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.