Long-Term Followup of Patients Treated With Total Lymphoid Irradiation for Lupus Nephritis


Objective. To describe the long-term survival, renal condition, and morbidity outcomes in patients who received total lymphoid irradiation (TLI) for the treatment of lupus nephritis.

Methods. Twenty-one patients with biopsy-proven, diffuse membranoproliferative glomerulonephritis and significant proteinuria of >2.5 grams/day received TLI from 1980 to 1987 at Stanford University Medical Center. All patients had previously failed to respond to treatment with high-dose corticosteroids or therapy with corticosteroids plus immunosuppressive agents (azathioprine, cyclophosphamide, or chlorambucil).

Results. The mean duration of followup since TLI was 10.7 years. Fifteen of 21 patients (71%) remained alive at the time of this assessment. Nine of the 21 patients (43%) survived without developing end-stage renal disease (ESRD). The probability of long-term survival without ESRD and without need for additional immunosuppressive agents after TLI was 19% (4 of 21). Factors predicting renal failure at the time of TLI included elevated creatinine levels, increased interstitial fibrosis on renal biopsy, and increased fractional excretion of immunoglobulin and albumin. Malignancies were found in 4 patients, and opportunistic infections occurred in 7 patients.

Conclusion. Overall, patients with lupus nephritis treated with TLI do not appear to have better 10-year survival with lower incidence of ESRD compared with patients in published series treated with conventional immunosuppressive therapies. However, in this series of patients, treatment with conventional immunosuppressive therapies had been unsuccessful and given the limited number of adverse events and the efficacy seen in some patients, TLI appears to be a reasonable therapeutic option for the treatment of severe lupus nephritis among patients who fail to respond under standard cytotoxic regimens.

Total lymphoid irradiation (TLI) has been used extensively in the treatment of Hodgkin's lymphoma and it has also come into experimental use as an immunosuppressive therapy for various autoimmune conditions (1). TLI has been shown to induce long-term remission in several animal models of autoimmune disease, including adjuvant arthritis in rats and lupus-like disease in NZB/NZW mice (1). There are published reports of experience in using TLI in the treatment of rheumatoid arthritis (RA) (1–3), multiple sclerosis (4), and systemic lupus erythematosus (SLE) (1,3,5–9). TLI has also been studied as an alternative agent to cytotoxic drug therapy for patients with refractory lupus nephritis (1,3,5–9). Currently, there is extensive evidence supporting the efficacy of corticosteroids and cyclophosphamide and growing evidence for mycophenolate mofetil in the treatment of diffuse proliferative lupus nephritis (10–13), but there still remain those patients whose disease is refractory to the standard therapies and for whom alternative treatments may need to be considered.

Previous studies of TLI as a treatment for intractable lupus nephritis have shown improvement, on average, in the extent of renal disease and in the serologic parameters of disease activity (proteinuria, serum levels of albumin, serum levels of anti–double-stranded DNA antibodies) within 3 months of therapy, which persisted for at least 3 years (3,6,7). Although there was a significant reduction in the number and function of T
helper cells, recovery of these parameters was not associated with recurrence of disease activity. Overall, the risks of malignancy, infection, and sterility appear to be lower than with alkylating agents (6). However, one study demonstrated that TLI in the treatment of lupus nephritis had unfavorable outcomes, primarily related to infectious complications (9).

The objective of this study was to review the long-term outcomes in 21 patients with biopsy-proven, diffuse proliferative lupus nephritis and severe proteinuria who received TLI after failing treatment with corticosteroids alone or in combination with cytotoxic agents. Many of these patients have been described in earlier reports (3,5–8). The main outcomes of this study were overall survival, renal survival, and morbidities such as development of severe infections and malignancies.

**PATIENTS AND METHODS**

The patients studied comprised those who received TLI for lupus nephritis at Stanford University Medical Center between 1980 and 1987. To receive treatment with TLI, patients were required to meet the American College of Rheumatology diagnostic criteria for SLE (14), to have recent (<6 months) histopathologic evidence of lupus nephritis involving >85% of glomeruli, to have significant proteinuria (>2.5 grams/day of protein), and to have a history of failure to respond to prednisone therapy or prednisone with immunosuppressive agents for >3 months. Exclusion criteria for original treatment with TLI included severe leukopenia, thrombocytopenia, or anemia. Patients were also excluded if they were <18 years of age, had received >6 months of treatment with alkylating agents during the previous 3 years, had chronic or acute infections, or had end-stage renal disease (ESRD) (serum creatinine >4 mg/dl or creatinine clearance <20 ml/minute).

TLI therapy was given as described in previously published protocols (3,5–8) and included irradiation of the supradiaphragmatic mantle field encompassing the cervical, axillary, infraclavicular, pulmonary hilar, mediastinal lymph nodes, and the thymus gland. This field was treated with 200 cGy/day, 5 days/week, for a total of 2,000 cGy. The subdiaphragmatic field was treated after completion of the mantle, with 150–200 cGy/day for 4 days/week, to a total dose of 2,000 cGy. Cytotoxic drugs were discontinued prior to the initiation of TLI.

Followup information was obtained on all 21 patients, and all were contacted by the principal investigator to ensure accuracy of medical records. All renal biopsy reports were re-read for this study to assess the activity and chronicity indices. Analysis of the primary outcome, which is characterization of the factors predictive of the “hazard of death or dialysis,” was performed using univariate analysis with a Cox proportional hazard model. Univariate factors evaluated as potential predictors of death or dialysis included sex, body surface area, age at time of TLI, duration of disease prior to TLI, prior use of chemotherapy, levels of serum albumin, levels of serum creatinine, inulin clearance, fractional excretion of albumin or of immunoglobulin, 24-hour urine protein loss, activity index, chronicity index, % of globally sclerosed glomeruli, % of segmentally sclerosed glomeruli, and % of fractional interstitial area on biopsy.

**RESULTS**

Table 1 summarizes the baseline and followup characteristics of the 21 patients studied. As noted, the majority of patients were young women. All patients had received prior treatment with corticosteroids and 76% had received prior treatment with immunosuppressive agents. No patients were lost to followup. The average duration of followup was 10.7 years. Six patients (29%) died during the followup period (3 of whom developed ESRD prior to their death), while 9 patients in total (43%) developed ESRD. All patients required additional corticosteroids and 62% required additional immunosuppressive therapy following TLI. Four patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>Age at TLI, years</td>
<td>27.1 ± 7.0</td>
</tr>
<tr>
<td>Female, no.</td>
<td>16</td>
</tr>
<tr>
<td>Male, no.</td>
<td>5</td>
</tr>
<tr>
<td>No. previously treated with corticosteroids</td>
<td>21</td>
</tr>
<tr>
<td>No. previously treated with immunosuppressives</td>
<td>16</td>
</tr>
<tr>
<td>Duration of SLE, years</td>
<td>6.2 ± 4.5</td>
</tr>
<tr>
<td>Serum creatinine, gm/dl</td>
<td>1.54 ± 1.0</td>
</tr>
<tr>
<td>GFR by inulin clearance, ml/minute/1.73 m²</td>
<td>54.3 ± 30.0</td>
</tr>
<tr>
<td>Serum albumin, gm/dl</td>
<td>2.54 ± 0.5</td>
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<tr>
<td>WBC count, cells/mm³</td>
<td>10.0 ± 4.7</td>
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<tr>
<td>Renal biopsy activity index</td>
<td>7.4 ± 4.1</td>
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<tr>
<td>Renal biopsy chronicity index</td>
<td>6.5 ± 3.0</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140 ± 21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>95 ± 15</td>
</tr>
</tbody>
</table>

† Includes 3 of the 6 who died.
remained alive without developing ESRD and without requirement for additional immunosuppressive therapy. Table 2 shows the morbidity and mortality results in this patient cohort. As noted, 7 patients developed opportunistic infections, the majority of which were due to herpes zoster. No patients died as a result of infection. Malignancies occurred in 4 patients: 2 with lymphomas, 1 with thyroid carcinoma, and 1 with cervical carcinoma. All malignancies responded to treatment and none were fatal. Three of these 4 patients had received cytotoxic treatments prior to and after TLI. Six patients died during the followup period, with a mean duration of time from TLI to death of 6 years. Fifty percent of these deaths (3 patients) were due to cardiac causes. The remaining 3 deaths were due to aortic aneurysm, vasculitis, or renal failure.

Table 2 shows the results of the univariate analysis for predictors of the hazard of death or dialysis in the 21 TLI-treated patients. Twelve patients (57%) met the primary outcome of death or dialysis. The univariate analysis suggests that small (milligram) increases in the fractional excretion of albumin and immunoglobulin, as well as small (percentage) increases in interstitial fibrosis on biopsy were the strongest predictors of death or dialysis. Fractional excretion is expressed as a ratio, based on the excretion of urine albumin:serum albumin divided by the excretion of urine inulin:serum inulin. Small changes in the “leakiness” of the glomeruli can lead to 10–100-fold changes in the fractional excretion, suggesting that although the hazard ratios appeared small in this cohort, as greater quantities of protein (albumin and immunoglobulin) are lost, the hazard of death or dialysis increases significantly. Other predictors that approached significance were the glomerular filtration rate, serum creatinine level, and the prevalence of glomeruli that were globally sclerosed on biopsy.
DISCUSSION

TLI has been used to treat a variety of autoimmune disorders such as RA, SLE, and multiple sclerosis, as well as solid organ allograft rejection (1,4). TLI induces long-lasting CD4 T lymphocyte depletion as well as reduced humoral and cell-mediated responses (1). Studies in RA have shown tolerability and initial clinical efficacy but potential short- and long-term risks (2). TLI has been used to treat SLE since the early 1980s, showing initial efficacy in the NZB/NZW mouse model for lupus (1), and later, in human studies, in suppressing the activity of lupus nephritis (1,3,5–9). However, the long-term safety and efficacy of TLI for the treatment of lupus nephritis has remained controversial. Reported complications of TLI treatment have included the development of opportunistic infections, particularly herpes zoster, as well as hematologic malignancies (2,9).

Lupus nephritis varies in its severity and rate of progression, and is an important determinant of overall prognosis in patients with SLE. Over the last decade, advances in the treatment of lupus nephritis have led to improvements in renal survival, but there are still questions about therapeutic options in patients with disease that is refractory to standard therapies. A metaanalysis of clinical trials in lupus nephritis reported that a regimen of immunosuppressives in conjunction with oral prednisone was more effective than oral prednisone alone for reducing total mortality and the occurrence of ESRD (10). More recent studies have shown that monthly bolus therapy with methylprednisolone was less effective than cyclophosphamide in treating proliferative lupus nephritis. Efficacy was greater when the 2 therapies were used in combination (12). Recent evidence supports the efficacy of mycophenolate mofetil in treating proliferative lupus nephritis, and other novel therapies are also being investigated, including intensive induction regimens (fludarabine and cyclophosphamide), immunoablative cyclophosphamide with or without stem-cell rescue, and costimulatory blockade (13,15,16). Despite these potential advances in therapy, lupus nephritis continues to pose a therapeutic challenge when conventional treatment regimens are not effective.

The first 10 of our patients to receive TLI for lupus nephritis were reported in 1985 (5). Each patient had severe proteinuria and their condition had been refractory to therapy with azathioprine and prednisone (5). TLI was noted to halt the decline in the glomerular filtration rate, to reduce proteinuria, and to improve serologic markers, including complement levels and anti–double-stranded DNA antibodies. Side effects included gastrointestinal distress, cytopenias, herpes zoster infections, and cellulitis. One patient died of cardiac arrhythmia. Subsequent followup by Strober et al suggested persistent improvement and reduction in steroid therapy in the same cohort of patients (6,7). Overall, the risks of sterility, hematologic malignancy, and infections appeared to be lower than with alkylating agents. Another group of investigators reported unfavorable results in 2 patients treated with TLI for lupus nephritis. One patient developed herpes zoster, gram-negative sepsis, and worsening renal function requiring dialysis; the second patient died from bronchopneumonia and progressive renal failure (9). However, because there have never been any controlled trials comparing TLI directly with conventional cytotoxic therapy, it is difficult to draw solid conclusions about the risks and benefits of TLI when compared with cytotoxic therapies.

This present study of 21 patients treated with TLI at Stanford University Medical Center for severe lupus nephritis, refractory to prednisone with or without immunosuppressive therapy, is the largest cohort of patients reported to date. Our results reveal that during the 10-year followup, 15 of the 21 patients remained alive, the disease has not progressed to ESRD in 9 of these patients, and 4 patients no longer require additional immunosuppressive therapies other than low-dose steroids. Of the 6 deaths, 3 were due to cardiac causes, reflecting the known cardiovascular risks of SLE and the effects of prolonged glucocorticoid therapy, which is often used to treat it. Although 7 patients developed opportunistic infections and 4 developed malignancies, all responded to appropriate therapy and none died from these causes.

The outcome parameter chosen for this study was death or dialysis. These end points were chosen because of the high mortality and dialysis rates of patients with lupus nephritis, particularly in those patients refractory to cytotoxic therapy. Dialysis was chosen as an outcome, rather than a doubling of the creatinine level, because ultimately, an important long-term goal of therapy is the avoidance of the total loss of renal function. The best predictors of death or dialysis appeared to be reduction in the glomerular filtration rate at baseline, prominent glomerulosclerosis and interstitial fibrosis on renal biopsy, and marked “leakiness” of the glomerular filtration barrier to proteins at baseline. Although all biopsy samples were scored for activity and chronicity, neither score had a statistically significant association with the outcome of death or dialysis. While traditionally the degree of scarring based on chronicity scores from a renal biopsy has been of use in predicting response to
therapy, this was not the case in this study. Scarring, reflected as the percentage of interstitial fibrosis and percentage of globally sclerosed glomeruli, appeared to be more useful, but no more so than the noninvasive measures of glomerular function. Overall, the baseline assessments of the glomerular filtration rate and fractional excretion of proteins (albumin and immunoglobulin) proved to be the best predictors of death or dialysis. Noninvasive measures have been utilized in the past and were found to be of utility (17,18).

We recognize that there are limitations in this study. There is no matching cohort, no adjustment for multiple statistical comparisons, and no multivariate modeling. The uniqueness of the cohort made it impossible to identify a comparable cohort of patients with refractory lupus nephritis by which to develop a matched control set.

We have described a group of patients with severe and refractory lupus nephritis who received TLI in the 1980s. A number of patients had apparent long-term benefit from this therapy, and a small number of nonfatal opportunistic infections and malignancies occurred. On average, patients with lupus nephritis treated with TLI do not appear to have better 10-year survival with retention of renal function than do those in published series treated with conventional cytotoxic regimens. However, TLI remains a salvage therapy with potential long-term benefit but also potential risks for patients with lupus nephritis. Because of its potential risks, it should be reserved for those with the most refractory disease and used only after standard therapies have failed.

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REFERENCES