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Bcl-2, an Antiapoptotic Gene Indicator of Good Prognosis in Breast Cancer: The Paradox

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Breast cancer is the most frequently diagnosed cancer among women. Alterations in different genes are involved in the development of this tumour [1] and alterations in crucial pathways related to proliferation and apoptosis have been used as targets for treatment [2]. Bcl-2 protein is a member of the bcl-2 family that regulates apoptosis. The bcl-2 gene encodes a MR 26000 protein that is mainly localized in the mitochondrial membrane and, to a lesser extent, in the nuclear membrane and the endoplasmic reticulum. Its implication in carcinogenesis and progression makes this gene worthy of investigation. Its tumourigenic potential has been demonstrated: bcl-2 protein blocks apoptosis and cooperates with c-myc in cell transformation [3]. In addition, in the MCF-7 breast cancer cell line the overexpression of bcl-2 enhances both tumourigenicity and metastatic potential [4]. However, in many solid organ tumours, including breast cancer, bcl-2 expression, paradoxically, is associated with favourable prognostic features and good outcome [5,6]. Interestingly, the expression of bcl-2 is higher in screen-detected cancers than in symptomatic cancers [7] and, in a recent report, bcl-2 expression was shown to be lower in the stroma of precancerous fibroadenoma lesions than in those of non-cancerous lesions [8]. In their metaanalyses, Dawson et al. [6] supported the prognostic role of bcl-2 in breast cancer, as assessed by immunochemistry, and showed that this effect is independent of other variables.

The mechanisms through which bcl-2 might exert its protective effect in breast cancer are unclear. Thus, it has not been determined whether bcl-2 is involved directly in contributing to this more indolent phenotype or is simply an epiphenomenon that is a marker for another molecular or biologic process. The anti-apoptotic role of bcl-2 is well characterised but its function in cell cycle control has received less attention. Cell line studies have shown that bcl-2 exerts growth inhibitory effects by prolonging G0 and G1 progression [9], and it has been postulated that the dominance of one of these functions over another may depend on the cell type. Therefore, as bcl-2 does not promote cell proliferation, in the absence of additional genetic alteration, bcl-2 positive tumours tend to be relatively non-aggressive. Furthermore, it should be considered that other components of the apoptotic pathway might also play an important role. It is well recognized that apoptosis regulation is very complex and that bcl-2 is only one member of a family of genes, each with different roles in the regulation of cell death. The mechanisms by which the interactions between the various members of the bcl-2 family finally lead to apoptosis are still unknown. On the other hand, it could be hypothesized that the favourable clinical outcome of patients with high bcl-2 expressing tumours could be better explained by a relationship between bcl-2 expression and differentiation than by the role played by the proto-oncogene in the apoptosis process. In this sense, the presence of bcl-2 immunostaining in normal tissue and its persistence in tumour tissue could indicate a predisposition to differentiation. However, in some series the expression of bcl-2 shows no statistical relationship with differentiation [5,10]. On the other hand, gene-transfer-mediated elevations in bcl-2 protein have been shown to protect tumour cells from cell death induced by radiation and a wide range of anticancer drugs in hematologic malignancies [11]. The down-regulation of bcl-2 during anti-oestrogen treatment would probably produce a favourable response to this therapy. However, significantly longer survival times, irrespective of the type of adjuvant therapy, have been reported [6]. Clearly, therefore, the prognostic power of bcl-2 as a single marker in breast cancer has been demonstrated, but the therapeutic implication of these findings and the question of how bcl-2 might improve the selection of patients for treatment remains to be determined. Accordingly, large-scale studies including clinical trials are needed to confirm its clinical utility.

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