Treatment Results in Renal Transplant Recipients With Non-Hodgkin’s Lymphoma

Z. Akcali, O. Ozyilkan, G. Moray, R. Emiroglu, and M. Haberal

ABSTRACT
The purpose of this study was to investigate the incidence of non-Hodgkin’s lymphoma (NHL), response to treatment, and survival time in renal transplant recipients at our center who developed this form of neoplasia. Between October 1985 and August 2002, 1077 renal transplants were carried out at our center. The incidence of NHL after transplantation was 1.1% (12/1077). All patients had their immunosuppressive doses reduced after they were diagnosed with NHL. Complete remission was achieved in eight cases, and five of these individuals were still alive at the time of writing. The circumstances for each of the three deaths in this group were as follows: (1) progressive gastric adenocarcinoma 9 years after being diagnosed with NHL, (2) stage III NHL cured with chemotherapy, but died of infection 2 years after NHL diagnosis, and (3) recurrent intestinal lymphoma, with death during second line chemotherapy. Of the five survivors in the remission group, one had to return to hemodialysis. The four patients who did not enter remission all died. The median time from transplantation to diagnosis of NHL was 66 months. At the time of writing, the median survival time for the eight patients who achieved complete remission was 41.5 months. The study showed that treatment of localized disease (skin or intestinal NHL) with surgery and/or radiotherapy/chemotherapy leads to complete remission and long survival times; however, patients in remission are at risk for other causes of death.

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Patient characteristics are presented in Table 1. The kidneys came from live donors in 12/1077. Three of the affected patients were female (12%). Nine of the affected patients were male (75%). The median age was 33.5 years (range, 21 to 58 years). The incidence of NHL after transplantation was 1.1% (12/1077). Results of the 1077 kidney recipients developed NHL. In each of these cases, the doses of immunosuppressive drugs were tapered after NHL was diagnosed.

RESULTS

The incidence of NHL after transplantation was 1.1% (12/1077). Three of the affected patients were female (25%), nine were male (75%), and the median age was 33.5 years (range, 21 to 58 years). The immunosuppressive regimens were prednisolone (P), azathioprine (Aza), cyclosporine (CsA), and mycophenolate mofetil (MM). The kidneys came from live donors in eight cases and from cadaver donors in four cases. The patient characteristics are presented in Table 1.

Eight of the 12 NHL patients went into complete remission and four patients died fairly soon after diagnosis due to disease progression. Of the eight initial survivors, five were still alive at the most recent follow-up check. The circumstances for each of the seven patients (58.3%) who died were as follows: (1) NHL diagnosed after jejunal perforation; (2) intestinal NHL with malignant ascites; (3) stage IV intestinal lymphoma; (4) stage IV disease (death occurred in the first month of hospitalization); (5) progressive gastric adenocarcinoma in the first year after surgical treatment for this condition (patient had also undergone partial gastrectomy and radiotherapy for gastric NHL 8 years prior to gastric adenocarcinoma); (6) stage III NHL was cured with chemotherapy, but a lethal infection developed 2 years after patient entered complete remission; (7) recurrent intestinal lymphoma, with death during second-line chemotherapy. In the seventh case, the primary treatment modality was chemotherapy only. The patient did not undergo surgery at the time of diagnosis. Of the five cured survivors, one patient had to return to

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age (Years)</th>
<th>Donor</th>
<th>Immunosuppression</th>
<th>TTM</th>
<th>PS</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>male</td>
<td>52</td>
<td>cadaver</td>
<td>PRD + AZA + CsA</td>
<td>14</td>
<td>1</td>
<td>B-cell skin + Kaposi’s sarcoma</td>
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<tr>
<td>2</td>
<td>male</td>
<td>58</td>
<td>cadaver</td>
<td>PRD + AZA + CsA</td>
<td>9</td>
<td>4</td>
<td>jejunum</td>
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<tr>
<td>3</td>
<td>male</td>
<td>29</td>
<td>cadaver</td>
<td>PRD + AZA</td>
<td>84</td>
<td>1</td>
<td>stomach</td>
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<tr>
<td>4</td>
<td>female</td>
<td>29</td>
<td>living</td>
<td>PRD + CsA</td>
<td>7</td>
<td>3</td>
<td>ovaries, peritoneum</td>
</tr>
<tr>
<td>5</td>
<td>male</td>
<td>31</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>48</td>
<td>2</td>
<td>cervical and abdominal LAP</td>
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<tr>
<td>6</td>
<td>male</td>
<td>35</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>112</td>
<td>1</td>
<td>small intestine</td>
</tr>
<tr>
<td>7</td>
<td>male</td>
<td>35</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>91</td>
<td>3</td>
<td>duodenum, peritoneum</td>
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<tr>
<td>8</td>
<td>female</td>
<td>50</td>
<td>cadaver</td>
<td>PRD + AZA + CsA</td>
<td>13</td>
<td>1</td>
<td>T-cell skin</td>
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<tr>
<td>9</td>
<td>male</td>
<td>29</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>97</td>
<td>3</td>
<td>small intestine</td>
</tr>
<tr>
<td>10</td>
<td>female</td>
<td>32</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>110</td>
<td>2</td>
<td>small intestine</td>
</tr>
<tr>
<td>11</td>
<td>male</td>
<td>21</td>
<td>living</td>
<td>PRD + MMM + CsA</td>
<td>8</td>
<td>2</td>
<td>liver + spleen + peripheral LAP</td>
</tr>
<tr>
<td>12</td>
<td>male</td>
<td>48</td>
<td>living</td>
<td>PRD + AZA + CsA</td>
<td>116</td>
<td>1</td>
<td>small intestine</td>
</tr>
</tbody>
</table>

PRD, prednisolone; AZA, azathioprine; CsA, cyclosporine; MMM, mycophenolate mofetil; PS, performance status; LAP, lymphadenopathy; TTM: time from transplantation to malignancy diagnosis (months).

Table 1. Characteristics of the Patients With Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Pt</th>
<th>Stage</th>
<th>IPI</th>
<th>Treatment</th>
<th>Response</th>
<th>DFS (Months)</th>
<th>OS (Months)</th>
<th>Status**</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>2</td>
<td>CT (CHOP)</td>
<td>CR</td>
<td>50</td>
<td>56+</td>
<td>alive</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>IE</td>
<td>2</td>
<td>palliative surgery</td>
<td>—</td>
<td>0</td>
<td>1−</td>
<td>dead perforation</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>IE</td>
<td>1</td>
<td>surgery + RT</td>
<td>CR</td>
<td>93</td>
<td>105−</td>
<td>dead gastric cancer</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>IV</td>
<td>3</td>
<td>palliation</td>
<td>—</td>
<td>0</td>
<td>1−</td>
<td>dead PD</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>III</td>
<td>1</td>
<td>CT (CHOP)</td>
<td>CR</td>
<td>24</td>
<td>30−</td>
<td>dead infection</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>IE</td>
<td>1</td>
<td>surgery</td>
<td>CR</td>
<td>76</td>
<td>76+</td>
<td>alive</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>IV</td>
<td>3</td>
<td>palliation</td>
<td>—</td>
<td>0</td>
<td>0−</td>
<td>dead PD</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>IE</td>
<td>1</td>
<td>excision and RT</td>
<td>CR</td>
<td>45</td>
<td>52+</td>
<td>alive</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>IV</td>
<td>2</td>
<td>palliative surgery</td>
<td>—</td>
<td>0</td>
<td>1−</td>
<td>dead PD</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>IE</td>
<td>2</td>
<td>CT*</td>
<td>Recurrence</td>
<td>24</td>
<td>31−</td>
<td>dead PD</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>IV</td>
<td>2</td>
<td>CT (CHOP)</td>
<td>CR</td>
<td>18</td>
<td>24+</td>
<td>alive</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>IIE</td>
<td>2</td>
<td>surgery + CT (CVP)</td>
<td>CR</td>
<td>4</td>
<td>4+</td>
<td>alive</td>
<td>—</td>
</tr>
</tbody>
</table>

IPI, International prognostic index; CR, complete response; CT, chemotherapy; RT, radiotherapy; OS, overall survival (+ means alive); DFS, disease-free survival; PD, progressive disease; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CVP, cyclophosphamide + vincristine + prednisolone.

*CHOP for first line, MINE (mesna + ifosfamide + mitoxantrone + etoposide) after recurrence.

**At most recent follow-up.

Table 2. Management and Outcomes for the Non-Hodgkin’s Lymphoma Cases
hemodialysis due to graft rejection after reduced immuno-
suppression and curative resection of gastric NHL. Another
patient who had concomitant Kaposi’s sarcoma and NHL
was treated with chemotherapy alone. A third survivor with
T-cell skin NHL was treated with several courses of radio-
therapy after diagnostic excision of the first skin mass. The
fourth surviving patient had stage IV NHL and was treated
with chemotherapy. He was still in remission at the most
recent follow-up. The fifth survivor had small intestinal lym-
phoma and underwent surgical resection. The pathologic
diagnosis was multifocal high-grade intestinal lymphoma and
the stage was IIE. In this case, the immunosuppressive drug
doses were reduced, and six cycles of the cyclophosphamide +
vincristine + prednisolone chemotherapy protocol were ad-
mixed. At the most recent follow-up, 4 months postsur-
gery, the patient was still in complete remission.

The results of treatment are presented in Table 2. The
median and mean times from transplantation to diagnosis
of NHL were 66 and 59 months, respectively (range, 7 to
116 months). Lymphoma developed during the first year
posttransplantation in three cases, and two of these patients
died in the first month after diagnosis. The median disease-
free survival time for the eight patients who were cured was
34.5 months (range, 4 to 93 months). The median overall
survival time for these patients was 41.5 months (range, 4 to
105 months). Figure 1 shows the Kaplan-Meier survival
curve for the 12 patients with NHL.

DISCUSSION
The incidence of NHL in renal transplant recipients at our
center is 1.1%, a figure similar to other rates documented in
the literature. The incidence rates of posttransplantation
malignancy differ according to geographic location. In
Western countries, the most common forms of malignancy
in organ transplant recipients are skin cancer and lympho-
ma. In renal transplant recipients in Japan, the predomi-
nant malignancies are cancers of the digestive organs and
renal cell carcinoma. In kidney transplant recipients of
Jewish, Arabic, sub-Saharan African, or Mediterranean ances-
try, Kaposi’s sarcoma is the most common malignant tumor.
According to a previous study conducted at our center, the
tumors mostly frequently encountered in Turkish renal
transplant recipients are Kaposi’s sarcoma, skin cancer, and
NHL (incidence rates 30%, 12%, and 12%, respectively).

Monoclonal NHL is suspected to represent as a response
to infection with Epstein-Barr virus (EBV). Immunosup-
pressive agents are known to inhibit T-cell function, en-
abling unrestricted polyclonal B-cell proliferation in re-
sponse to primary viral infection. Eleven of our NHL
patients had B-cell lymphoma; one individual had T-cell
skin lymphoma. T-cell NHL is rarely encountered in organ
transplant recipients. Primary brain lymphomas, central
nervous system (CNS) involvement, and allograft involve-
ment are frequently reported in transplant recipients with
lymphoma. None of our 12 kidney recipients with NHL...
exhibited CNS or allograft involvement; however, the frequency of gastrointestinal involvement was high (7 of 12 cases) in this group.

According to a report by Penn based on the Cincinnati Tumor Registry, the mean time from transplantation to diagnosis of any form of malignancy (time to malignancy: TTM) is approximately 61 months; however, Kaposi’s sarcoma and NHL tend to occur earlier, at around 20 and 33 months, respectively. In our 12 patients with NHL this period was roughly twice as long (59 months). The same study by Penn also indicated that inclusion of CsA in the immunosuppressive treatment protocol is associated with earlier appearance (15 vs 48 months in patients not treated with CsA) and less frequent CNS involvement (15% vs 38%) of posttransplantation lymphoma. However, we believe that factors other than CsA must also influence CNS involvement and time to NHL diagnosis, because 11 of 12 patients were treated with CsA. Some small series of Pakistani and Iranian renal transplant recipients with NHL have reported similar results. A research group from Pakistan documented a mean TTM of 85.5 months in 6 NHL patients, and investigators in Iran noted a mean TTM of 48.8 months in seven NHL patients (none with CNS involvement).

Reduction or withdrawal of immunosuppressive treatment frequently leads to regression of NHL. It is easier to reduce or eliminate this therapy in renal transplant recipients than in liver or heart transplant patients. Indeed, only 1 of the 12 NHL patients in our study had to return to hemodialysis. The literature notes conflicting results for factors that are considered to be predictors of response to reduction of immunosuppression in transplant recipients. These controversial prognostic factors include bcl-6 mutations, high serum lactate dehydrogenase level, presence of bacterial and/or fungal infection, organ failure, disseminated malignancy, older age, and short TTM.

Even though EBV-transformed B cells are not susceptible to acyclovir or gancyclovir, some patients with NHL show tumor regression after antiviral therapy. Anti-B-lymphocyte antibodies may also be effective in organ transplant recipients with NHL. Radiotherapy and/or chemotherapy are usually not recommended and both are known to increase mortality in these patients. However, Hauke et al claim that patients with posttransplantation lymphoma tolerate intensive chemotherapy. In our series, only one patient died during chemotherapy after recurrence. In this case, intestinal lymphoma had been previously treated with chemotherapy alone, no surgery. The other four individuals who received chemotherapy all tolerated the treatment without dose reduction, even though they had stage III or stage IV disease. Two patients underwent effective radiotherapy after primary tumor resection.

Surgery is the definitive treatment for localized NHL in organ transplant recipients. We were able to achieve complete remissions and long survival times in our three patients who had resection of gastrointestinal lymphomas. Due to the risk of local recurrence, it is our opinion that patients with gastrointestinal involvement should always be treated with surgery, never with chemotherapy alone. Chemotherapy and/or radiotherapy may be applied after surgery. When a patient is diagnosed with intestinal NHL prior to the development of complications such as perforation or peritoneal involvement, curative intestinal surgery may achieve long-standing remission. Even when NHL in a renal transplant recipient is cured, there is still an increased mortality risk due to factors such as secondary malignancy or infection.

REFERENCES