T-Cell–Rich B-Cell Lymphoma

By Jose Rodriguez, William C. Pugh, and Fernando Cabanillas

We analyzed 23 cases of T-cell–rich B-cell lymphomas (BCL) to determine if the clinical features are characteristic of a discrete entity. Cases encoded as T-cell–rich BCL in the hematopathology archives of the University of Texas M.D. Anderson Cancer Center between 1988 and 1991 formed the basis of this study. At least 50% of the total population of cells were required to be of T-cell phenotype. Actually, all but one patient had more than 70% T cells in the total population. Sixty-five percent of all cases were actually all but one patient had more than 70% T cells in the total population. Sixty-five percent of all cases were required to be of T-cell phenotype.

The major importance of identifying this entity is to distinguish it pathologically from other disorders such as Hodgkin’s disease and PTCL, which would be treated in a different manner.

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prednisone, bleomycin), CHOP-Bleo alternating with OPEN (On-
covin, prednisone, etoposide, Novantrone [mitoxantrone] [Le-
derle, Pearl River, NY]), and alternating triple therapy (ATT) with
ASAP (Adriamycin, Solu-Medrol [methylprednisolone] [Upjohn,
Kalamazoo, MI], ara-C [cytarabine], cisplatin), MBACOS (metho-
trexate, bleomycin, Adriamycin, cyclophosphamide, Oncovin,
Solu-Medrol), MINE (mesna, ifosfamide, Novantrone, etoposide).
Initial therapy also included MOPP (mechlorethamine, Oncovin,
procarbazine, prednisone), MOPP-ABVD (Adriamycin, bleomy-
cin, vinblastine, dacarbazine), or ABVD (two of which also in-
cluded local radiotherapy) for patients with a referring diagnosis of
Hodgkin’s disease. One patient received cyclophosphamide-pred-

Clinical features. Clinical features at presentation are de-
detailed in Table 1. Twenty-three patients comprised 12
women and 11 men, ranging in age, from 21 to 82 years
(median, 58). Eighteen patients presented with peripheral
lymphadenopathy, four with mediastinal adenopathy, and one
with no adenopathy. Eight patients had splenomegaly, which
was characterized as massive in two. Sites of extran-
domal involvement included liver, lung, colon, base of tongue,
central nervous system, and bone marrow. A primary vagi-
nal tumor was observed in one case. One patient had Ann
Arbor stage I disease, nine had stage II, five had stage III,
and eight had stage IV. Only six patients presented with B
symptoms. Tumor burden was assessed in accordance with
previously published institutional criteria. Five patients
were considered to have high tumor burden, eight interme-
diate, and 11 low. Using the same criteria, eight patients
were classified as having bulky disease. LDH was high in
eight of 19 patients in whom it was measured before ther-
apy. Serum β2-microglobulin levels were ≥3 mg/dL in six of
10 patients (normal, ≤2.0 mg/dL).

Response to therapy. Response to therapy is detailed in
Table 2. Of nine patients who were originally diagnosed
with non-Hodgkin’s lymphoma of various histologic types
and who were treated at their referring institutions, eight
received a doxorubicin-based regimen and one received sur-
gery. Of the eight who received chemotherapy, four (50%)
achieved a CR, two a PR, one a minor response, and one
was refractory to treatment. Of the four patients who
achieved a CR, two subsequently relapsed. Neither re-

turned to second-line therapy, and both died of disease.
The management of 5 of these 9 patients merits further
comment. One patient, diagnosed before referral as having
centrocytic lymphoma, was treated initially with cyclophos-
phamide, prednisone, and interferon, and sustained only a
minimal response. On transfer to our institution, the diag-
nosis was revised to T-cell–rich BCL. The patient was begun
on our standard alternating triple therapy (ATT) regimen.
She achieved a CR and was free of disease at 12 months of
follow-up. A second patient received only a single course of
Pro-MACE from an anticipated Pro-MACE-CytaBOM (cy-
tarabine, bleomycin, Oncovin, methotrexate) regimen because
of a severe allergic reaction. The treatment was
changed to CHOP after referral to M.D. Anderson. The
patient achieved a CR, but subsequently relapsed and re-
fused further chemotherapy. Two patients diagnosed with
large-cell lymphoma received MACOP-B. One patient did
not respond to this therapy, whereas the second achieved a
PR. Both patients’ disease failed to respond to salvage treat-
ment at our institution. Finally, the ninth patient was still in
CR 8 months after a right hemicolectomy and partial ileec-
tomy for intestinal lymphoma that involved regional lymph
nodes. No adjuvant therapy was administered.

Six patients were diagnosed with Hodgkin’s disease at
their referring hospitals. Of these, four patients were treated with MOPP, MOPP-ABVD, or ABVD before coming to our institution. Three of these four patients died of disease. Two initially attained a CR, but relapsed within 12 months of starting treatment.

Eight patients had been initially evaluated and treated at M.D. Anderson. Three are currently receiving therapy and are not assessable for response. All five remaining patients are not assessable for response. All five remaining patients are currently receiving therapy.

In summary, of the 13 patients treated with regimens considered standard for intermediate grade lymphomas, nine (70%) attained a CR. At the time of this report, eight of these (62%) were alive with no evidence of disease (median follow-up, 8 months).

**DISCUSSION**

The occurrence of clonal B-cell neoplasms with a preponderant infiltrate of presumably reactive T lymphocytes was first recognized by Jaffe et al. Their description of T-cell–rich BCL was coined by Ramsay et al, who described five B-cell lymphomas in which clonal B cells were estimated to comprise less than 10% of lymphoid cells. A relatively large series of T-cell–rich BCL composed of 19 cases was recently published by Macon et al. These findings are parallel to ours in regard to the confusion with other histologic types and the favorable response to therapy when treated appropriately. Because of the paucity of neoplastic cells, histologic examination and evaluation of light-chain restriction may be insufficient to establish a diagnosis of T-cell–rich BCL. Osborne et al found Southern blotting to be a consistently reliable and definitive method of distinguishing such cases from peripheral T-cell lymphoma. However, clonal proliferations accounting for less than 5% of a cell population may be difficult to detect by conventional Southern blot analysis. Special modifications of the polymerase chain reaction using primers for complementary determining regions and consensus JH and variable region sequences have proven useful in our hands in documenting the presence of B-cell clones that elude detection by Southern blotting (unpublished observations, February 1992).

The patient population reported herein exhibited clinical features and responses to doxorubicin-based regimens that were comparable to those of B-cell large cell lymphoma of usual type. The 35% incidence of splenomegaly was higher than expected and is perhaps a characteristic clinical sign. However, the number of patients was small, and the potential clinical importance of splenomegaly will require examination in larger patient cohorts. A long history of localized peripheral adenopathies, as noted by Cooper et al, was not seen in our series. Conclusions about therapeutic response are limited by the number of patients and the short follow-

**Table 2. Response to Therapy**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Treatment</th>
<th>1st Line</th>
<th>2nd Line</th>
<th>Relapse</th>
<th>Status</th>
<th>Follow-up (mo)</th>
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<tr>
<td>1</td>
<td>CYT/PRED, IFN, ATT</td>
<td>MR</td>
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<td>A, NED</td>
<td>32+</td>
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<tr>
<td>2</td>
<td>MOPP-Bleo/XRT; MOPP-ABV/XRT</td>
<td>PR</td>
<td>PR</td>
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<td>DD</td>
<td>11</td>
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<tr>
<td>3</td>
<td>DNAP/CHOD</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
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</tr>
<tr>
<td>4</td>
<td>CHOP-Bleo/OPEN</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
<td>13+</td>
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</tr>
<tr>
<td>5</td>
<td>CHOP/XRT</td>
<td>PR</td>
<td>NR</td>
<td>Y</td>
<td>AWD</td>
<td>18+</td>
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<tr>
<td>6</td>
<td>Surgery</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
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</tr>
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<td>7</td>
<td>MACOP-B/MINE/ESHAP</td>
<td>CR</td>
<td>NR</td>
<td>Y</td>
<td>DD</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Pro-MACE/CHOP</td>
<td>NR*</td>
<td>CR</td>
<td>Y</td>
<td>AWD</td>
<td>23+</td>
</tr>
<tr>
<td>9</td>
<td>ATT</td>
<td>CR</td>
<td>N</td>
<td>A, NED</td>
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<tr>
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<td>A, U</td>
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<td>CR</td>
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<td>DD</td>
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<td>PR</td>
<td>Y</td>
<td>DD</td>
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<tr>
<td>14</td>
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<td>A, NED</td>
<td>7+</td>
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</tr>
<tr>
<td>20</td>
<td>ATT</td>
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<td>U</td>
<td>A</td>
<td>2+</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>ABVD; MINE/ESHAP</td>
<td>CR</td>
<td>U</td>
<td>Y</td>
<td>A</td>
<td>8+</td>
</tr>
<tr>
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<td>CHOP/OPEN/XRT</td>
<td>U</td>
<td>U</td>
<td>A</td>
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<td></td>
</tr>
<tr>
<td>23</td>
<td>CHOP/OPEN</td>
<td>U</td>
<td>U</td>
<td>A</td>
<td>1+</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A, alive; ATT, alternating triple therapy; AWD, alive with disease; CR, complete response; CYT, cytarabine; DD, dead of disease; IFN, interferon; NED, no evidence of disease; N, no; NR, no response; PR, partial response; PRED, prednisone; U, unassessable (currently receiving treatment); XRT, radiotherapy; Y, yes.
up interval. Of 13 patients treated with standard regimens for intermediate-grade lymphomas, 9 (70%) achieved a CR, a result consistent with the norm. The clinical significance of the preponderant T-cell response that characterizes these lymphomas is uncertain. Various investigators have postulated a host-immune response to the neoplastic clone, analogous to that seen in Hodgkin's disease. In keeping with this hypothesis is the observation by some that the T-cell reaction tends to diminish as the disease progresses and escapes immune surveillance. Alternatively, it could represent a response of the reactive T cells to some cytokine secreted by the tumor cells. In our study, histologic progression to large cell lymphoma of usual type was noted in 9 of 11 cases in which multiple biopsies, either from different sites or from different times, were studied. In four instances, this was observed in concurrent biopsies from different anatomic sites, and in five patients progression was observed over periods ranging from a few weeks to 10 months. Thus, T-cell-rich histology apparently is a highly unstable parameter of this disease. If this is true, it is not surprising that T-cell-rich BCL exhibits a clinical behavior that closely parallels that of B-cell large cell lymphoma of usual type.

Based on the foregoing and the accumulated experience to date, it would seem that the critical issue in T-cell-rich BCL is the need to distinguish it pathologically from Hodgkin's disease and other non-Hodgkin's lymphomas, principally peripheral T-cell lymphomas, with which it may be easily confused. Underscoring this imperative is the fact that six of our cases were referred with diagnosis of Hodgkin's disease. Of the four patients who received treatment based on this diagnosis, three have died of disease. Thus, the administration of inadequate initial therapy may compromise the potential for salvage and long-term survival. In summary, many aspects of T-cell-rich BCL remain unsolved. Among these are the precise immunophenotype and modulatory role of the infiltrating T cells and the question of whether, with longer follow-up, the response to therapy (including time to treatment failure and overall survival) will differ significantly from that obtained in patients with diffuse large-cell lymphomas of usual type. Prospective studies with more patients and sufficient follow-up periods will be required to answer these queries; however, the preliminary data presented herein do not support the contention that the T-cell-rich infiltrate exerts a significant clinical impact on the behavior of large cell lymphomas of B lineage.

REFERENCES

T-cell-rich B-cell lymphoma

J Rodriguez, WC Pugh and F Cabanillas