a moderately severe anemia developed that required 13 transfusions in four months. He was treated with ECI from October 12 to November 5 and again from December 1 to December 10, 1964. His course during and immediately after ECI has been described (Case 3). Following ECI, his white blood cell count increased to 350,000/mm.$^3$ in April of 1965. At that time the platelet count was 120,000/mm.$^3$ and the hematocrit 24.5 percent. During that time, he received several transfusions. Treatment with 15 mg. of prednisone per day was begun in February of 1965 and was followed by a slow rise of the hematocrit over the next eight months to values between 30 and 40 percent without transfusion. The platelet count remained essentially unchanged, and the white blood cell count fell to 40,000/mm.$^3$ by June of 1965. Despite the continued prednisone, the white blood cell count gradually rose to 334,000/mm.$^3$ within the subsequent eight months. Treatment with chlorambucil was resumed in January of 1966, and the white count fell to 75,000/mm.$^3$. A reduction of the drug dose was again followed by a white blood cell rise, and this pattern was seen twice during the last half of 1966 and early 1967. Platelet counts and hematocrits remained at satisfactory values. During this time, the patient was in satisfactory clinical condition and hospitalization was not required.

In March of 1967, he developed an acute febrile illness, apparently a septi-cemia. He received several antibiotics before admission to the hospital, and blood cultures in the hospital were negative. He died three days after the onset of the illness. Autopsy showed extensive intra-abdominal and intra-thoracic tumor involvement.
Comment. A significant decline of the leukocyte level was observed during both courses of ECI and was followed by a rapid rise in white blood cell count. There was no evidence of change in the tissue stores of leukemic cells, and there was no improvement in platelet counts or hematocrits. The patient was then managed satisfactorily with prednisone and chlorambucil for two years. He died 27 months after ECI from an infection.

Case 4

A 43-year-old man had had chronic lymphocytic leukemia since 1956. He was treated first with irradiation and then with chlorambucil beginning in November of 1962. In May of 1964, he developed anemia, thrombocytopenia and a rising white blood cell count despite steroids and increased doses of chlorambucil. Drug therapy was discontinued, and he was treated with ECI from November 11 through December 21, 1964. His course during the first period of ECI has been described previously (Case 4).3

For three months following ECI, the patient felt well and was able to work. During this time, however, the white blood cell count rose to 250,000/mm.3 and lymphadenopathy and splenomegaly increased. On March 24, 1965, therapy with chlorambucil, 6 mg. per day, was resumed. On June 4 chlorambucil was discontinued because of a low platelet count. At that time physical findings were unchanged, and the white blood cell count was 131,000/mm.3

On July 2, 1965, the patient was readmitted to the hospital for a second course of ECI. Physical examination, chest X-ray and bone marrow aspiration did not show significant changes. The white blood cell count was 174,600/mm.3, the platelet count 15,600/mm.3 and the hematocrit 27 percent. Extracorporeal irradiation was carried out from July 4 to July 24 for 8 hours daily (Fig. 3). ECI was discontinued when the patient developed a peritonsillar abscess which was treated with amphotericin and large doses of prednisone. ECI was
resumed on August 4 and 5 but was discontinued because of the renal insufficiency, probably secondary to amphotericin. At that time the blood urea nitrogen was 116 mg. percent and the serum uric acid was 7.9 mg. percent. After clearing of the pharyngeal lesion and discontinuation of amphotericin, ECI was resumed from August 18 to August 23 (Fig. 3). At the end of ECI the white blood cell count was 50,000/mm.³, and the platelet count was 44,000/mm.³. Physical examination showed a decrease in the size of the spleen and the liver, both organs being barely palpable. The patient was discharged on August 24, 1965, on 20 mg. of prednisone per day.

On September 21 the white blood cell count was 160,000/mm.³, the platelet count 74,000/mm.³ and the hematocrit 33 percent. The patient felt well and the physical examination was unchanged. Nine days later he died suddenly at home.

Comment. Prior to ECI, this patient appeared to be unresponsive to chlorambucil and steroids. The first course of ECI lowered the white blood cell count, but it returned to preirradiation levels within 3 months and lymphadenopathy and splenomegaly increased. Another course of chlorambucil was only partially successful in lowering the white blood cell count but did cause a significant thrombocytopenia. A second course of ECI, seven months after the first, was complicated by an intercurrent infection and renal insufficiency, but the white blood cell count was significantly reduced. By physical examination there was a marked reduction in the size of the spleen and liver that may have been due to ECI, prednisone or combination of both. Following the second course of ECI the white blood cell count again rose rapidly, and the patient died suddenly of an unknown cause.

Case 5

In 1950, at the age of 39, a male salesman developed cervical lymphadenopathy. His white blood cell count was found to be 400,000/mm.³, and a diagnosis of chronic lymphocytic leukemia was made. He was treated initially with four weeks of spray irradiation with shrinkage of the lymph nodes. In 1960 his white blood cell count was 492,000/mm.³ and hematocrit 35 percent, and he was started on chlorambucil therapy. He did well and the white blood cell count was less than 50,000/mm.³ until 1964 when it went up despite increased doses of chlorambucil. In April of 1964 the white blood cell count was 144,000/mm.³ and chlorambucil was discontinued. He was then given 2.5 mc. of P³² on two occasions with no significant change in the white blood cell count. In November of 1964 he was given prednisolone 40 mg. per day for one month with an initial fall in white blood cell count to 90,000/mm.³ but a subsequent rise to 200,000/mm.³. In December of 1964, 500 r of splenic irradiation were administered in divided doses with a fall in white blood cell count to 61,000/mm.³. However, by January of 1965 the white blood cell count had reached 300,000/mm.³. He was given prednisone, 15 mg. per day, and chlorambucil therapy was reinstituted at 12 mg. per day. The white blood cell count did not change significantly, and the hematocrit fell to 32 percent. In preparation for extracorporeal irradiation, chlorambucil was discontinued at the end
of June 1965, but prednisone was continued at 15 mg. per day. Over the next two months the white blood cell count rose from 200,000 to 300,000/mm$^3$, platelets rose from 100,000 to 150,000/mm$^3$ and the hematocrit declined to 28 percent.

The patient was admitted to the University Hospital for extracorporeal irradiation on September 7, 1965. Physical examination showed the liver to be 6 cm. below the right costal margin and the spleen 8 cm. below the left costal margin. There was no significant lymphadenopathy. The white blood cell count was 356,000/mm$^3$, the platelet count 142,000/mm$^3$ and the hematocrit 27 percent. The serum uric acid was 7.4 mg. percent, and the urinary uric acid excretion was 1.16 gm. per 24 hours. On the day of admission, arterio-venous cannulae were placed in the left forearm. On September 8 he was started on a 7-day course of ECI, 8 hours per day. Six additional 8-hour treatments were given at intervals of 1–2 weeks. Figure 4 shows the hematologic and therapeutic data, and Table 1 lists the irradiation data. The white blood cell count fell to 87,000/mm$^3$ at the time of the last ECI treatment on November 8. The platelet count fell temporarily to 40,000/mm$^3$ but was 160,000/mm$^3$ at the end of treatment. The hematocrit rose to 34 percent. The absolute granulocyte count remained unchanged at values between 4,000 and 5,000/mm$^3$. Spleen size did not change.

Over the next three months, the white blood cell count continued to decline to values between 15,000 and 20,000/mm$^3$. The subsequent hematologic changes are shown in Figure 4. In the summer of 1965, the patient developed herpes zoster involving the left eye with subsequent loss of vision. Prednisone was discontinued in April of 1966. The patient has continued to do well and has returned to work as a salesman.
Comment. This patient had a 15-year history of chronic lymphocytic leukemia reasonably well controlled until 1½ years before extracorporeal irradiation. Treatment with chlorambucil, P₃₂ and steroids had become ineffective. Two and one-half months before ECI, all therapy except 15 mg. per day of prednisone was discontinued. During this time there was a moderate rise in platelet count, a significant rise in white blood cell count, and a decline in hematocrit. Following ECI, the platelet count and hematocrit returned to normal, and the white blood cell count has remained under 30,000/mm³ until the present time, 21 months after ECI.

Case 6

A 71-year-old man was found to have chronic lymphocytic leukemia in October of 1963. Over the next two years, he was treated intermittently with prednisone, cytoxan and chlorambucil. He showed no significant response to these drugs, and antileukemic therapy had not been given during the year prior to admission.

On April 18, 1966, the patient was admitted to the University of Washington Hospital for ECI. Physical examination showed the liver 3 cm. below the right costal margin, and the spleen 1–2 cm. below the left costal margin. There was no significant lymphadenopathy. Hematologic values during the month before admission are shown in Figure 5. A bone marrow examination showed 890 lymphoid cells/1,000 nucleated cells. Immunoglobulin values, in mg. percent, were as follows: IgG 420, IgM 26.5 and IgA 42.

ECI was carried out from April 22 to May 18 as shown in Figure 5 and table 1. The white blood cell count fell rapidly to 15,000/mm³ at the end of
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Table 2.—Summary of Six Cases of Chronic Lymphocytic Leukemia Treated with ECI

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<td>Two courses ECI. Retreated with chlorambucil. Died of infection.</td>
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<tr>
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*At time of first ECI.

treatment. The absolute granulocyte count, platelet count and hematocrit remained essentially unchanged during this period. The bone marrow aspiration at the end of the period of ECI showed 450 lymphoid cells/1,000 nucleated cells. Spleen scan before and after ECI showed a diminution of the organ size of 30 percent. Changes in serum uric acid and excretion of uric acid are shown in Figure 5. Immunoglobulin values at the end of ECI were as follows: IgG 400, IgM 20 and IgA 56. There was no change in clinical condition or physical findings. The patient was discharged without medication.

Hematologic changes for nine months following ECI are shown in Figure 5. The white blood cell count rose steadily to values of 350,000/mm³ while the platelet count and hematocrit remained stable at about 200,000/mm³ and 32 percent respectively. There has been a moderate increase in the size of the spleen and the liver without significant symptoms.

Comment. Prior to ECI, this patient had maintained white cell counts from 200,000 to 400,000/mm³ with and without drug treatment. ECI reduced the white blood cell count to 15,000/mm³ and also reduced the mass of leukemic tissue as judged from spleen scans and bone marrow morphology. The absolute granulocyte count, platelet count and hematocrit did not change significantly. Despite the initial favorable result, the white blood cell count gradually returned to preirradiation values over a nine-month period with an increase in the size of the spleen and liver.

DISCUSSION

Table 2 summarizes our experience with six cases of chronic lymphocytic leukemia treated by ECI and followed for periods of 1–3 years. Three of these patients are dead, two having died of infection after retreatment with chlorambucil. The average survival of these six cases from the time of diagnosis is now six years. Boggs and co-workers⁷ have recently summarized the available
survival data for patients with chronic lymphocytic leukemia and have emphasized the difficulty of providing definite evidence that any form of leukemia-directed therapy prolonged the life of patients with chronic lymphocytic leukemia. Clearly, our small group of patients does not permit any statement in that regard, even though they were considered to be “drug resistant” at the time of ECI. Nevertheless, two (Cases 1 and 5) of our six patients have done better than expected and are in good partial remission 37 and 22 months after the initial course of ECI. The first patient had a good response to a second course of ECI. Possible benefit from spaced, regular treatment by ECI remains to be evaluated.

Three of our six patients have shown an improvement in platelet and hematocrit levels after ECI, perhaps due to discontinuation of cytolytic therapy. However, Case 5 was treated with only maintenance doses of prednisone for two months before ECI, and the return to normal hematocrit and platelet levels did not occur until several weeks after ECI. In two patients there appeared to be a decrease of leukemic tissue stores as judged by a decrease in lymph node cellularity (Case 4) and in spleen size (Case 6). The other patients did not show such changes. The absolute granulocyte count in all patients did not appear to be influenced by ECI and remained within normal limits.

The role of prednisone given in Cases 1 and 5 before and during ECI remains to be determined. Administration of large doses of corticosteroids in patients with chronic lymphocytic leukemia is usually followed by shrinkage of lymph nodes and spleen and by concomitant elevation of the peripheral lymphocyte level lasting for several weeks. This would suggest that the steroids cause mobilization of the tissue lymphocytes and their subsequent release into the peripheral blood. ECI treatment at this point may thus have destroyed the bulk of the total leukemic lymphocytes which lead to the prolonged remissions in Cases 1 and 5.

The efficiency of ECI depends upon two factors: The fraction of the patient’s blood volume irradiated per unit time and the radiation dose received per transit. These two factors depend in turn on the dose rate of the X-ray source, the flow rate of blood through the shunt and the volume of blood in the irradiation field. The flow rate varied from case to case depending upon the size of the vessels and of the teflon tips. The transit dose was varied from patient to patient by altering the output of the X-ray source or the number of coils of silastic tubing in the irradiation field. The time of irradiation per day and the total length of treatment were selected arbitrarily. Despite these differences in irradiation dose from case to case, ECI was similarly effective in all six patients and reduced profoundly the level of circulating leukemic cells at comparable rates of decline. This similarity in response to rather arbitrarily selected irradiation doses suggests that small transit doses and small cumulative mean doses, as in Cases 1 and 6, may indeed be adequate for efficient lymphocyte destruction. Development of radioresistant lymphocytes was not observed in the three patients (Cases 1, 3, and 4) who were subjected to a second course of ECI. Their peripheral lymphocyte counts were as successfully reduced in the second treatment as in the first.
The use of teflon-silastic arterio-venous shunts originally designed for renal hemodialysis has made repeated sessions of ECI over prolonged periods of time a practical procedure. Although no anticoagulation was used, clotting of the extracorporeal shunts was rarely of concern in these patients. Hemolysis due to radiation damage to the red cells was not recognized with the radiation doses employed. Schiffer and co-workers have found that hemolysis occurred when the cumulative mean dose to the red cells exceeded 60,000 r. The highest dose accumulated in one of our patients was 48,000 r. The rapid destruction of large numbers of lymphocytes induced the production and subsequent excretion of increased amounts of uric acid in most of the patients. In no case was this followed by clinical problems with urate precipitation.

SUMMARY

Six patients with advanced chronic lymphocytic leukemia were treated with extracorporeal irradiation and followed for one to three years. There was a marked reduction in the circulating white cells in all patients, but in four cases the white cell counts returned to high levels in 3–7 months. Two patients are in good partial remission 37 and 22 months after the initial course of ECI. Clinical and hematological events in these cases are detailed.

It was concluded that ECI is effective in lowering leukocyte levels without systemic toxicity and is beneficial in some cases of chronic lymphocytic leukemia.

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