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Prediction of Survival by Thymidine Labelling Index in Patients with Resistant Ovarian Carcinoma

Angela Alama, Franco Merlo, Silvana Chiara, Maria Pia Muttini, Tiziana Guido, Guido Nicolò, Pier Franco Conte and Nicola Ragni

The relationship between tumour proliferative activity, evaluated by thymidine labelling index (TLI), clinicopathological variables and clinical outcome, was analysed in a series of 64 chemotherapy-resistant, ovarian cancer patients. The median TLI of 4.6% (range 0.01–45.7) was used as the cut-off to discriminate rapidly from slowly proliferating tumours. Univariate analyses showed a significant advantage in survival for patients with TLI ≤ 4.6 ($P = 0.0004$), ECOG performance status ≤ 1 ($P = 0.0001$) and residual disease after primary surgery ≤ 2 cm ($P = 0.019$). Multivariate analysis demonstrated that performance status was the only independent prognostic variable, although TLI was the last covariate removed from the Cox's regression model.
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INTRODUCTION

THE IDENTIFICATION of independent prognostic factors by the application of Cox's multivariate analysis has provided a better understanding of the natural history of primary ovarian cancer. However, findings of such analyses are not univocal and no data on refractory or relapsing tumours are available [1–4]. Moreover, biological prognostic factors have not been thoroughly investigated and their role is still conflicting. Tumour proliferative activity and DNA ploidy are peculiar features of malignancy and a significant correlation between cell kinetics and DNA content with survival in primary ovarian cancer has been already reported [5–7]. To define the predictive value of thymidine labelling index (TLI) in resistant ovarian cancer, 64 patients were studied. The analysis of tumour kinetics in relation to clinico-pathological variables and survival is reported.

PATIENTS AND METHODS

64 patients with pathologically confirmed ovarian carcinoma were entered in this study: 34 patients relapsing (median time to relapse: 12 months) and 30 with persistent residual disease at second-look surgery, after receiving cisplatin-based chemotherapy.

Cell kinetics, as the percentage of thymidine-labelled cells in DNA synthesis over all the tumour population, were evaluated on ascitic fluid samples and/or tumour specimens by the method previously described [8].

The correlations between prognostic parameters and TLI were investigated by χ^2 statistics ($P = 0.05$). Univariate survival analyses were investigated by the Kaplan–Meier step function and differences between curves tested according to the Log-Rank test. Multivariate analysis was carried out according to Cox's multiple regression model with a backward stepwise procedure [9].

Table 1. TLI and clinicopathological characteristics of patients

Covariate	Patients No.	TLI median (range)	P
Age			
≤ 57	32	5.1 (0.16–45.7)	0.70
> 57	32	4.2 (0.01–21.8)	
Performance status			
≤ 1	33	2.8 (0.01–12.7)	0.006
> 1	31	8.4 (0.26–18.7)	
Grading			
1–2	30	4.2 (0.26–18.7)	1.00
3	29	4.8 (0.01–45.7)	
Histology			
Serous	40	4.4 (0.16–21.8)	
Undifferentiated	11	6.3 (0.01–45.7)	0.35
Others	13	3.3 (0.26–18.7)	
Residual disease			
≤ 2 cm	18	3.1 (0.20–20.1)	0.35
> 2 cm	46	5.3 (0.01–45.7)	

RESULTS

The relation between tumour proliferative activity and characteristics of ovarian carcinoma are listed in Table 1. TLI values were not related to any of the variables considered except performance status ($P = 0.006$).

The overall median TLI (4.6%; range 0.01–45.7) was used as a cut-off value to discriminate rapidly from slowly proliferating tumours. Univariate survival analysis showed that patients with TLI ≤ 4.6% did better than those with TLI > 4.6%, with a mean survival time of 15.5 and 5.3 months, respectively ($P = 0.0004$), as shown in Fig. 1. Moreover a significant advantage in survival for patients with performance status ≤ 1

Correspondence to A. Alama at the Istituto Nazionale per la Ricerca sul Cancro, Department of Pharmacology, V.le Benedetto XV,10,16132 Genova, Italy.
F. Merlo, S. Chiara, M.P. Muttini, T. Guido and G. Nicolò are at the Istituto Nazionale per la Ricerca sul Cancro, Genova; P.F. Conte is at the Div. Oncologia Ospedale S.Chiara, Pisa; and N. Ragni is at the Clinica Ostetrico, Ginecologica Università di Genova, Italy.
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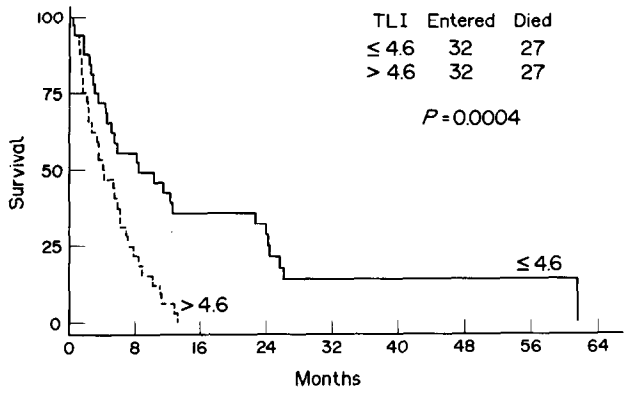

Fig. 1. Relation between TLI and survival in patients with resistant ovarian cancer.

(P = 0.0001) and residual disease ≤ 2 cm (P = 0.019) was also reported.

Multivariate analysis demonstrated that performance status was the only independent prognostic variable (HR = 3.5; P = 0.0002), while all the other covariates were removed from the model in the following order: grading, histology, residual disease, age, TLI.

DISCUSSION

While several independent prognostic factors have been identified in primary ovarian cancer, no data on resistant tumours are available. Results from the current study demonstrated that the prognostic importance of performance status and residual disease is retained even after chemotherapy failure while the predictive role of tumour grading remains controversial [1–3]. Moreover, the tumour proliferative activity is shown to be a significant determinant of survival in this series of resistant ovarian carcinoma: patients whose tumours had a low TLI survived longer than did patients with high TLI. In the multivariate analysis performance status has shown most consistently to have independent significant influence on outcome, while all the other clinicopathological variables were not of additional prognostic relevance. Hence, we were unable to find any independent association between tumour kinetics and survival; even though, despite the lack of a formal statistical significance, we believe that TLI still retains its prognostic role, being the last biological covariate removed from the Cox's regression model.

Data from the literature on the association between the S-phase and survival in ovarian cancer are, however, still conflicting. Some studies reported that cell kinetics are significantly associated to clinicopathological parameters and prognosis while others failed to find any relationship [10–13]. In interpreting the findings published so far, it should be taken into account that highly proliferating cancers are more sensitive to cytotoxic therapy. Therefore, cell kinetics in primary tumours may lose prognostic importance following aggressive first line treatment modalities. A confirmation of this assumption comes from one of our studies on previously untreated ovarian cancer reporting that the advantage of an objective response, after chemotherapy regimens containing cisplatin and doxorubicin, was reached in the group with higher tumour proliferative activity. However, TLI was not a predictor of survival in this series of patients [14].

Conversely, tumour proliferative activity represents a peculiar feature of tumour aggressiveness in chemotherapy resistant ovarian cancer. Since the clinical outcome of these tumours is no longer affected by current second line treatments, the relevance of TLI as a marker of natural history for resistant neoplasms needs to be further investigated.

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