Aggressive Treatment for Postcardiac Transplant Lymphoproliferation

By Lode J. Swinnen, G. Martin Mullen, Thomas J. Carr, Maria R. Costanzo, and Richard I. Fisher

Posttransplant lymphoproliferative disorder (PTLD) is a frequently fatal complication of organ transplantation, occurring in 2% to 6% of cardiac recipients. Treatment remains poorly defined. Reduction in immunosuppression is effective in a proportion of cases, but mortality on the order of 80% is reported for patients requiring chemotherapy. The reason for such poor outcomes is unclear, but may be partly caused by the concomitant use of immunosuppressives. Nineteen consecutive cardiac recipients with PTLD were studied retrospectively in terms of clinical features and outcome. Patients were managed according to a uniform treatment approach. Initial therapy was a trial of reduced immunosuppression with concomitant acyclovir followed, if unsuccessful, by aggressive combination chemotherapy. The regimen used was predominantly ProMACE-CytaBOM. Six patients with phenotypically polyclonal PTLD presented less than 6 months after transplantation (median 6 weeks). Only 1 of 4 (25%) treated patients responded to reduced immunosuppression; the remainder died of multiorgan failure. Thirteen patients presented with phenotypically monoclonal disease >6 months after transplantation. In 8 of 12 (75%) treated patients initial therapy was reduction in immunosuppression. None achieved complete remission (CR) and 2 experienced fatal rejection. Two patients achieved durable surgical CR. The remaining 8 patients received chemotherapy; 2 of 8 (25%) died during treatment, 6 of 8 (75%) achieved CR. None have relapsed, at a median duration of follow-up of 38 months. Neutropenic sepsis and subclinical doxorubicin cardiotoxicity at a mean cumulative dose of 63 mg/m² were the principal toxicities. Our data indicate that aggressive chemotherapy is both feasible and effective in phenotypically monoclonal PTLD refractory to reduced immunosuppression. ProMACE-CytaBOM is well suited to cardiac recipients, minimizing doxorubicin exposure and obviating the need for concurrent immunosuppressives.

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OFTEN DEVASTATING complication of organ transplant, posttransplant lymphoproliferative disorder (PTLD) develops in approximately 2% to 6% of cardiac transplant recipients. Lymphoproliferative disorder is the third leading cause of death beyond the immediate perioperative period in heart transplant recipients. Although the disease occurs with all forms of immunosuppression used to date, the incidence is likely to increase rather than decrease with the use of new, highly potent and specific immunosuppressive agents. Posttransplant lymphoproliferations differ significantly from classic non-Hodgkin's lymphoma (NHL) in terms of clinical course, pathology, and treatment options. Virtually all are of B-cell origin, and a strong association with the Epstein-Barr virus (EBV) has been established. Lymphoproliferations that appear identical in all respects to what is seen posttransplantation have been described in a number of congenital immunodeficiency states. Although similar in many respects, acquired immunodeficiency syndrome (AIDS)-related lymphomas are much less consistently EBV-associated.

Histologically, the disease comprises a spectrum ranging from reactive-looking proliferations to frank NHL morphology. Diffuse large cell lymphoma and immunoblastic lymphoma are frequent histologies after heart transplantation. Tumors may appear to be polyclonal when assessed immunohistochemically; however, one or more clonal subpopulations are usually detectable by the more sensitive technique of Ig gene rearrangement analysis.

Presentation and clinical course vary from multifocal, rapidly progressive disease with diffuse organ involvement, often fatal within a few weeks at one extreme, to more localized mass lesions that grow relatively slowly over a period of months. The former presentation tends to occur early after transplantation, with tumors frequently being phenotypically polyclonal; the latter presentation tends to occur late after transplantation, with tumors tending to be phenotypically monoclonal. Considered rare in the past, presentation with multiorgan involvement and a fulminant clinical course may have become more common as a result of the use of potent anti-T-cell antibodies in the immunosuppressive regimen.

No uniform treatment strategy exists. Experience has varied, and the literature is highly anecdotal. However, certain general principles do emerge from the existing body of knowledge.

Reduction in immunosuppression can result in complete and durable tumor regression in some cases, and is generally the first treatment tried. Resection of anatomically limited lesions can be curative. Regression of lymphoproliferations has been described after the use of high-dose acyclovir in a small number of cases. However, the value of acyclovir remains very unclear.

Published reports indicate both a high mortality and a high failure rate for cytotoxic chemotherapy (mortality on the order of 80%). However, it is not clear why outcomes are so poor in organ transplant recipients and why mortality with aggressive chemotherapy is so high, as specific response and toxicity data have as yet not been reported.

We present our experience with 19 consecutive cases of lymphoproliferation after cardiac transplantation. The large number of cases seen over a short period of time (<5 years) is partly the result of intensive immunosuppression with the monoclonal anti-T-cell antibody OKT3. We formulated a uniform treatment approach based on the general principles described above, in which we also attempted to eliminate the use of concomitant immunosuppressives during chemo-

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therapy, on the assumption that this might reduce the toxicity of chemotherapy in this setting.

**PATIENTS AND METHODS**

A retrospective study of 19 patients with lymphoproliferative disorders occurring after cardiac transplantation was performed to assess treatment results and outcome. The patients are part of a cohort of 352 cardiac allografts performed between March 11, 1984 and September 1, 1994 in the Loyola University Chicago heart transplantation program.

**Histopathology**

Diagnosis was based on examination of histologic material, obtained by open biopsy or by core needle biopsy, in all cases. Lesions were classified according to the Working Formulation scheme. Immunophenotyping by Ig staining, immunogenotyping by DNA analysis for clonal Ig-gene rearrangements, and Southern blot analysis for the presence of EBV-DNA, were performed on tumor specimens whenever technically feasible. Tumor-associated EBV was identified in all 13 patients in whom Southern blot analysis for EBV DNA was performed.

**Immunosuppressive Regimens**

In all patients the immunosuppressive regimen consisted of azathioprine, prednisone, and cyclosporine (CsA). Patients fall into one of three categories with regard to prophylactic immunotherapy, determined by the clinical practice prevailing at the time they received transplants: (1) One patient received antithymocyte globulin (ATG); (2) 14 patients received OKT3 (muromonab-CD3) prophylaxis (Orthoclone OKT3; Ortho Biotech, Raritan, NJ); and (3) 4 patients who received transplants subsequent to January 1, 1990 received no prophylactic immunotherapy, as it was by then clear to us that the use of prophylactic OKT3 was associated with a marked increase in the incidence of PTLD.

Rejection episodes were treated in a uniform manner throughout the period of this study. Endomyocardial biopsy samples were histologically graded as mild, moderate, or severe rejection. Intensified immunosuppression was used only for moderate or severe rejection. In the absence of hemodynamic compromise, oral steroid dose was increased; if hemodynamic compromise was present, 1 g methylprednisolone per day was administered intravenously (IV) for 3 days. Refractory rejection was treated with either OKT3 or ATG.

**Staging**

All patients diagnosed as having PTLD were staged according to the Ann Arbor staging system. The extent of disease was determined by means of computed tomographic (CT) scans of the chest, abdomen and pelvis, bilateral bone marrow biopsies, complete blood count, and screening chemistries. CT scan of the brain, cerebrospinal fluid examination, and pulmonary or gastrointestinal endoscopic studies were performed when clinically indicated. Restaging was performed at the end of a treatment maneuver (reduction in immunosuppressives, chemotherapy). Complete remission (CR) was defined as the disappearance of all clinical evidence of active tumor for at least 4 weeks. Residual abnormalities on chest or abdominal radiography had to be less than 2.5 cm in diameter, with no new lesions. All patients had negative human immunodeficiency virus (HIV) antibody tests.

**Treatment**

A uniform approach to treatment was used. Reduction in immunosuppressives was the initial therapeutic maneuver in all but three cases, with concomitant IV high-dose acyclovir in all but four cases (500 mg/m² every 8 hours, with standard adjustment for impaired renal function). Immunosuppressives were reduced as follows: discontinuation of azathioprine; simultaneous discontinuation of CsA or reduction by 50% to 75% of CsA dose; and simultaneous reduction of prednisone dose to physiologic levels. End points to the reduction in immunosuppression maneuver were as follows: rejection, as determined by endomyocardial biopsy, of any severity; progressive disease; and no response after an arbitrary period of 10 to 14 days. Endomyocardial biopsy to monitor for rejection was performed at least weekly and for any potential sign or symptom of rejection. Patients generally remained hospitalized for the duration of the reduced immunosuppression maneuver, and always remained hospitalized if CsA had been discontinued completely.

Patients showing no response or progressive disease with reduction in immunosuppressives were treated with an aggressive NHL chemotherapy regimen, predominantly ProMACE-CytaBOM, in all but the most recent case (patient 14), in whom interferon-α2b (IFN-α2b) (Intron A; Schering Corp, Kenilworth, NJ) was used before resorting to chemotherapy. All immunosuppressives were stopped at the outset of ProMACE-CytaBOM chemotherapy, and were not re-instituted until day 21 of the final (sixth) cycle. ProMACE-CytaBOM was administered in a standard fashion and included trimeprprim-sulphamethoxazole prophylaxis. However, prednisone was not discontinued between days 14 and 21 of the cycle, but continued at 15 mg/d, in view of the prior long-term steroid exposure of heart transplant recipients. Central nervous system prophylaxis was not given. Colony-stimulating factors were used only in the most recent case (patient 14), in whom granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/d was administered from day 2 of the ProMACE-CytaBOM cycle until recovery of white blood cells (WBCs) ≥10,000/μL.

Patients were monitored closely for rejection and for anthracycline cardiotoxicity. A multi-gated acquisition scan (MUGA) was performed before each dose of doxorubicin, and doxorubicin was held if left ventricular ejection fraction (LVEF) had decreased by ≥10% below normal. Endomyocardial biopsy to monitor for rejection was performed in every cycle in most cases; electron microscopic studies for anthracycline toxicity were performed if LVEF as assessed by MUGA decreased ≥10% below normal.

In two patients all known disease was technically resectable, and was deliberately completely resected during the initial diagnostic procedure, achieving a surgical complete response. After completing a period of reduced immunosuppression and a 3-week course of IV acyclovir, no further therapy was administered.

**RESULTS**

**Interval From Transplantation**

The clinical features of 19 cases are listed in Table 1, grouped according to the interval since transplantation.

Six patients presented with posttransplant lymphoproliferation at less than 6 months from the time of transplantation, at a median of 6 weeks. Five of six had received two courses of OKT3, and were profoundly immunosuppressed at the time of presentation. The disease was rapidly progressive, prominent B-symptoms were present, and all had systemic sepsis at the outset (bacterial and/or cytomegalovirus). Multiple visceral sites were involved in five of six patients, with progressive multisystem failure. All were phenotypically polyclonal, although one or more monoclonal subpopulations were detectable on genotyping in all but one of the tumors studied.

Thirteen patients presented at ≥6 months after trans-
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Disease presenting from sepsis or multisystem failure. Interestingly, presented with lung nodules as the only site of disease. Of the 13 patients in this group received no treatment for posttransplant lymphoproliferation: 1 was diagnosed only at autopsy. Of the 5 patients whose lack of response in 3 cases. Of the 5 patients whose diagnosis (patients 1 and 5). Of the remaining 4 patients, reduction in immunosuppression was the initial treatment in 3 (patients 2, 4, and 6) with concomitant IV acyclovir. Immunosuppressives were discontinued, except for physiologic glucocorticoids. The suspension of immunosuppressives was maintained for a period ranging from 4 to 7 days, until one of two unequivocal end points had been reached: rejection or progressive disease. The maneuver resulted in progressive disease in two cases; rejection and CR in one case. The CR has persisted for 54 months without further therapy, and the patient remains alive and well (patient 4).

Two of the patients with progressive disease, and one patient not treated with reduced immunosuppression, received aggressive cytotoxic chemotherapy: ProMACE-CytaBOM in two, ProMACE (day 1)-MOPP (day 8) in one. None survived cycle 1, all succumbing to uncontrollable sepsis and progressive multisystem failure, although tumor response was evident clinically or at autopsy (patients 6 and 3).

Only one patient presenting at less than 6 months after transplantation responded to reduced immunosuppression, and no patient in this group survived chemotherapy. Patients presenting at ≥6 months posttransplantation. One of the 13 patients in this group received no treatment for PTLD, being diagnosed only at autopsy. In 8 of 12 (75%) treated patients initial therapy was a reduction in immunosuppression (patients 8, 9, 11, 14, 15, 16, 17, and 18), in conjunction with IV acyclovir in all but patient 17. Immunosuppressives were discontinued (except for physiologic glucocorticoids) for a period ranging from 7 to 15 days. The maneuver was terminated by rejection (determined by endomyocardial biopsy) in 5 cases, and abandoned for lack of response in 3 cases. Of the 5 patients whose trial of reduced immunosuppression ended in rejection, 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Race/Sex</th>
<th>Path</th>
<th>P/G</th>
<th>Cum OKT3 (IMG)</th>
<th>Time from Trsp</th>
<th>Stage</th>
<th>LDH</th>
<th>Disease Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60/B/F</td>
<td>IBL</td>
<td>P/ND</td>
<td>135</td>
<td>1</td>
<td>IV B</td>
<td>899</td>
<td>LN, heart, multiple organs</td>
</tr>
<tr>
<td>2</td>
<td>33/W/F</td>
<td>IBL</td>
<td>P/M</td>
<td>120</td>
<td>1</td>
<td>IV B</td>
<td>980</td>
<td>Visc LN, BM</td>
</tr>
<tr>
<td>3</td>
<td>56/W/M</td>
<td>IBL</td>
<td>P/M</td>
<td>120</td>
<td>1</td>
<td>IV B</td>
<td>298</td>
<td>Heart, spleen, Visc + Sup LN, CSF</td>
</tr>
<tr>
<td>4</td>
<td>27/W/F</td>
<td>DM</td>
<td>P/M</td>
<td>105</td>
<td>1.5</td>
<td>III B</td>
<td>351</td>
<td>LN, tonsils, spleen</td>
</tr>
<tr>
<td>5</td>
<td>64/W/F</td>
<td>IBL</td>
<td>P/ND</td>
<td>120</td>
<td>2</td>
<td>IV B</td>
<td>375</td>
<td>Gut, Visc LN, spleen</td>
</tr>
<tr>
<td>6</td>
<td>66/W/M</td>
<td>IBL</td>
<td>P/P</td>
<td>75</td>
<td>3.5</td>
<td>IV B</td>
<td>1088</td>
<td>LN, lung, heart, multiple organs</td>
</tr>
</tbody>
</table>

| Disease presenting <6 mo after transplantation |
|-----------------|-----------------|-----------------|-----------------|
| 7               | 54/W/F          | IBL             | M/ND            | 0              | 6              | II B  | 753 | Visc LN |
| 8               | 49/W/F          | DLCL            | M/ND            | 0              | 6              | IV B  | 456 | Gut, Visc LN, lung |
| 9               | 43/W/M          | IBL             | M/M             | 70             | 9              | IV A  | 256 | Lung nodules |
| 10              | 59/W/M          | IBL             | M/M             | 55             | 9              | IV A  | 200 | Lung nodules |
| 11              | 54/W/M          | DM              | -/M             | 0              | 9              | IV A  | 382 | Lung nodules |
| 12              | 59/W/M          | DLCL            | M/M             | 70             | 9.5            | IV A  | 289 | Lung, Visc LN |
| 13              | 58/B,M          | DM              | -/M             | 65             | 11             | IV A  | 188 | Lung nodules |
| 14              | 59/W/M          | DLCL            | M/M             | 0              | 11.5           | IV A  | 214 | Visc LN, spleen |
| 15              | 57/W/M          | DLCL            | -/M             | 70             | 12             | IV A  | 243 | Lung nodules |
| 16              | 46/W/M          | DLCL            | -/M             | 80             | 12             | IV A  | 202 | Lung nodules |
| 17              | 44/W/M          | DLCL            | ND/ND           | 70             | 13             | I A   | 271 | Neck nodes |
| 18              | 51/W/M          | IBL             | M/M             | 70             | 18             | IV B  | 317 | Visc LN, heart, kidneys |
| 19              | 32/W/M          | DUL (BL)        | M/ND            | 0              | 50             | IV A  | 312 | CSF, BM, nasopharynx |

Abbreviations: Path, pathology; P/G, phenotype/genotype; Cum, cumulative; Trsp, transplant; LDH, lactate dehydrogenase; IBL, immunoblastic lymphoma; DM, diffuse mixed; DLCL, diffuse large cell; DUL, diffuse undifferentiated; BL, Burkitt’s; P, polyclonal; M, monoclonal; ND, not done; -, no surface Ig; LN, lymph nodes, Visc, visceral; Sup, superficial; BM, bone marrow; CSF, cerebrospinal fluid.

Response to Treatment

Treatment and outcome are summarized in Table 2.

Patients presenting at less than 6 months posttransplantation. Two of the 63% patients in this group received no treatment for posttransplant lymphoproliferation: 1 was diagnosed postmortem, 1 was moribund with cerebral hemorrhage at the time of diagnosis (patients 1 and 5). Of the remaining 4 patients, reduction in immunosuppression was the initial treatment in 3 (patients 2, 4, and 6) with concomitant IV acyclovir. Immunosuppressives were discontinued, except for physiologic glucocorticoids. The suspension of immunosuppressives was maintained for a period ranging from 4 to 7 days, until one of two unequivocal end points had been reached: rejection or progressive disease. The maneuver resulted in progressive disease in two cases; rejection and CR in one case. The CR has persisted for 54 months without further therapy, and the patient remains alive and well (patient 4).

The two patients with progressive disease, and one patient not treated with reduced immunosuppression, received aggressive cytotoxic chemotherapy: ProMACE-CytaBOM in two, ProMACE (day 1)-MOPP (day 8) in one. None survived cycle 1, all succumbing to uncontrollable sepsis and progressive multisystem failure, although tumor response was evident clinically or at autopsy (patients 6 and 3).

Only one patient presenting at less than 6 months after transplantation responded to reduced immunosuppression, and no patient in this group survived chemotherapy.

Patients presenting at ≥6 months posttransplantation. One of the 13 patients in this group received no treatment for PTLD, being diagnosed only at autopsy. In 8 of 12 (75%) treated patients initial therapy was a reduction in immunosuppression (patients 8, 9, 11, 14, 15, 16, 17, and 18), in conjunction with IV acyclovir in all but patient 17. Immunosuppressives were discontinued (except for physiologic glucocorticoids) for a period ranging from 7 to 15 days. The maneuver was terminated by rejection (determined by endomyocardial biopsy) in 5 cases, and abandoned for lack of response in 3 cases. Of the 5 patients whose trial of reduced immunosuppression ended in rejection, 2
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Disease presenting &lt;6 mo after transplantation</th>
<th>Treatment</th>
<th>Result</th>
<th>Duration*</th>
<th>Status/Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No treatment. Autopsy diagnosis</td>
<td>D/C AZA + CsA x 5 d</td>
<td>PD</td>
<td></td>
<td>Dead/sepsis</td>
</tr>
<tr>
<td>2</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 5 d</td>
<td>ProMACE 1 d antemortem</td>
<td>PD</td>
<td></td>
<td>Multiorgan failure</td>
</tr>
<tr>
<td>3</td>
<td>IV acyclovir</td>
<td>ProMACE D1 MOPP D8 + intrathecal methotrexate. Died cycle 1 d20</td>
<td>PR</td>
<td></td>
<td>Septicemia</td>
</tr>
<tr>
<td>4</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 7 d, + IV acyclovir</td>
<td>(rejection on d 7)</td>
<td>CR</td>
<td>54'</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>5</td>
<td>No treatment. Lymphoma diagnosed 3 d antemortem</td>
<td>No treatment. Autopsy diagnosis</td>
<td>PD</td>
<td></td>
<td>Dead/sepsis</td>
</tr>
<tr>
<td>6</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 4 d, + IV acyclovir</td>
<td>ProMACE-CytaBOM. Died cycle 1 d16</td>
<td>PD</td>
<td></td>
<td>Multiorgan failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Disease presenting ≥6 mo after transplantation</th>
<th>Treatment</th>
<th>Result</th>
<th>Duration*</th>
<th>Status/Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>No treatment. Autopsy diagnosis, Ganciclovir x 17 d for CMV</td>
<td>D/C AZA + CsA x 7 d + IV acyclovir, resulting in rejection on d 7</td>
<td>CR</td>
<td>3</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>8</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 7 d + IV acyclovir, resulting in rejection on d 7</td>
<td>ProMACE-CytaBOM x 6 cycles</td>
<td>PD</td>
<td></td>
<td>Dead/sepsis, CNS CMV</td>
</tr>
<tr>
<td>9</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 12 d + IV acyclovir resulting in rejection on d 12</td>
<td>NR</td>
<td></td>
<td></td>
<td>Dead/rejection</td>
</tr>
<tr>
<td>10</td>
<td>Surgical resection</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 12 d + IV acyclovir</td>
<td>CR</td>
<td>8</td>
<td>Dead/sepsis, clinically no lymphoma</td>
</tr>
<tr>
<td>11</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 7 d + IV acyclovir (rejection on d 7)</td>
<td>CHOP x 1 cycle, ProMACE-CytaBOM x 6 cycles</td>
<td>CR</td>
<td>39'</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>12</td>
<td>Surgical resection</td>
<td>Reduced immunosuppression: D/C AZA + CsA at 75% x 14 d + IV acyclovir, resulting in rejection on d 14</td>
<td>CR</td>
<td>47'</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>13</td>
<td>Postop reduced immunosuppression: D/C AZA, CsA at 75% x 14 d + IV acyclovir</td>
<td>D/C AZA + CsA x 7 d + IV acyclovir</td>
<td>CR</td>
<td>16</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>14</td>
<td>Reduced immunosuppression: D/C AZA, CsA at 50% x 14 d + IV acyclovir, resulting in rejection on d 14</td>
<td>IFN-α2b 3 MU/mL x 3 mo + maintenance TIW x 6 mo</td>
<td>CR</td>
<td>1'</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>15</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 10 d + IV acyclovir</td>
<td>ProMACE-CytaBOM x 6 cycles</td>
<td>CR</td>
<td>47'</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>16</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 15 d + IV acyclovir resulting in rejection on d 15</td>
<td>D/C AZA + CsA x 15 d + IV acyclovir</td>
<td>PD</td>
<td></td>
<td>Dead/sepsis</td>
</tr>
<tr>
<td>17</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 8 d</td>
<td>ProMACE-CytaBOM, Died C1 d17</td>
<td>PR</td>
<td></td>
<td>Dead/sepsis</td>
</tr>
<tr>
<td>18</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 13 d + IV acyclovir resulting in rejection on d 13</td>
<td>CHOP x 3 cycles + involved field RT</td>
<td>PR</td>
<td>&quot;8&quot;</td>
<td>Alive/free of disease</td>
</tr>
<tr>
<td>19</td>
<td>Reduced immunosuppression: D/C AZA + CsA x 13 d + IV acyclovir resulting in rejection on d 13</td>
<td>CTX/ADR/ARA-C/HDMTX/IT ARA-C MTX (BL regimen) x 2 cycles</td>
<td>PR</td>
<td></td>
<td>Alive/free of disease</td>
</tr>
</tbody>
</table>

Abbreviations: PD, progressive disease; NR, no response; PR, partial response; CR, complete response; D/C, discontinue.

* Duration of response, in months from completion of the applicable treatment.
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had progressive disease, 2 had no response, and 1 had a partial response at the end of the maneuver. Two patients experienced fatal rejection with this maneuver.

Complete surgical resection of all visible disease was possible in two patients (patients 10 and 13), both of whom had lung nodules. Resection was followed by a period of reduction in immunosuppressives and administration of IV acyclovir. Neither has recurred.

Eight of 12 patients received chemotherapy with an aggressive NHL regimen (6 patients who survived the trial of reduced immunosuppression and 2 whose initial treatment was chemotherapy). One patient had achieved a 16-month CR with IFN-α2b before chemotherapy was used on relapse (patient 14). Five of the 8 patients received ProMACE-CytaBOM, 1 patient received ProMACE (day 1)-MOPP (day 8), 1 received three cycles of CHOP followed by local radiation therapy for limited-stage disease, and 1 received an intensive Burkitt’s lymphoma regimen for his t(8,22)-positive diffuse undifferentiated lymphoma.

All 6 of the 8 patients who completed therapy achieved CR. None have relapsed, at a median duration of follow-up of 38 months (range, 1 month to 78 months). Two patients died during therapy: 1 of sepsis and 1 of progressive Burkitt’s lymphoma. Two patients have died while in remission: 1 at 3 months and 1 at 37 months. There was no evidence of PTLD in either at autopsy.

Therefore, of 8 patients treated with chemotherapy for lymphoproliferations presenting at ≥6 months after transplantation, 6 of 8 (75%) achieved durable CR.

Kaplan-Meier overall survival and disease-free survival (DFS) curves for all treated patients are shown in Fig 1. Figure 2 compares DFS for treated patients presenting at less than 6 months after transplantation with that of treated patients presenting at ≥6 months.

Toxicity

Reduction in immunosuppression. Immunosuppressives were modified in 13 patients; in 12 patients the modification was complete discontinuation, and in 1 patient it was a reduction to less than 25% of prior dosage. Six patients (46%) experienced an acute rejection episode as a result of the maneuver. Rejections were mild or moderate, and reversible in all but 2 cases. Two patients died of refractory rejection. The median time to rejection was 9.5 days, with the shortest time being 7 days and the longest 15 days off all immunosuppressives. Rejection was otherwise unpredictable, with negative biopsy samples being obtained as little as 2 days before the rejection episode in several cases.

Chemotherapy. Seven patients were evaluable for doxorubicin cardiotoxicity. In 4 of 7 (57%) patients doxorubicin had to be discontinued because of a reduction in left ventricular ejection fraction on MUGA of ≥10% below normal and/or electron microscopic evidence of anthracycline toxicity (patients 8, 11, 14, and 15). Doxorubicin was discontinued after a mean cumulative exposure of 63 mg/m² (range, 37 to 76 mg/m²) in those patients. Grade 2 anthracycline toxicity occurred after 44 mg/m² and grade 2.5 toxicity after continued dosing to 63 mg/m² in patient 14; grade 3 changes were found after 64 mg/m² cumulative dose in patient 11; and grade 2 changes after 137 mg/m² in patient 17 (biopsied after completion of planned therapy). No patient has developed clinical congestive heart failure attributable to doxorubicin exposure. Three patients who had no reduction in ejection fraction received 104 mg/m², 137 mg/m², and 100 mg/m² cumulative dose (patients 12, 17, and 19).

No rejection episode occurred in 23 cycles of ProMACE-CytaBOM administered to four patients, despite the fact that...
no immunosuppressive drugs were administered other than the chemotherapy regimen. One patient initially received a cycle of CHOP, and sustained a severe rejection on day 16, requiring treatment. Immunosuppressives were again discontinued when this patient was switched to ProMACE CytaBOM; no further rejection episodes occurred over the following five cycles (patient 11).

Neutropenic sepsis occurred in 7 of 8 patients presenting later than 6 months who received chemotherapy. None had been septic at the outset of treatment. All episodes occurred in cycle 1; neutropenic sepsis was fatal in one case (patient 16).

**DISCUSSION**

This series of 19 patients differs from prior retrospective studies of posttransplant lymphoproliferation in that treatment, including chemotherapy, was administered in a relatively uniform fashion, and in that all patients had received the same type of organ transplant, further facilitating treatment uniformity.

Several attempts at formulating a clinicopathologic classification capable of predicting the course of disease and the likelihood of response to a reduction in immunosuppression have been made, but the categories defined overlap considerably. Among heart recipients, the interval since transplantation is the only factor that has been found to correlate with the likelihood of response to reduced immunosuppression, this measure proving largely ineffective for PTLD presenting a year or more after transplantation. We grouped the patients in our series on the basis of both clinicopathologic features and the interval since transplantation.

The mode of presentation and the response rate to reduced immunosuppression among patients presenting at less than 6 months after transplantation in our series are markedly at variance with what is reported for heart recipients from the University of Pittsburgh. An unusually large proportion of our patients presented very early after transplantation, with very extensive and rapidly progressive disease. This was most probably the result of intense immunosuppression with OKT3 during the early posttransplant period, an observation that has subsequently also been made in other series. Further, there is a statistically highly significant correlation between increasing cumulative OKT3 dose and shortening of the interval between transplantation and the appearance of PTLD. The increased incidence of PTLD after administration of OKT3, first identified in this series of patients, has resulted in modifications in the use of that drug at our transplant center and elsewhere. In the Pittsburgh series, disseminated disease at presentation was seen in only 23% of patients presenting early (<1 year), 89% responded to reduction in immunosuppressives, and mortality was only 36% (mainly among patients with disseminated disease). In our series, all patients presenting at less than 6 months after transplantation had widely disseminated disease, a much larger proportion than was seen among early patients in the Pittsburgh series. That alone could account for the much poorer outcome for our early patients. However, our poor results with chemotherapy in disease presenting early is very much in keeping with prior reports describing the use of cytotoxics in that setting. Other forms of treatment are clearly needed for such patients.

Our results with reduced immunosuppression in patients presenting late after transplantation, one partial response out of eight cases, closely parallel what has been seen in other series, despite our vigorous application of the concept. The majority of patients had complete discontinuation of immunosuppressives; having done that, logical end points that would allow assessment of the efficacy of the maneuver would be progressive disease, rejection, or CR. In all but three cases, those were the end points used. An empiric time limit was imposed on later cases in view of the sudden onset of at times fatal rejection in heart recipients, a risk that has probably been underestimated in prior reports.

On the other hand, our results with chemotherapy in late-presenting patients not amenable to local resection are considerably better than the approximately 80% mortality previously reported. Mortality during chemotherapy in our series was 25%, and the surviving patients all achieved CR. No patient has relapsed, at a median follow-up of 38 months. These results represent the best outcome for patients unresponsive to reduced immunosuppression of any series yet reported. The factors responsible for this favorable outcome are not clear.

We believe that the choice of ProMACE-CytaBOM as the preferred regimen and the ability to withhold immunosuppressives for the duration of chemotherapy may be significant factors. The use of immunosuppressives and the presence of the allograft are primarily what distinguish a heart recipient from an immunocompetent individual. Therefore, it seemed logical to consider those two elements as potential factors in the high mortality reported for chemotherapy. Azathioprine is significantly myelosuppressive, and the dose is normally maintained at a level that produces mild leukopenia. CSA therapy usually results in renal impairment, with moderate elevations in serum creatinine. The drug significantly affects the metabolism and elimination of several other drugs, including the few antineoplastics with which it has been studied.

ProMACE-CytaBOM is an effective regimen for aggressive NHLs. Although those data were not available at the time, ProMACE-CytaBOM did not cause significantly more fatal or life-threatening toxicity than did CHOP in a prospective randomized trial in the general population. The dosing schedule is such that drugs are administered for 2 of every 3 weeks (cytotoxics on day 1 and day 8, high-dose prednisone from day 1 to day 14, with the next cycle beginning on day 21). It seemed reasonable that such a regimen might be sufficiently immunosuppressive to maintain an allograft. Extremely close monitoring for rejection was nonetheless performed, with a MUGA in every cycle and, in all but the most recent patient, an endomyocardial biopsy in every cycle also. No rejection episode occurred in all cycles of ProMACE-CytaBOM. When tried once with CHOP, this strategy resulted in severe rejection by day 16. Standard ProMACE-CytaBOM dosages, dose reductions, and treatment delays were used. Neutropenic sepsis was confined to cycle 1, most cycles were delivered on an outpatient basis, treatment delays were rare, and colony-stimulating factors were
used only in the most recent patient. Serum creatinine normalized within about 1 month of stopping CsA in all patients.

ProMACE-CytaBOM delivers half the doxorubicin dosage per cycle compared with the CHOP regimen, making it an attractive regimen in heart recipients. However, no data existed on whether a cardiac allograft might be more sensitive to the cardiotoxic effects of doxorubicin. Prior studies of doxorubicin cardiotoxicity in the native heart have shown a dose-related increase in the frequency and severity of the electron micrographic myocardial abnormalities specific to doxorubicin. Few data exist for very low cumulative doses. In one series of 60 patients, the lowest cumulative dose at which morphologic changes were detected was 180 mg/m², and the lowest cumulative dose at which grade 3 changes were detected was 272 mg/m²; all patients who had received between 200 mg/m² and 300 mg/m² and manifested an abnormal biopsy furthermore had scores less than 1.20,21 Regression analysis was performed in a related series of 98 patients, linking cumulative doxorubicin dose and biopsy score. Cumulative doses of =100 mg/m² were associated with scores of =1, and cumulative doses of =200 mg/m² with scores of =1.5.22 In our series, more than half of the evaluable patients showed evidence of cardiac toxicity, by MUGA and/or biopsy assessment, at a mean cumulative dose of only 63 mg/m². The biopsied patients had a median biopsy score of 2.5 at a median cumulative exposure of 64 mg/m²; two of three patients with abnormal biopsy results experienced a significant reduction in LVEF by MUGA. Therefore, our data strongly suggest that a cardiac allograft is more sensitive to the toxic effects of doxorubicin than is the native heart. Our experience also indicates that clinical congestive heart failure can be avoided by means of close surveillance for cardiac toxicity.

Reduction in immunosuppression is currently the best initial therapy in patients presenting early, but even complete discontinuation of immunosuppressives appears to be insufficient for those with widespread disease. IFN-α2b has shown promising activity,33 but its efficacy, at present anecdotally, remains to be clearly defined.

Although it is a life-threatening maneuver, a trial of reduced immunosuppressives is currently viewed as the best initial therapy even in late-presenting cases, because success with this maneuver cannot be excluded in any specific individual, and because outcomes with the alternative, chemotherapy, have been so poor in the past as to have been considered virtually contraindicated in this setting.1 However, that situation would change if our favorable results with chemotherapy in late-presenting patients were validated in larger numbers. It is moreover likely that the routine use of G-CSF will further reduce the morbidity and mortality of chemotherapy.

A phase II clinical study in postcardiac transplant lymphoproliferation is currently being conducted by the Southwest Oncology Group. A sequential treatment approach is being tested, with acyclovir and controlled reduction in immunosuppression as the initial maneuver in disease not amenable to resection or involved-field radiation therapy, followed, if not successful at inducing remission in that patient, by a course of IFN-α2b, followed, if not successful, by ProMACE-CytaBOM with G-CSF.

REFERENCES


Aggressive treatment for postcardiac transplant lymphoproliferation

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