Eur J Cancer, Vol. 29A, No. 1, p. 169, 1993.
Printed in Great Britain
0964–1947/93 $5.00 + 0.00

Cell Kinetics in Management of Ovarian Cancer

Valter Torri and Nicola Scorpiglione

Silvestrini *et al.* [1] report on the usefulness of labeling index (LI) as a prognostic factor and criterion for selecting treatment. They report an association between LI, type of chemotherapy and survival. Comparison of results according to LI indicated that among patients with lower LI values the 3 year survival was 63% for those receiving platinum-based monochemotherapy and 46% for those receiving platinum-based polychemotherapy. Conversely, for patients with higher LI values, the 3 year survival was significantly better for those receiving platinum-based polychemotherapy (51%) than for those receiving platinum-based monochemotherapy (21%). The conclusion (although the hypothesis was not formally tested) is the existence of an interaction between LI and treatment. In explanation, the authors suggest a biological relation between cell proliferation and treatment aggressiveness. Differences in "aggressiveness" between the two treatments are presumably due to either a substantial difference in the mechanism of actions of the drugs used or in the dosage or schedule delivered, or both. These issues are not thoroughly dealt with in the paper. While information on planned dose for cisplatin or carboplatin in monochemotherapy regimen was given (100 and 400 mg/m^2, respectively), no proper information on the actual dose and dose-intensity achieved for both monochemotherapy and polychemotherapy regimens used in the study was provided. Thus, whether or not the two treatments were "equi-intensive" and equi-toxic remains unknown. It can be argued, however, that cisplatin, generally considered as the most active drug in ovarian cancer, is usually not delivered at dosages higher than 100 mg/m^2 when given in association: therefore the effect attributed to polychemotherapy would depend mostly on cyclophosphamide, since the majority of patients treated with polychemotherapy (33/46: 72%) received only this alkylator in addition to cisplatin which also acts, among other mechanisms, as a bifunctional alkylating agent.

Finally, the authors do not take into account any possible effect of confounders in their analysis. For example, even a small (and, given the sample size, not statistically significant) imbalance in residual tumour size could have affected their conclusion. Results based on stratified analysis by prognostic factors or on multivariate analysis would have been more valid.

Thus, while we agree that a prospectively collected large case series may provide the patients for exploring the value of LI, we believe that biological, pharmacological and clinical factors need to be taken into account before claiming potentially relevant prognostic associations.

1. Silvestrini R, Daidone MG, Valentinis B, *et al.* Potentials of cell kinetics in the management of patients in ovarian cancer. *Eur J Cancer* 1992, **28A**, 386–390.

Correspondence to V. Torri, Lab. di Epidemiologia Clinica, Unità di Clinical Trials, Istituto di Ricerche Farmacologiche 'Mario Negri', via Eritrea 62, 20157 Milan, Italy; and N. Scorpiglione is at the Lab. di Epidemiologia Clinica, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy.
Received 8 May 1992; accepted 16 July 1992.

Eur J Cancer, Vol. 29A, No. 1, pp. 169–170, 1993.
Printed in Great Britain
0964–1947/93 $5.00 + 0.00

Potentials of Cell Kinetics in the Management of Patients with Ovarian Cancer

A reply by R. Silvestrini *et al.*

Dr Torri and Dr Scorpiglione query the possible interpretation of a retrospective analysis of clinical outcome as a function of cell kinetics in 85 patients with advanced ovarian cancer subjected to different treatment regimens [1]. Their doubts concern the type and dose intensity of administered drugs and confounding factors disregarded in data analysis.

The planned doses for the polychemotherapy regimens were as follows: cisplatin, 1 mg/kg weekly for seven cycles, plus cyclophosphamide, 800 mg/m^2 on weeks 1, 4 and 7; cisplatin, 1 mg/kg weekly for seven cycles, plus doxorubicin, 60 mg/m^2 on weeks 1, 4 and 7; cisplatin, 50 mg/m^2, plus doxorubicin, 50 mg/m^2, plus cyclophosphamide, 600 mg/m^2, every 28 days for a total of six cycles. Because of the relatively small number of cases analysed and to avoid the interpretation of data beyond the intent of a retrospective study, we preferred not to calculate the actual dose received by individual patients in the different treatment regimens. On a larger series enrolled in an ongoing multicentre clinical protocol we will analyse the results taking into consideration the actual dose for individual patients.

With regard to the effects observed following polychemotherapy, it is conceivable that they mostly depend on cyclophosphamide, since most of the patients treated with multiple drugs received this alkylator in addition to cisplatin. Studies on experimental systems showed patterns of incomplete cross-resistance between these two drugs [2–4]. The effect of the different treatments as a function of pretreatment proliferative activity needs to be more thoroughly investigated.

Finally, with regard to eventual confounding factors not considered in the data analysis, we have reported in the paper the results on the overall series, since they were quite similar to those obtained for the 69 patients with bulky residual disease (Table 1). Patients with minimal residual disease accounted for only 19% of the series, and a separate analysis would have been meaningless.

Table 1. Survival (%) as a function of ^{3}H-dT LI and treatment in ovarian cancer patients with bulky residual disease

	Survival (%) at 3 years			
	Overall series		Non responders	
	Low LI	High LI	Low LI	High LI
Monochemotherapy	57	24	56	12
Polychemotherapy	36	50	0	45

Correspondence to R. Silvestrini, Oncologia Sperimentale C, Istituto Nazionale Tumori, via Venezian 1, 20133 Milan, Italy.
Received 16 June 1992; accepted 16 July 1992.

In conclusion, as we state in the paper, these data need to be verified and confirmed on a prospectively collected large case series, in which, in addition to clinical and biological factors, pharmacological ones are also considered. However, the present data, although preliminary and obtained on a retrospective series of cases, are consistent with evidence suggesting a greater benefit from multiple or intensive drug regimens for rapidly proliferating tumours [5–9].

1. Silvestrini R, Daidone MG, Valentinis B, *et al.* Potential of cell kinetics in the management of patients with ovarian cancers. *Eur J Cancer* 1992, **28A**, 386–390.
2. Hill BT. Biochemical and cell kinetic aspects of drug resistance. In Bruchovsky N and Goldie JH, eds. *Drug and Hormone Resistance in Neoplasia*. Vol. 1. *Basic Concepts*. Boca Raton, CRC Press 1982, 21–53.
3. Connors TA. Alkylating agents, nitrosoureas and alkyltriazenes. In Pinedo HM, Longo DL, Chabner BA, eds. *Cancer Chemotherapy and Biological Response Modifiers*. Annual 10. Amsterdam, Elsevier Science 1988, 23–31.
4. Teicher BA, Cucchi CA, Lee JB, Flatow JL, Rosowsky A, Frei III E. Alkylating agents: in vitro studies of cross-resistance patterns in human cell lines. *Cancer Res* 1986, **46**, 4379–4383.
5. Zambetti M, Bonadonna G, Valagussa P, *et al.* Adjuvant CMF for node-negative and estrogen receptor-negative breast cancer patients. *J Natl Cancer Inst Monogr* 1992, **11**, 77–83.
6. Sulkes A, Livingston RB, Murphy WK. Tritiated thymidine labeling index and response in human breast cancer. *J Natl Cancer Inst* 1979, **62**, 513–515.
7. Remvikos Y, Beuzeboc P, Zajdela A, Voillemot N, Magdelenat H, Pouillart P. Correlation of pretreatment proliferative activity of breast cancer with the response to cytotoxic chemotherapy. *J Natl Cancer Inst* 1989, **81**, 1383–1387.
8. Molinari R, Costa A, Veneroni S, Mattavelli F, Salvadori P, Silvestrini R. Cell kinetics and response to primary intra-arterial chemotherapy in patients with advanced oral cavity tumors. *J Oral Pathol* 1991, **20**, 32–36.
9. O'Reilly MS, Camplejohn RS, Rubens RD, Richards MA. DNA flow cytometry and response to preoperative chemotherapy for primary breast cancer. *Eur J Cancer* 1992, **28A**, 681–683.

Eur J Cancer, Vol. 29A, No. 1, p. 170, 1993.
Printed in Great Britain
0964–1947/93 $5.00 + 0.00

c-*erb*B-2/*neu* in Colorectal Carcinoma: A Potential Prognostic Value?

S. Kapitanović, R. Spaventi, B. Kušić and K. Pavelić

THE OVEREXPRESSION of c-*erb*B-2/*neu* has been demonstrated in a broad range of glandular tumours including breast, ovary, stomach, salivary, renal, colon carcinomas and adenocarcinomas of the lung (reviewed in ref. 1). Amplification of this gene in breast cancer has been correlated with the stage of disease, relapse and disease-free survival [2]. We report a immunohistochemical study of c-*erb*B-2/*neu* overexpression in 17 c-*erb*B-2/*neu*-positive colorectal carcinomas. The study was carried out on paraffin embedded tumour samples using mouse monoclonal antibody (c-*neu* AB-3, Oncogene Science) raised against carboxy-terminal domain of c-*erb*B-2/*neu* peptide according to the experimental and evaluation procedures that we described previously [3]. A positive correlation was observed between overexpression rate and survival monitored over the 30 months period (Fig. 1). A similar correlation was found between c-*erb*B-2/*neu* overexpression and the time of liver metastases detection. In Dukes A tumours c-*erb*B-2/*neu* status appears to be a better prognostic factor for metastatic potential than CEA [4]. The tumours that showed a weak expression (+) of oncoprotein had a longer metastases-free period than the tumours with strong expression (i.e., 14 compared with 5 months). In the same cases there was a converse relationship between the raised level of serum CEA values and metastases-free period. The results also suggest another potential value of monitoring the c-*erb*B-2/*neu* overexpression in colorectal carcinoma. In Dukes B c-*erb*B-2/*neu*-positive tumours with histologically negative nodes, using c-*neu* antibodies we were able to detect micrometastases in regional lymph nodes. Further monitoring of these patients showed greatly reduced liver metastases-free interval. Although more extensive studies are needed in a larger number of patients, we believe these observations suggest that c-*erb*B-2/*neu* could be a potentially useful prognostic factor in the colorectal carcinoma. They also indicate that immunohistochemical analysis of c-*erb*B-2/*neu* positive tumours can serve as a usful tool in detecting the micrometastases in the regional lymph nodes.

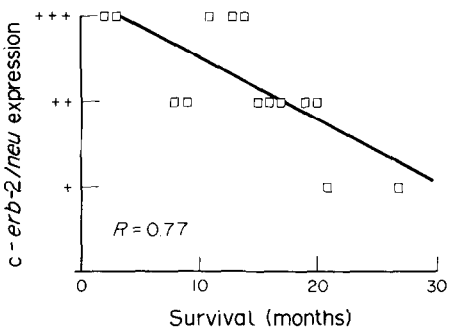

Fig. 1. Correlation between c-*erb*B-2/*neu* overexpression and survival of patients bearing colorectal carcinoma. The categories of overexpression are weak (+), moderate (++) and strong (+++).

Correspondence to K. Pavelić.
The authors are at the Laboratory for Molecular Oncology, Ruder Boskovic Institute, Bijenicka 54, 41000 Zagreb, Croatia.
Received 30 June 1992; accepted 16 July 1992.

1. Gusterson BA. Identification and interpretation of epidermal growth factor and c-*erb*B-2 overexpression. *Eur J Cancer* 1992, **28A**, 263–267.
2. Slamon DJ, Clark GM, Wong SG, *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. *Science* 1987, **235**, 177–182.
3. Pavelić K, Pavelić ZP, Denton D, *et al.* Immunohistochemical detection of c-*myc* oncoprotein in paraffin embedded tissues. *J Exp Path* 1990, **5**, 143–153.
4. Hine KR, Dykes PW. Serum CEA testing in the post-operative surveillance of colorectal carcinoma. *Br J Cancer* 1984, **49**, 689–693.