Bcl-2, Bcl-X, Bax, and Bak Expression in Short- and Long-Lived Patients with Diffuse Large B-Cell Lymphomas

Osnat Bairey, Yael Zimra, Mati Shaklai, Elimelech Okon, and Esther Rabizadeh

Institute of Hematology and Pathology [O. B., O. Z., M. S., E. O.] and Felsenstein Medical Research Center [O. B., Y. Z., M. S., E. R.], Rabin Medical Center, Petah Tiqva 49100, Israel, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel [O. B., M. S., E. O.]

ABSTRACT

Long-term cure is now possible for ~50% of all patients with aggressive non-Hodgkin’s lymphoma (NHL). Apoptosis-related proteins play an important role in the chemosensitivity or chemoresistance of tumors. We examined the role of Bcl-2 family proteins in aggressive NHL. We retrospectively selected two groups of patients by clinical outcome: 24 patients with chemoresponsive disease and long survival (median, 88 months); and 20 patients with chemoresistant disease and short survival (median, 8 months). The expression of the apoptosis-regulating proteins, Bcl-2, Bcl-X, Bax, and Bak, in the initial biopsy samples was examined with immunohistochemical methods. Specimens containing >10% immunostained tumor cells were considered immunopositive. An inverse association was found between length of patient survival and expression of Bcl-2, Bcl-X, and Bax. Bcl-2 was expressed in 75% of short-lived patients but in only 42% of the long-lived ones (P = 0.026). Bcl-X expression was also higher in the short-lived patients (40% versus 12.5%; P = 0.036). Unexpectedly, Bax expression was strongly associated with short survival (60% versus 21%; P = 0.008). Several combinations of protein expression, i.e., Bcl-2 with Bax, Bcl-2 with Bcl-X, and Bcl-X with Bax, were different between the groups: a positive expression of these proteins was found in the short-lived patients. Furthermore, a strong association was found between the expression of Bcl-2 and Bcl-X, suggesting that Bcl-X potentiates rather than replaces the effect of Bcl-2 in NHL. In diffuse large B-cell NHL, Bcl-2, Bcl-X, and Bax expression alone or in combination is associated with chemoresistance and short-term survival.

INTRODUCTION

NHL is one of the tumors with increasing incidence, with ~53,000 new cases diagnosed annually in the United States (1). Diffuse forms of large B-cell NHL are the most common types of lymphomas, comprising 31% of all NHL (2). They have heterogeneous clinical features and vary markedly in response to treatment and in prognosis. These NHL are among the few aggressive tumor types that are curable with chemotherapy alone, suggesting that the tumor cells undergo apoptosis in response to treatment. NHL patients with similar histology types show marked differences in probabilities of survival; about 40–50% enjoy long-term disease-free and overall survival, 20–30% have resistant disease, and the remainder respond to chemotherapy but have only short-term disease-free survival.

Evidence has accumulated in the last few years that many and perhaps all agents of cancer chemotherapy affect tumor cell killing in vitro as well as in vivo by inducing apoptosis (3). Tumors that are intrinsically resistant to chemotherapy are unable to activate the apoptotic machinery and may therefore be fundamentally resistant to chemotherapeutic cell death. Many cancer cells circumvent the normal apoptotic mechanisms to prevent their self-destruction. The Bcl-2 protein, because of its antiapoptotic effects, is considered to be an important multidrug resistance agent. Bcl-2 is a member of a family of related and interacting proteins, some of which (e.g., Bcl-XL) are antiapoptotic as well, whereas others (e.g., Bax, Bak, Bcl-XS, Bik, and Bid) display proapoptotic functions (4–6). These proteins are known to dimerize with themselves or with each other, and it is thought that if this balance favors the presence of free Bcl-2, apoptosis is inhibited, whereas when Bax predominates, apoptosis is initiated. Thus, the ratio of the antiapoptotic to the proapoptotic proteins determines whether a given cell will respond to or ignore an apoptotic stimulus. Given the existence of multiple dimeric partners, the identity of the precise complex that actively regulates the death pathway remains unclear.

Several studies have assessed the association between Bcl-2 expression and disease-free survival in aggressive NHL (7–12). The first studies showed little impact on survival; the more recent ones suggested that Bcl-2 protein expression is an important predictor of short disease-free survival. A significant effect on overall survival has been documented in only one study (12). In the present study, we have attempted to establish whether the expression of apoptosis-related proteins in the presenting tumor in NHL can serve as a predictor of apoptosis and response or resistance to chemotherapy. For this purpose, we retrospectively selected two groups of patients from the large B-cell NHL population treated at our medical center, long-term and short-term survivors, and compared immunohistochemical...
cally the expression of several Bcl-2 family proteins in the biopsy tissue.

PATIENTS AND METHODS

Patient Selection. All patients with aggressive B-cell lymphoma [diffuse mixed, diffuse large-cell, and diffuse immunoblastic lymphoma according to the Working Formulation, or large B-cell NHL as defined by the Revised European-American Lymphoma classification (13)] treated at the Institute of Hema-

tology, Rabin Medical Center, Beilinson Campus, between 1983 and 1997 were considered for the study. From this cohort, we selected patients for whom adequate pathological specimens were available for analysis and who met one of our two clinical outcome criteria: complete remission and long-term survival (>3.5 years); or resistant disease with death soon after diagnosis (survival time, <1.5 years). Patients with known transformation from a low-grade lymphoma were excluded. In addition to clinical parameters and treatment modalities, the outcome was also recorded. Follow-up data were updated for surviving pa-

Immunohistochemistry. Biopsy specimens from the time of initial presentation were chosen. All specimens were archival material that had been fixed in neutral-buffered formalin and embedded in paraffin by routine methods. The tumors were stained with H&E and classified histologically by an expert hematopathologist. Paraffin-embedded tumor specimens were cut into 5 μm sections and mounted on glass slides pre-
treated with aminopropyltriethoxy (Silane; Sigma Chemical Co., St. Louis, MO). Deparaffinization and hydration were performed through xylenes and graded alcohol series. Endoge-
nous peroxidase activity was then blocked by incubation for 15 min at room temperature in 3% H2 O2 in methanol. After wash-

ing with PBS, the slides were incubated overnight at 4°C either with monoclonal anti-Bcl-2 (Dako, Glostrup, Denmark) as the primary antibody, at a dilution of 1:20 in PBS, or with polyclonal antisera specific for Bax, Bak, and Bcl-X pro-
teins (Oncogene Research, Cambridge, MA), at a dilution of 1:20. Staining was completed with the Strept A-B immunoper-
oxidase staining universal kit (DPC, Llanberis, United King-
dom) according to the manufacturer’s instructions, followed by light staining with hematoxylin. Identical slides with horse serum instead of primary antibody were used as controls for nonspecific binding. For positive controls, we immunostained sections of tissue known to be immunopositive for the specific antibody (e.g., follicular lymphoma for Bcl-2 and colon adenocarcinoma for Bcl-X, Bax, and Bak) for side-by-side compari-
son in the same experiment.

Immunohistological Scoring. The areas of highest protein expression evident at low-power scanning were taken for analysis. Staining was considered negative only after careful examination of the entire tissue section under high power (×1000). Quantitation of the number of positive tumor cells was performed simultaneously by two investigators (O.B. and Y.Z.) blinded to the clinical outcome. A double-headed light microscope was used to score at least 500 cells in high-power fields. In cases in which the investigators disagreed, the immuno-

histochemical staining was repeated, and a third reviewer scored the slides in a blinded fashion. Specimens that contained >10% immunostained tumor cells were defined as immuno-

positive; those with ≤10% were defined as immunonegative.

Statistical Analysis. Statistical analysis was performed using an SPSS statistical software program (SPSS, Inc., Chi-

cago, IL). Either t test (for mean age) or χ2 analysis was used for statistical comparison of the clinical characteristics between the short-lived and long-lived patients and of immunostaining re-

sults. Stepwise logistic regression was used as multivariate analysis to find which parameter correlates best with the group to which the patients belong (long-lived or short-lived).

RESULTS

Characteristics of the Patient Population

Twenty-four patients met the criteria for the long-survival group (median, 88 months), and 20 met the criteria for the short-survival group (median, 8 months). Their clinical and pathological characteristics are described in Table 1. There were no significant between-group differences in mean age, sex, pathological classification, initial treatment protocol, or tumor bulkiness (size, >6 cm). As expected by our patient selection, there was a significant difference in clinical parameters shown by the International NHL Prognostic Factor Project (14) to have a prognostic impact. All long-lived patients had a favorable IPI score of 0–2, whereas 80% of the short-lived patients had an unfavorable IPI score of 3–5 (P = 0.00001). Clinical stage distribution also showed a significant difference, with 83% of the long-lived patients in stages I and II and 85% of the short-

lived patients in stages III and IV (P = 0.00001). Only 17% of the long-lived patients had B symptoms compared with 70% of the short-lived patients (P = 0.0003), and only 21% of the long-lived patients had high LDH levels compared with 80% of the short-lived patients (P = 0.00009).

Expression of Bcl-2 Family Proteins in the Entire Patient Population

The biopsy specimens from all 44 patients were success-

fully immunostained for all four antibodies (Bcl-2, Bcl-X, Bax, and Bak). Thirty-one sections showed positive staining to at least one antibody; negative sections (<10% stained cells) showed only scattered positive cells or internal positive control stained by normal cells. The Bcl-2 family proteins were detected in the cytoplasm, sometimes in a granular pattern typical of these proteins, which are usually associated with cytosolic organelles such as mitochondria and endoplasmic reticulum. Of the entire group of 44 samples, 25 (57%) showed Bcl-2 staining, 11 (25%) showed Bcl-X staining, 17 (39%) showed Bax staining, and 16 (36%) showed Bak staining.

Analysis of coupled protein expression yielded high associ-
ation between Bcl-2 and Bcl-X (P = 0.0008), with both being negative in 19 samples (43%) and positive in 11 samples (25%). The remaining 14 samples were positive only for Bcl-2; inter-
estingly, no sample was Bcl-X positive and Bcl-2 negative. There was also an association between Bcl-X and Bak expression (P = 0.049) and between Bcl-X and Bak expression (P = 0.029). A trend for an association was found between Bcl-2 and
Bak, Bax and Bak, but no coupling was found for Bcl-2 with Bax.

Expression of Bcl-2 Family Proteins by Patient Group

Single Protein Expression

The percentages of Bcl-2, Bcl-X, Bax, and Bak immunopositive tumor cells in the samples from each group are shown in Fig. 1. The percentages of immunopositive samples in each group is shown in Fig. 2. A significant inverse relationship was found between length of patient survival and expression of three of the Bcl-2 family proteins, Bcl-2, Bcl-X, and Bax (Fig. 2). Bcl-2 was expressed by 75% of the short-lived patients but only 42% of long-lived patients (P = 0.026). Bcl-X expression was also significantly higher in short-lived patients (40% versus 12.5% positive; P = 0.036). Unexpectedly, Bax expression was associated with short survival, with 60% of the nonresponsive, short-lived patients expressing Bax compared with only 21% of the responsive, long-lived ones (P = 0.008). The expression of Bak was similar in the two groups (40 and 33%, respectively).

Combined Protein Expression

Several combinations of Bcl-2 protein family expression (concomitant presence in the same specimen) were found to be significantly different between the short- and long-lived NHL patients: Bcl-2 and Bax; Bcl-2 and Bcl-X; and Bcl-X and Bax (Table 2). Other combinations showed either a borderline association (Bax and Bak) or no association (Bcl-2 and Bak; and Bcl-X and Bak) with a specific group of patients.

Bcl-2 and Bax. A strong association was found between concomitant expression of Bcl-2 and Bax and short-term survival (P = 0.0002). In the short-lived group, only four patients (20%) did not express these proteins, and 11 patients (55%) were positive for both. By contrast, in the long-lived group, 10 patients (42%) had negative staining for both Bcl-2 and Bax, whereas only one (4%) stained positively for both. That is, of the 12 patients who expressed both Bcl-2 and Bax, 11 (91.7%) were short-lived, and only 1 (8.3%) was long-lived.

Bcl-2 and Bcl-X. A negative finding for both these proteins (Bcl-2− and Bcl-X−) was associated with long survival, and a positive finding (Bcl-2+, Bcl-X+) was associated with

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**Table 1** Characteristics of short- and long-lived NHL patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 44)</th>
<th>Short-lived patients (n = 20)</th>
<th>Long-lived patients (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>57.5</td>
<td>58.7</td>
<td>56.5</td>
<td>NS*</td>
</tr>
<tr>
<td>Range (yr)</td>
<td>20–81</td>
<td>20–79</td>
<td>33–81</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20 (45.5%)</td>
<td>10 (50%)</td>
<td>10 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>24 (54.5%)</td>
<td>10 (50%)</td>
<td>14 (58%)</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse mixed</td>
<td>4 (9%)</td>
<td>3 (15%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse large cell/immunoblastic</td>
<td>38 (86%)</td>
<td>16 (80%)</td>
<td>22 (92%)</td>
<td>NS</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>2 (5%)</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>16 (36%)</td>
<td>2 (10%)</td>
<td>14 (58%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (16%)</td>
<td>1 (5%)</td>
<td>6 (25%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>7 (16%)</td>
<td>3 (15%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>14 (32%)</td>
<td>14 (70%)</td>
<td>0 (0%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>26 (59%)</td>
<td>6 (30%)</td>
<td>20 (83%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>B</td>
<td>18 (41%)</td>
<td>14 (70%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (25%)</td>
<td>0 (0%)</td>
<td>11 (46%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (21%)</td>
<td>3 (15%)</td>
<td>6 (25%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (18%)</td>
<td>1 (5%)</td>
<td>7 (29%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (14%)</td>
<td>6 (30%)</td>
<td>0 (0%)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>4</td>
<td>5 (11%)</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 (11%)</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Median survival (months + SD)</td>
<td>43.5 (51.4)</td>
<td>8 (7.6)</td>
<td>88 (39.9)</td>
<td></td>
</tr>
<tr>
<td>Organ biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal</td>
<td>33 (75%)</td>
<td>12 (60%)</td>
<td>21 (87.5%)</td>
<td>0.036</td>
</tr>
<tr>
<td>Extranodal</td>
<td>11 (25%)</td>
<td>8 (40%)</td>
<td>3 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>LDH levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>(52%)</td>
<td>4 (20%)</td>
<td>19 (79%)</td>
<td>0.00009</td>
</tr>
<tr>
<td>Above normal</td>
<td>21 (48%)</td>
<td>16 (80%)</td>
<td>5 (21%)</td>
<td></td>
</tr>
<tr>
<td>Initial treatment protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACOP-BB</td>
<td>13 (29.5%)</td>
<td>4 (20%)</td>
<td>9 (37%)</td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>25 (57%)</td>
<td>15 (75%)</td>
<td>10 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>6 (14%)</td>
<td>1 (5%)</td>
<td>5 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

* NS, not significant.

* MACOP-B, methotrexate, doxorubicin (Adriamycin), cyclophosphamide, vincristine, prednisone, and bleomycin.

* CHOP, cyclophosphamide-doxorubicin (Adriamycin)-vincristine-prednisone.
short survival. As mentioned, no patient was Bcl-2 negative and Bcl-X positive.

**Bcl-X and Bax.** An association similar to that for Bcl-2 and Bcl-X was found for the combination of Bcl-X and Bax expression.

**Association Between Clinical Parameters and Bcl-2 Family Proteins**

A direct association was found between Bax expression and disease stage. Bax was positive in 22% of the samples from patients in stages I and II and in 57% of those from patients in advanced stages III and IV (P = 0.016). A similar association was found for Bax expression and LDH, with Bax positivity noted in 22% of patients with normal LDH but in 57% of patients with elevated LDH levels (P = 0.016).

**Multivariate Analysis for Predicting Survival**

The variables entered into stepwise logistic regression were: Bcl-2, Bcl-X, and Bax staining; disease stage (I, II versus III, IV); LDH level (above or below normal); and IPI (0–2 versus 3–5). The results showed that the best predictor of survival (long) was IPI (coefficient, –21.1; P < 0.0001), followed by Bcl-X staining (coefficient, –3.045; P = 0.011).

**DISCUSSION**

In this work, we studied the expression of Bcl-2 family proteins (Bcl-2, Bcl-X, Bax, and Bak) in tissues from long-lived patients with chemosensitive NHL and short-lived patients with chemoresistant NHL. The high curability of NHL large-cell type with chemotherapy allowed us the rare opportunity to study the reasons for the success or failure of the present chemotherapeutic approach in patients with similar pathology. Bcl-2 and Bcl-X...
proteins are implicated in multidrug chemoresistance in tumors. Individual cell types vary considerably in their levels of the Bcl-2 family members. Bcl-2, the most thoroughly investigated, is a potent suppressor of apoptosis and is found at inappropriately high levels in probably >50% of all cancers in humans (15). Moreover, the relationship between Bcl-2 and chemoresistance has been borne out by clinical correlative studies showing that elevated expression of this protein may be associated with short survival and other indicators of poor clinical outcome in patients with several types of cancer, including aggressive NHL (8–12), acute myelogenous leukemias (16), and adenocarcinomas of the prostate (17).

We found that short-lived NHL patients had significantly higher expression of Bcl-2 and Bcl-X than the long-lived ones. It should be pointed out, however, that antibodies that discriminate among the various forms of Bcl-X protein, produced as a result of alternative mRNA splicing, are not yet available. Still, in all normal tissues surveyed and in all tumors examined to date, by far the most abundant form of Bcl-X is the antiapoptotic Bcl-XL, and very little, if any, of the proapoptotic Bcl-XS (18). In addition, reverse transcription-PCR study has revealed that Bcl-X mRNA is the predominant isofrom in lymphoid tumors (19). For this reason, we speculate that the immunostaining we observed when using anti-Bcl-X antibodies reflects predominantly the presence of Bcl-XL.

The concomitant, coupled expression of Bcl-2 and Bcl-X was associated with short survival, and its absence was associated with long survival (Table 2). These results are in line with the assumed antiapoptotic role of Bcl-2 and Bcl-X deduced from in vitro studies (15, 20).

Recent studies indicate that Bcl-2 and Bcl-X can regulate apoptosis by different mechanisms. Some researchers propose that Bcl-X may either replace or potentiate the antiapoptotic effect of Bcl-2 (21). Because in our work none of the tumor samples were simultaneously negative for Bcl-2 but positive for Bcl-X, although many of the samples from the short-lived group expressed both of them, we suggest that in aggressive NHL, Bcl-X potentiates rather than replaces the effect of Bcl-2. This observation should be taken into consideration in the design of novel therapeutic interventions that target only on Bcl-2, such as antisense oligonucleotides (22–25), because abolishing this protein may leave the Bcl-X active and the cells resistant to chemotherapy.

In vitro studies have led to the conclusion that Bax is a proapoptotic protein (26–28). Experiments with transgenic knockout mice indicated that Bax deficiency can be manifested as hyperplasia or hypoplasia, depending on the cellular context (29). We found that Bax expression is associated with short survival. Our results, and those of others in patients with different tumors, seem to be contrary to the conclusions reached from the in vitro studies. In patients with radically resected stage I non-small cell lung cancer, longer survival was noted in those whose tumors expressed both Bax and Bcl-2 than patients whose tumors expressed only Bax (30). Likewise, aggressive thyroid carcinomas coexpressed Bcl-2 and Bax, whereas anaplastic thyroid carcinomas expressed only the Bax protein (31).

Other authors reported the same picture in in situ and invasive duct breast carcinomas (32), although one report in patients with advanced breast cancer showed the contrary (33). In tumors of nervous system origin (34), Bax immunostaining was typically higher in more advanced tumors compared with earlier stage neoplasms. Thus, of immunohistochemical studies conducted over the past 3 years in vivo, Bax expression is associated with more undifferentiated and aggressive tumors.

While this report was in preparation, Gascoyne et al. (35) reported on the prognostic significance of Bax protein expression in diffuse, aggressive, advanced-stage NHL. They defined sections as Bax immunonegative if there was no staining of large neoplastic cells and as low positive if there was staining of 1–10% of the cells. They found that Bax expression by itself was not of apparent prognostic significance. However, among the subgroup of patients with Bcl-2-positive tumors, a higher percentage of Bax-immunostained tumor cells (>10%) was associated with shorter survival. This is similar to our finding. These authors noted that their results seem counterintuitive, based on the notion that Bax promotes apoptosis. They therefore suggested that Bcl-2 and Bax may collaborate in the suppression of cell death, presumably by forming heterodimers. Another theory they raise for the paradoxical association of lower levels of Bax with better outcome is that Bcl-2 overexpression can slow cell cycling in the G1 phase of the cell cycle in at least some types of cells, and Bax can overcome this checkpoint.

Recently, Meijerink et al. (36) found that hematopoietic malignancies possess mutation in Bax. Although highly speculative, another potential explanation of our findings is that in the group of short-lived NHL patients, the overexpressed Bax was mostly mutated, although it still preserved its antigenic capabilities.

The expression of Bcl-2, Bcl-X, Bax, and Mcl-1 in NHL was described for the first time by Sclaifer et al. (37). Interestingly, they noted that all Bax-positive tumors expressed either Bcl-2 or Mcl-1 antiapoptosis proteins, suggesting that the presence of Bax in the tumor cells must be associated with apoptosis-inhibiting proteins for allowing malignant cell survival.

Multivariate analysis of our findings (clinical parameters and Bcl-2 protein family expression) showed that the best pre-
dictor of outcome remains the readily available IPI index. Although Bcl-X staining by itself is a somewhat poorer prognostic indicator than IPI, it may add to its predictive value.

In summary, our findings demonstrate that in diffuse large B-cell NHL, the expression of Bcl-2, Bcl-X, and Bax proteins, singly or in combination, is associated with a chemoresistant, short-lived group of patients. This study is based on a small number of selected patients with an opposite clinical outcome; it should be confirmed in the future with a prospective analysis of a larger cohort of uniformly treated patients, and multivariate analysis will need to be performed to determine whether Bcl-X staining is an independent prognostic variable that may be used to aid treatment stratification.

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