European Journal of Cancer Vol. 31A, No. 12, pp. 2118–2119, 1995.

0959–8049/95 $9.50 + 0.00

0959-8049(95)00413-0

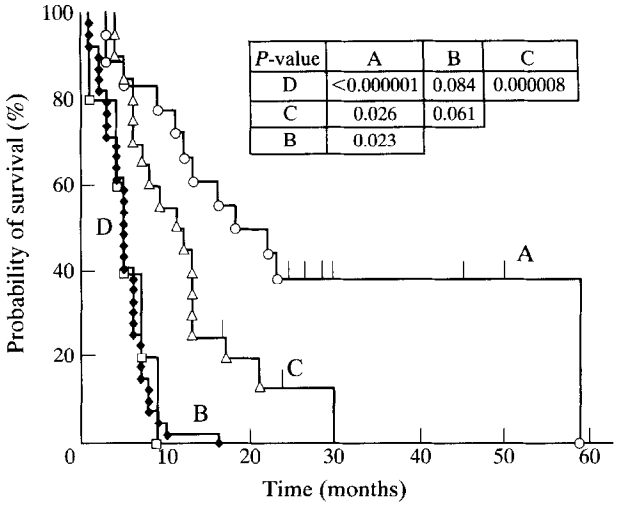
The Use of the Tumour Marker CA19-9 in Evaluating the Response to Tamoxifen Therapy in Patients with Unresectable Adenocarcinoma of the Pancreas

A. Wong[1] and A. Chan[2]

[1]Department of Medical Oncology; and [2]Department of Radiation Oncology, Tom Baker Cancer Centre, Southern Alberta Cancer Program and University of Calgary, Alberta, Canada

ELEVATED SERUM levels of CA19-9 have been found in 70% of patients with adenocarcinoma of the pancreas at initial diagnosis [1]. Several investigators [2–4] have reported a correlation between overall tumour burden of pancreatic cancer and serum levels of CA19-9. A serial decrease in this tumour marker may serve as indicator of therapeutic efficacy of a treatment modality. In a previous case–control study [5], we reported that patients with unresectable ductal adenocarcinoma of pancreas may have a prolonged survival benefit with tamoxifen treatment. Between 1989 and 1993, 82 consecutive patients (43 women and 39 men) with biopsy-documented adenocarcinoma of the pancreas were entered into a study to evaluate the use of serial measurement of serum CA19-9 levels in assessing the response to tamoxifen treatment, and to examine the pretreatment CA19-9 levels as well as their subsequent pattern of change as a prognostic indicator for survival. Local ethics committee approval and informed consent of patients were obtained. Patients were treated with tamoxifen 20 mg orally, twice daily. Serial measurement of CA19-9 levels were determined before initiation of tamoxifen treatment and at each follow-up examination at 1–2 month intervals while receiving tamoxifen therapy. Quantitative determination of CA19-9 was carried out using a radioimmunoassay kit (TruQuant GI, Biomira Inc., Edmonton, Alberta, Canada). The upper limit of a normal value for CA19-9 is 37 U/ml. A fall or rise in the tumour marker was defined as a greater than 15% decrease or increase in the tumour marker as compared to the pretreatment value, on at least two occasions 1 month apart. A plateau in the tumour marker was defined as a less than 15% decrease or increase in the marker.

Among 82 tamoxifen treated patients, 60 had pretreatment CA19-9 greater than 37 U/ml. 17 patients (10 women and 7 men) exhibited a decrease in serial measurement of serum CA19-9 levels while receiving tamoxifen therapy. The median duration of the reduction in CA19-9 levels was 5 months (range 1–15 months) prior to a subsequent rise in CA19-9 due to disease progression. Another 20 patients showed a plateau in CA19-9 for a median duration of 6 months (range 2–16 months). The remaining 45 patients had a progressive rise in CA19-9 indicating no response to tamoxifen therapy. Median survival for the 17 patients exhibiting a reduction in CA19-9 and the 20 patients showing a plateau in CA19-9 were 13 and 12 months respectively, as compared to a median survival of 5 months for the 45 patients with a serial rise in the tumour marker. Median survival of the entire group of 82 patients was 7 months. The 1, 2 and 3 year survivals were 28%, 11% and 9%, respectively. Figure 1 shows the survival of patients stratified according to both pretreatment CA19-9 values and CA19-9 response. Patients with a pretreatment CA19-9 greater than 37 U/ml with a reduction or plateau in the tumour marker on treatment (Group C, Figure 1) had prolonged survival as compared with patients with pretreatment CA19-9 less than 37 U/ml with a serial rise in the tumour marker (Group B, Figure 1). This tumour burden stabilisation seen in patients with a decrease or plateau of serum CA19-9 levels may contribute to this survival advantage, and constitutes biochemical evidence of therapeutic efficacy supporting the use of tamoxifen in the treatment of pancreatic cancer. Our findings suggest that patients with unresectable or incompletely resected ductal adenocarcinoma of the pancreas may have stabilisation of the overall tumour burden, as manifested by a decrease in serial measurement of CA19-9 levels, while receiving tamoxifen therapy. Serial monitoring of this serum marker may be useful for assessing the therapeutic efficacy of treatment in pancreatic cancer.



P-value	A	B	C
D	<0.000001	0.084	0.000008
C	0.026	0.061	
B	0.023		

Figure 1. Survival curves of tamoxifen-treated patients stratified according to pretreatment CA19-9 levels (U/ml) and CA19-9 response: (A) ≤ 37, reduction or plateau (n = 16); (B) ≤ 37, rise (n = 6); (C) > 37, reduction or plateau (n = 21); (D) > 37, rise (n = 39).

Correspondence to A. Wong at the Tom Baker Cancer Centre, 1331 - 29th Street N.W., Calgary, Alberta, Canada T2N 4N2.
Revised 1 Jun. 1995; accepted 14 Jul. 1995.

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Acknowledgements—Supported by a research grant from Alberta Cancer Board, Research Initiative Clinical Trials Program, Project No. CT-6. The authors wish to thank Dr Michael Weaver and Mrs Doris Schuh of the Immunochemistry Laboratory, Foothills Hospital for their assistance in this study.

European Journal of Cancer Vol. 31A, No. 12, pp. 2119–2120, 1995.
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50 + 0.00

0959-8049(95)00404-1

Detection of *BCL-2* RNA in Low Grade Tumours of the Urinary Bladder

P. Gazzaniga,[1] M. Gallucci,[2] A. Gradilone,[1] O. Gandini,[1] A. Vincenzoni,[2] W. Gianni,[3] G. Naso,[1] L. Frati[1] and A.M. Agliano[1]

[1]Dipartimento di Medicina Sperimentale e Patologia, Università degli Studi di Roma "La Sapienza"; [2]Divisione di Urologia, Ospedale Cristo Re; and [3]I Clinica Medica, Università degli Studi di Roma "La Sapienza", Rome, Italy

THE MAINTENANCE of homeostasis in normal tissues can be considered a balance between cell proliferation and cell death; thus any condition that alters these parameters may contribute to tumour development. While most oncogenes are believed to influence the cellular proliferation rate or differentiation, *BCL-2* overexpression suppresses the active cell death process referred to as apoptosis [1].

BCL-2 proto-oncogene, originally described at the breakpoint site of the chromosomal translocation t(14;18) in a follicular lymphoma [2], is now known to be involved in a variety of haemopoietic [3] and solid tumours [4, 5], where its presence is often associated with chemotherapy resistance [6]. Despite its association with some forms of human cancer, a number of normal tissues examined by immunohistochemistry have been shown to lack *BCL-2*; these include lung, liver, heart, cervix, ovary, testis, kidney and bladder [7].

Bladder cancer is the fifth common cancer in men in the Western society, being responsible for 5% of all cancer deaths. The 5 year survival rate is highly dependent on the pathological stage, and ranges from 10% for patients with pT4 tumours to 70% for those with pT2. In recent years, molecular studies have concentrated on the identification of 'initiating' factors and markers for disease progression, with a view to early diagnosis and follow-up of patients with low grade disease [8].

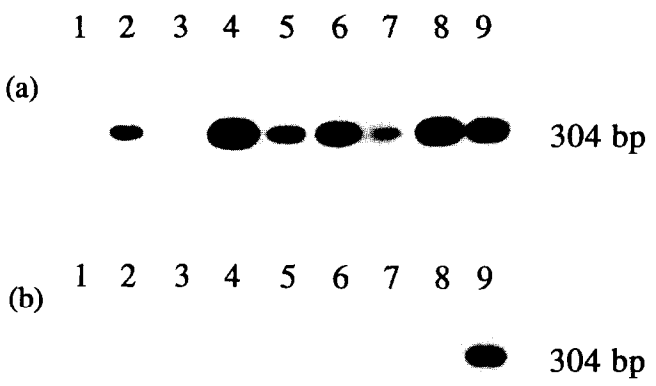

Figure 1. Autoradiography of RT-PCR products blotted and hybridised with a ^{32}P oligonucleotide probe specific for *BCL-2*. (a) Lane 1: negative control for *BCL-2* expression (HeLa cell line); lanes 2–8: urinary bladder tumour tissue; lane 9: positive control for *BCL-2* expression (CaSki cell line). (b) Lanes 1 and 9: the same as in (a); lanes 2–8: adjacent normal tissues corresponding to samples 2–8 shown in (a).

In order to better investigate the role of *BCL-2* in the very early stage of the disease, we analysed by RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) 30 low grade tumours from the urinary bladder (Ta, Tis, T1 and T2) and normal adjacent bladder tissue. While we found the expression of *BCL-2* at the RNA level in 19/30 (63%) of the tumour samples, no expression was detected in any normal tissue (Figure 1). To our knowledge, this is the first report of *BCL-2* expression in urinary bladder tumours.

BCL-2 is known to block programmed cell death, giving the cells that overexpress the protein a survival advantage over normal cells. Thus, the expression of *BCL-2* in low grade bladder tumours and its absence in adjacent normal tissue may suggest its possible implication in the initiation of the multistep process of bladder carcinogenesis. Alternatively, the finding that not all the low grade lesions examined expressed *BCL-2* at the RNA level suggests a possible role of this gene in the more rapid evolution, observed in some types of bladder cancer, toward metastatic growth and invasion.

In conclusion, *BCL-2*-expressing tumours may have different clinical behaviour in comparison with those that do not, as previously described for prostate tumours and other neoplasms, where the overexpression of this gene has been often correlated to chemotherapy resistance, poor prognosis, and decreased survival of the patients. This would be of some importance in the screening of low grade bladder cancer and in the follow-up of the post-TUR (transurethral resection) patients.

Correspondence to Anna Maria Aglianò, Dipartimento Medicina Sperimentale e Patologia, Viale Regina Elena, 324, 00161 Rome, Italy.
Revised 30 May 1995; accepted 14 Jul. 1995.

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