Advanced ovarian cancer is characterized by poor prognosis and the development of resistance to chemotherapy. We have found that Bcl-2 and p53, two proteins implicated in the control of apoptosis, are differentially expressed in the ovarian cell line A2780 and its cisplatin-resistant variant 2780CP, with the resistant line overexpressing both proteins. Transfection of the A2780 cells with a Bcl-2- or p53-expressing plasmid increases resistance to various drugs, including cisplatin, suggesting that Bcl-2 and p53 expression may influence the sensitivity of ovarian cancer cell lines to chemotherapy. Expression of these two proteins in vivo was determined by immunohistochemical staining of ovarian tumor biopsies from 70 patients. We found that Bcl-2 and p53 were expressed in 57 and 61% of specimens examined, respectively. Both p53 and Bcl-2 were found to be independent prognostic indicators of survival in ovarian cancer. Survival was poorer in patients with tumors expressing high levels of p53, whereas expression of Bcl-2 was associated with improved survival.

INTRODUCTION

The efficacy of cancer chemotherapy is restricted by the ability of tumors to resist or develop resistance to treatment. Ovarian cancer shows high response rates to first-line chemotherapy but is characterized by recurrence and the development of resistance to chemotherapy. Therefore, prognosis is poor, with only a minority of patients surviving 5 years. Resistance to chemotherapy has been associated with decreased susceptibility to apoptosis (1, 2), raising the possibility that cell death determinants may influence the outcome of treatment.

The Bcl-2 gene, the first negative regulator of cell death to be identified, was discovered through the t(14:18) translocation, which frequently occurs in B-cell lymphomas (3). The t(14:18) translocation juxtaposes bcl-2 with the immunoglobulin heavy chain locus, resulting in deregulation of expression (4). The mechanism of action of the Bcl-2 protein has not been fully defined but may involve oxidative phosphorylation and/or mitochondrial electron and metabolite transport (5), and its main effect is to prolong cell survival by avoidance of apoptosis (6–8).

Stem cells in epithelia, neurons, and memory B cells all express Bcl-2. In epithelial tissues, which are continually renewed, Bcl-2 expression in the basal layers of the epithelium but is lost as cells approach the surface of the epithelium prior to undergoing apoptosis (9). Bcl-2 is also expressed in glandular cells, such as those in the female breast, in which regulation of hyperplasia and involution may thus allow uncontrolled growth of damaged cells. Indeed, accumulation of the protein has been shown to be a prognostic marker of reduced survival in breast, gastric, and non-small cell lung cancer (19, 20). Whereas the expression of wild-type p53 can induce cell death or growth arrest in a number of cell systems (21, 22), expression of a mutated form of the protein in hematopoietic cells has been shown to protect against apoptosis induced by chemotherapeutic agents (7). Furthermore, fibroblasts from Li-Fraumeni patients heterozygous for a p53 mutation are radioresistant (23), suggesting that the loss of function of p53 could have an effect similar to that of the gain of function of Bcl-2.

Given the apparent role of Bcl-2 and p53 expression in oncogenesis and resistance to chemotherapy, we decided to establish whether Bcl-2 and p53 are expressed in ovarian carcinoma and whether expression of these genes has any prognostic significance or relationship to the response to chemotherapy.

MATERIALS AND METHODS

Cell Lines, Plasmids, and Transfections. The human ovarian carcinoma cell line A2780 and its cisplatin-resistant subclone 2780CP (24) were maintained in DMEM (Life Technologies, Inc., Uxbridge, United Kingdom) supplemented with 10% FCS (Flow Laboratories, Irvine, United Kingdom). The A2780 cell line was transfected with the plasmid pCMV-bcl2 (25), carrying the human bcl-2 cDNA or with a control plasmid only, using the calcium phosphate technique. Stable transfectants resistant to the selective marker gene bicin G418 (Life Technologies) were obtained. The A2780 cells were also cotransfected with the plasmids pLTRGval135, expressing a ts mutant p53 (tsp53) (kindly provided by Prof. M. Oren, Weizmann Institute of Science, Rehovot, Israel; Ref. 22), and pSV2gpt, conferring resistance to mycophenolic acid, or they were cotransfected with the control plasmid pSV2gpt.

Received 9/11/95; accepted 3/4/96.

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1 Supported by the Cancer Research Campaign of Great Britain.
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3 Supported by Asta Medica (Frankfurt, Germany) and the Local Endowment Fund (Birmingham, United Kingdom).

4 The abbreviations used are: ts, temperature sensitive; MTT, 3-(4,4-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; IC50, 50% inhibitory concentration; CI, confidence interval.
only, and resistant clones were isolated. Expression of Bcl-2 and p53 in the above transfectants was verified by Western blot analysis of cell protein extracts using a monoclonal anti-Bcl-2 antibody (Bcl-2:124; DAKO Diagnostics, Ely, United Kingdom) and the polyclonal SAPO antibody (kindly provided by Prof. D. Lane, Department of Biochemistry, University of Dundee, Dundee, United Kingdom), which recognizes both human and mouse p53. Immunoblots were performed as described previously (26).

**MTT Assay for Cytotoxicity.** The cytotoxic effects of cisplatin (Bristol-Myers, Syracuse, NY); lobaplatin (Asta, Frankfurt, Germany), a DNA-intercalating agent, were estimated using the MTT colorimetric assay of Mosmann (27). Cells were trypsinized and plated out at a density of 3000-4000 cells/well into a 96-well plate and allowed to attach overnight. They were then treated for 2 h with various drug concentrations before washing with PBS and adding 200 μl fresh medium. Forty-eight h later, 20 μl 5 mg/ml MTT (Sigma) in PBS were added to each well and incubated for 5 h at 37°C, and the formazan crystals formed were dissolved in DMSO. The absorbance was recorded at 550 nm, and the IC₅₀ values were calculated as the drug concentrations inducing a 50% reduction in absorbance.

**Patients and Tissue Specimens.** Representative paraffin-embedded tissue specimens were obtained from a subset of 70 of the 362 patients entered into the West Midlands second-look laparotomy and intervention debulking surgery trials (28, 29). The 8 patients who remain alive have a median follow-up of 7 (range, 4.5–10) years. Patients selected were those for whom a complete code specimens prior to statistical analysis. Specimens that displayed no either positive or negative staining and also according to the percentage of cells that were positively stained. A three-level classification system was used to rule out that this represented an epiphenomenon not significantly contributing to the two extremes, were classified as weakly positive (<75% stained cells). Statistical Methods. All analyses were carried out using SAS statistical software (SAS Institute, Inc., Cary, NC). Survival curves were calculated by the product-limit method (31), and the log-rank test (31) was used to test for differences between the curves. The χ² test was used to test for association between clinical response and p53 and between clinical response and Bcl-2. Survival has been calculated from the date of randomization to death. Patients were censored to January 1, 1994.

The Cox proportional hazards method was used to build a multivariate model for survival to identify independent prognostic factors and to assess relative risks. The model was built up using forward selection of variables and a significance level of 5%; i.e., first, find the single variable that gives the best model, as judged by −2 × logL; then, find the pair of variables that give the best model, until the addition of variables no longer adds significantly to the model. The proportionality assumption of the model was tested graphically by plotting the log[−logS(t)] against logt. Stability of the model was assessed by repeating the analysis without each variable in turn. Relative hazard ratios and their CIs were calculated from the regression coefficients. Predicted survival curves were then calculated from the final model to illustrate the effect of Bcl-2 and p53 on survival.

For assessment of the influence of p53 expression on prognosis, we chose to compare cases in which at least 75% of the tumor cells showed detectable p53 expression with the remaining cases, which were either p53 negative or expressed p53 in a smaller fraction of cells. We reasoned that in the first group, p53 expression represented a characteristic feature of the malignant cell clone and was probably indicative of an underlying gene mutation. In contrast, it was thought that in cases with p53 overexpression in <75% of cells, we could not rule out that this represented an epiphenomenon not significantly contributing to the biological behavior of the tumor cells.

For reasons of consistency, we used the same approach for evaluation of Bcl-2 expression.

**RESULTS**

**Expression of Bcl-2 and p53 in the Ovarian Cell Line A2780**

Confers Resistance to Chemotherapeutic Agents. Bcl-2 and p53 are differentially expressed in the ovarian cell lines A2780 and 2780CP, with the cisplatin-resistant 2780CP cells overexpressing both proteins (Fig. 1A). To determine whether Bcl-2 and p53 directly contribute to the development of resistance in vitro, A2780 cells were transfected with a Bcl-2- or tsp53-expressing plasmid. Western blot analysis was used to verify the expression of the genes in the isolated transfectants (Fig. 1B).

The Bcl-2 and p53 clones were subsequently tested for response to
cisplatin-induced cytotoxicity by the MTT colorimetric assay. Representative cytotoxicity curves for one of the Bcl-2 transfectants (A2780bcl-2/C1.10), one of the p53 transfectants (A2780ts/p53/C1.1) induced to express mutant p53, the parental A2780, and the 2780CP (cisplatin-resistant) cell lines are shown in Fig. 1C. The IC_{50} values were 4.0 x 10^{-6} M for the parental line, 5.1 x 10^{-5} M for the resistant 2780CP line, 1.4 x 10^{-5} M for the bcl-2-transfectant clone, and 7.5 x 10^{-6} M for the p53 transfectant. A two-way ANOVA was carried out to assess the relative resistance of the different cell lines to cis-platinum. A significant difference exists between the four dose-response curves (F = 43.46; P < 0.0001). To identify the source of this difference, the Student-Newman-Keuls method (32) was used and
found no significant difference between the dose-response curves for the A2780Bcl-2 and A2780ts/p53 cell lines. However, these dose-response curves were significantly different from those of the A2780 and 2780CP cell lines. Bcl-2 conferred a 2.3–3.5-fold and mutated p53 conferred a 1.7–2.4-fold resistance to platinum in the A2780 ovarian cell line. However, the levels of resistance in the Bcl-2 and p53 transfectants were lower than those for the 2780CP cell line (12.2-fold resistance compared with that of A2780), suggesting that additional factors contribute to the development of resistance.

Bcl-2 and p53 were also found to induce similar levels of resistance (2–4-fold) to other chemotherapeutic agents, such as lobaplatin, Adriamycin, and etoposide. Thus, Bcl-2 and p53 increased the IC_{50} value from $2.7 \times 10^{-6}$ to $1.2 \times 10^{-5}$ and $6.8 \times 10^{-6}$ M, respectively. Similarly, resistance to Adriamycin increased from $3.3 \times 10^{-6}$ to $6.9 \times 10^{-6}$ M (Bcl-2) and $4.2 \times 10^{-6}$ M (p53), and resistance to etoposide increased from $1.2 \times 10^{-6}$ to $4.8 \times 10^{-6}$ M (Bcl-2) and $3.0 \times 10^{-6}$ M (p53).

**Immunostaining for the Bcl-2 Protein.** Of the 70 specimens examined, 40 (57%) stained positive for the Bcl-2 protein [17 (24%) of 70, ≥75%; and 23 (33%) of 70, <75%], and 30 (43%) were negative. Positive staining was confined to the cytoplasm of carcinoma cells (Fig. 2, A and B). The pattern of staining showed great variation between specimens. Some sections showed labeling of the vast majority of cells (Fig. 2C), whereas in others, only small areas of tumor were found to be positive for the Bcl-2 protein (Fig. 2B). In the majority of positive sections, the focal nature of staining was a striking feature, with positively and negatively staining areas being found in close apposition (Fig. 2B). Positive staining for the Bcl-2 protein was also seen in normal ovarian tissue in the theca interna cells of the corpus luteum, granulosa cells of ovarian follicles, and also in ovarian stroma.

**Immunostaining for the p53 Protein.** Forty-three (61%) of the specimens showed positive staining for p53 protein [28 (40%) of 70, ≥75%; and 15 (21%) of 70, <75%], and 27 (39%) were negative.
Staining in carcinoma cells was nuclear, and, when positive, virtually all cells were labeled (Fig. 2, C and D). No staining was observed in normal ovarian tissue.

Survival and Expression of Bcl-2 and p53. Overall survival for these patients was poor, with 39% survival at 2 years (95% CI, 27–51%) and 12% survival at 5 years (95% CI, 4–20%). Log-rank univariate analysis was carried out as shown in Table 2. Performance status (P < 0.0001), residual disease (£2 cm, >2 cm, and £60, >60), creatinine clearance at entry to the trial (s60, >60), time from primary surgery to chemotherapy, age, menopausal status, Bcl-2 expression, and p53 expression are independent prognostic factors. No significant differences in survival between negative, weakly positive, and strongly positive tumors for either Bcl-2 (P = 0.47) or p53 (P < 0.45) were found.

Cox regression analysis was carried out on all 70 patients (Table 3). Variables considered were trial, treatment, performance status, residual disease, stage, histological grade and type, albumin level, creatinine clearance, time from primary surgery to chemotherapy, age, menopausal status, Bcl-2 expression, and p53 expression. The first factor to be selected was histological type (clear cell or not clear cell), followed by creatinine clearance at entry to the trial (£60, >60), residual disease (£2 or >2 cm), Bcl-2 (£75 or >75%), and finally, p53 (£75 or >75%). No other variables enter the model. These five factors were shown to be independently prognostic by excluding each in turn from the set of possible prognostic variables and allowing those remaining to compete to enter the model in its place. Histological type, creatinine clearance, and residual disease always entered the model when either are dropped. The regression coefficients, risk ratios, and their CIs are shown in Table 2. This multivariate analysis demonstrates that histological type, residual disease, creatinine clearance, Bcl-2 expression, and p53 expression are independent prognostic factors.

Histological type, creatinine clearance, and residual disease are widely accepted as prognostic factors. To demonstrate the effect of p53, survival curves were obtained from the model containing histological type, creatinine clearance, residual disease, and p53 expression (Fig. 3A). Patients with <75% of cells stained positive have a better prognosis than those with £75%. The size of this effect for patients with the worst prognosis is small. However, having <75% of cells positively stained improves survival at 2 years by 10% (46 versus 36%) for the intermediate prognostic group and 6% (74 versus 68%) for the best prognostic group. Similarly, predicted survival curves were obtained from the model containing histological type, creatinine clearance, residual disease, and Bcl-2, only to demonstrate the prognostic effect of Bcl-2 (Fig. 3B). Patients with £75% of cells positively stained have the better prognosis, but again, the effect is small in patients with the worst prognosis. In the intermediate prognostic group, having £75% of cells positively stained improves survival at 2 years by 13% (41 versus 28%), and for the best prognostic group, an improvement of 9% (74 versus 65%) at 2 years is seen. Finally, predicted survival curves for the full model with all five factors were obtained (Fig. 3C).

Response to Chemotherapy. There was no significant association between overall response to chemotherapy (complete or partial response versus static or progressive disease) and p53 (P = 0.69) or Bcl-2 expression (P = 0.47).

DISCUSSION

This study reports on a subset of patients from two completed Phase III randomized trials. We have found that Bcl-2 and p53 are widely expressed in epithelial ovarian tumors (57 and 61%, respectively). The proportion of tumors found to be positive for p53 is concordant with previously published work (33–35), whereas no data are available for Bcl-2 expression. Bcl-2 but not p53 staining showed heterogeneity in the majority of positive cases. No relationship between the expression of these two proteins was found. It is accepted that overexpression of the p53 protein as detected by immunohistochemistry is usually due to an underlying mutation of the p53 gene, leading to the expression of an abnormal and stabilized protein (36). Loss of p53 function, together with stabilization of the protein, however, may be caused by other mechanisms, such as interaction of the wild-type p53 protein with other cellular or viral proteins (37). Thus, although immunohistochemical detection of p53 does not necessarily indicate expression of a mutated protein, it may be a useful marker for the presence of a functionally abnormal p53 protein (38).

Table 2 Univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Grouping</th>
<th>Log-rank</th>
<th>P</th>
<th>Favorable feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Negative</td>
<td>27</td>
<td>1.61</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>&lt;75%</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Negative</td>
<td>30</td>
<td>4.69</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>&lt;75%</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>positive</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td>WHO grade 0</td>
<td>24</td>
<td>6.80</td>
<td>0.03</td>
</tr>
<tr>
<td>Residual disease</td>
<td>£2 cm</td>
<td>27</td>
<td>19.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm</td>
<td>43</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td>Stage</td>
<td>IV</td>
<td>12</td>
<td>0.04</td>
<td>0.46</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>£60</td>
<td>55</td>
<td>27.57</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>&lt;60</td>
<td>15</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Albumin</td>
<td>£35</td>
<td>28</td>
<td>0.46</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>&lt;35</td>
<td>42</td>
<td>0.54</td>
<td>0.46</td>
</tr>
<tr>
<td>Histological type</td>
<td>Clear cell</td>
<td>6</td>
<td>45.69</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Not clear cell</td>
<td>10</td>
<td>0.01</td>
<td>0.90</td>
</tr>
<tr>
<td>Histological grade</td>
<td>Well</td>
<td>17</td>
<td>1.22</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>25</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>28</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Before</td>
<td>23</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>47</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Time to start of chemotherapy</td>
<td>&gt;21 days</td>
<td>24</td>
<td>0.01</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Table 3 Summary of the Cox multiple regression analysis (n = 70)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Regression coefficient</th>
<th>P</th>
<th>Ratio of risks</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological type</td>
<td>Clear cell, not clear cell</td>
<td>3.22</td>
<td>0.0001</td>
<td>25.10</td>
<td>7.6–82.7</td>
</tr>
<tr>
<td>Residual disease</td>
<td>£2 cm, &gt;2 cm</td>
<td>1.01</td>
<td>0.0013</td>
<td>2.75</td>
<td>1.47–5.14</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>£60, &gt;60</td>
<td>-1.21</td>
<td>0.0006</td>
<td>0.3</td>
<td>0.15–0.59</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>£75% positive</td>
<td>-0.35</td>
<td>0.03</td>
<td>0.70</td>
<td>0.51–0.96</td>
</tr>
<tr>
<td>P53</td>
<td>£75% positive</td>
<td>0.28</td>
<td>0.05</td>
<td>1.32</td>
<td>1.01–1.74</td>
</tr>
</tbody>
</table>

£10–15
Fig. 3. A, predicted survival curves showing the effect of p53 staining on prognosis for patients with the best, intermediate, and worst prognoses. Worst prognosis: clear cell; residual disease >2 cm; creatinine clearance <60 ml/min. Intermediate prognosis: not clear cell; residual disease >2 cm; creatinine clearance <60 ml/min. Best prognosis: not clear cell; residual disease ≤2 cm; creatinine clearance ≥60 ml/min. B, predicted survival curves showing the effect of Bcl-2 staining on prognosis for patients with the best, intermediate, and worst prognoses. Worst prognosis: clear cell; residual disease >2 cm; creatinine clearance <60 ml/min. Intermediate prognosis: not clear cell; residual disease >2 cm; creatinine clearance <60 ml/min. Best prognosis: not clear cell; residual disease ≤2 cm; creatinine clearance ≥60 ml/min. C, predicted survival curves for the model with all five factors. Worst prognosis: clear cell; residual disease >2 cm; creatinine clearance <60 ml/min; clearly positive for p53; weakly positive or negative for Bcl-2. Intermediate prognosis: not clear cell; residual disease >2 cm; creatinine clearance <60 ml/min; weakly positive or negative for p53; clearly positive for Bcl-2. Best prognosis: not clear cell; residual disease ≤2 cm; creatinine clearance ≥60 ml/min; weakly positive or negative for p53; clearly positive for Bcl-2.

Staining for Bcl-2 was also noted in normal ovarian tissue, e.g., in ovarian stroma, which is in accordance with a role for Bcl-2 in the survival of epithelial stem cells (9). Bcl-2 is also expressed in granulosa and theca cells. These cells are under cyclical control by estrogen and undergo rapid proliferation during each menstrual cycle before dying off, presumably by programmed cell death, should conception fail to occur after ovulation. Expression of Bcl-2 in these circumstances is similar to that reported in glandular tissues of the breast and would support the hypothesis of an association between Bcl-2 expression and estrogen production (10). No expression of p53 was found in normal ovarian tissue.

The Cox regression model identifies histological type, residual disease, creatinine clearance, p53 expression, and Bcl-2 expression as significant prognostic variables. Histological type, residual disease, and creatinine clearance are the most important, with the prediction of good, intermediate, and poor prognostic groups possible on the basis of these three factors alone. The risk of death for an individual with clear cell carcinoma is 25-fold higher that of an individual with other histological types. Although the CI is wide, the increased risk of death is at least 8-fold. Similarly, having residual disease of >2 cm increases the risk of death by at least 47%, and having creatinine clearance of ≥60 ml/min (i.e., being fit for platinum at full dose) reduces the risk of death by at least 40%.

p53 and Bcl-2 expression are weaker prognostic variables. The risk of death for individuals with ≥75% of cells staining positive for p53 is 32% greater than for those with <75% of cells positively stained. The CI is wide, however, and shows the risk to be between 1 and 74%. Similarly, our data show that the risk of death for patients with ≥75% of cells positively stained for Bcl-2 is 30% less than for those with
ovarian cell line A2780 confers relative resistance to cisplatin, the reduction in risk to be between 4 and 49%.

most active drug for the treatment of ovarian cancer, as well as other and might have a poor prognosis, given the important role of platinum in the management of ovarian cancer.

This seems to be the case for p53, which, in our study, was identified as an independent marker of poor prognosis. Our finding contradicts previous work, which has failed to find such an association, in either early or late stage disease (33, 34). Interestingly, however, Bcl-2 seem to be an independent prognostic factor of improved survival. This is in agreement with previous reports in lung and breast cancer, which correlated Bcl-2 expression with a survival advantage (8, 10, 17). The power of the study was not sufficient to correlate p53 or Bcl-2 expression to the clinical response to cisplatin. However, it is possible that residual cancer following platinum treatment will be enriched in p53 and foci of Bcl-2-positive cells. In vitro, there is some evidence to suggest that certain solid tumor cells transfected with Bcl-2 grow more slowly (39). This could explain the apparent paradox of a gene that confers resistance to chemotherapeutic agents in vitro being associated with good prognosis.

Another plausible explanation is that other members of the ever-growing bcl-2 family, such as bax and bcl-x, may interfere with the outcome of chemotherapy. Indeed, it has been postulated that Bcl-2 may not be the critical factor for susceptibility to an apoptotic stimulus per se, but that of greater importance is the ratio of bcl-2 to bax, a gene that encodes a dominant inhibitor of Bcl-2 (40). On the other hand, the Bcl-x protein has been shown to protect against apoptosis, and its expression in many tissues (41) raises the possibility of a significant, still unknown, role in vivo.

It is unlikely that, in the clinical setting, expression of Bcl-2 or p53 by a tumor would be valuable prognostic information. However, further elucidation of the mechanisms by which these two oncogenes affect prognosis may be important in our future attempts to improve chemotherapy for and survival in ovarian cancer.

REFERENCES

The Prognostic Significance of Bcl-2 and p53 Expression in Ovarian Carcinoma


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