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

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The relevance of ^{3}H-thymidine labeling index (^{3}H-dt LI) on clinical outcome was evaluated on 85 patients with advanced ovarian cancers treated with carboplatin or cisplatin alone (39 cases) or cisplatin in association with doxorubicin and/or cyclophosphamide (46 cases). ^{3}H-dT LI of the primary tumour was significantly related to the 3-year probability of survival in patients treated by monochemotherapy (low LI, 63%; high LI, 21%; $P = 0.013$) but not in those treated with polychemotherapy. Analysis of the relation between cell kinetics and clinical outcome as a function of treatment showed that in patients with rapidly proliferating tumours the 3-year survival was significantly higher following polychemotherapy than monochemotherapy (51 vs. 21%; $P = 0.04$). In patients with slowly proliferating tumours no significant difference in survival was observed following the two types of treatment for the overall series, whereas in patients not achieving a complete response survival was significantly higher following monochemotherapy than polychemotherapy (61 vs. 9%; $P = 0.008$).
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INTRODUCTION

FOR OVARIAN cancer as for other human tumour types, we have witnessed the intensive investigation of biological markers of potential clinical usefulness. The search has been developed by looking for features specific for ovarian cancers [1] or common to all tumour types. Among the latter, nuclear DNA content [2–15] and cell kinetics [4–9, 12, 14, 16, 17] have been investigated to define their contribution as independent prognostic variables or as indicators of response to clinical treatment.

In particular, nuclear DNA content has been investigated in ovarian cancer as a predictor of long-term clinical outcome [2–4, 6, 8, 10–14] and more recently of response to therapy [15]. Conversely, cell kinetics, which has consistently proved to be an important indicator of clinical progression in several solid and systemic human tumours [18–21], has been largely investigated for basic [4–7, 9] and less extensively for clinical purposes [4, 6, 12, 14, 16, 17] with conflicting results.

In a series of patients with advanced ovarian cancers treated with monochemotherapy (cisplatin or its analogue carboplatin), an inverse relation was found between patient survival and cell kinetics evaluated as ^{3}H-thymidine labeling index (^{3}H-dT LI) [16]. We concluded that pretreatment cell kinetics affected clinical outcome irrespective of systemic treatment. However, it was not possible to define the actual impact of monochemotherapy on the natural history of slowly or rapidly proliferating tumours for the lack of patients treated with surgery alone.

In the present study we analysed the relation between cell kinetics and short- and long-term clinical response to different treatment regimens. Such an analysis was possible owing to the availability of additional information from a series of patients with advanced ovarian cancers treated with polychemotherapy. Tumours were biologically characterised and patients were clinically followed by the same researchers and physicians involved in the previous monochemotherapy clinical study [16].

PATIENTS AND METHODS

Patient population

The study was comprised of 85 previously untreated patients for whom ^{3}H-dT LI information of the primary tumour was available. 68 tumours were classified as stage III and 17 as stage IV according to the FIGO classification. All patients had measurable disease, and 69 had bulky disease at first-look laparotomy. The histological grade according to FIGO was defined on the primary lesions: 6 tumours were classified as grade 1, 23 as grade 2, and 54 as grade 3; for 2 tumours such information was not available.

A group of 39 patients was treated by monochemotherapy: cisplatin (100 mg/m^2) or carboplatin (400 mg/m^2), intravenously every 28 days for a total of five cycles. The series has been described in detail elsewhere [22]. A group of 46 patients was treated with multidrug regimens [23]: cisplatin in association with doxorubicin (8 cases) and/or cyclophosphamide (5 and 33 cases, respectively). Stage, grade, residual disease and median ^{3}H-dT LI were similar for the two treatment groups.

Patients who did not respond after three cycles or had progressive tumours during treatment were crossed-over to the other platinum compound in the monochemotherapy trial or with miscellaneous treatments in the polychemotherapy trial, at the discretion of the attending physician. However, the alternate forms of chemotherapy only minimally influenced subsequent survival.

Study parameters and follow-up

Response to treatment was assessed by physical, gynaecological, and surgical evaluations. Evaluation of the serum CA-125 marker was routinely performed. A second-look laparotomy to define the clinical response was carried out 5 months after starting chemotherapy in patients with no clinical evidence of disease. Multiple random biopsy specimens were analysed from lymph nodes, liver, diaphragm, pelvic and peritoneal surfaces, and abdominal cytological washing. Responses were classified as complete response (i.e. the histological disappearance of disease), partial response (i.e. a decrease in the sum of the two greatest diameters of all the masses by > 50%), or no response (i.e. a ≤ 50% reduction, no change, progression or appearance of new disease manifestations). Computed tomography (CAT) scans, chest X-rays, and ultrasound assessment of clinical responses were done whenever indicated.

^{3}H-dT LI determination

Immediately after surgery, ^{3}H-dT LI was determined on small fragments sampled from the different areas of the tumour and incubated for 1 h at 37°C with the labeled precursor. A kit from Ribbon (Milan, Italy) was used, and it allowed for the recruitment of cases from other institutions. Autoradiography was performed on histological sections according to the stripping film (Kodak AR10) technique [16]. After an exposure time of 3 days at 4°C, autoradiograms were developed in Kodak D-19b for 5 min at 18°C and fixed in Kodak F5. The samples were stained with haematoxylin and eosin at 4°C. The ^{3}H-dT LI was determined by scoring from 3000 to 10000 cells on different specimens from the same lesion and was defined as the percentage ratio between the number of labeled and total number of tumour cells. The median value of 7.5% observed in a previous unselected series [16] and which is similar to the median value observed in the present study was used as a cut-off to define slowly and rapidly proliferating tumours.

Table 1. Clinico-pathological features in relation to ^{3}H-dT LI

	No. of cases	^{3}H-dT LI (%) Median	Range
Overall	85	8.4	0.9–23.2
Histology			
Endometrioid	11	9.2	2.8–17.4
Clear cells	5	8.7	0.9–17.7
Serous	55	8.4	0.9–23.1
Mixed	6	8.3	5.8–23.2
Undifferentiated	8	4.2	1.0–13.1
FIGO grade			
1	6	5.1	0.9–8.7
2	23	7.5	2.6–18.4
3	54	9.1	0.9–23.2
Stage			
III	68	8.0	0.9–23.2
IV	17	9.1	1.0–20.8
Residual disease			
< 2 cm	16	6.3	0.9–16.0
> 2 cm	69	9.0	0.9–23.2

Statistical analysis

The Wilcoxon rank–sum test and the Kruskal–Wallis non-parametric analysis of variance were used to assess the significance of differences in proliferative activity between subgroups with diffferent clinico-pathological features. The relationship between biological data and short-term response to therapy was assessed by the kappa test, which takes into account agreements that might be expected purely by chance. Overall survival was computed with the product-limit estimate. The median observation times were 38 and 34 months for patients entered in monochemotherapy and polychemotherapy trials, respectively. The log–rank test was used to assess the statistical significance of differences between the different subgroups. All hypothesis tests were two-sided.

RESULTS

The relation between the ^{3}H-dT LI of the primary tumour and clinico-pathological or biological features in the present case series is given in Table 1. Subsets of tumours defined on the basis of histotype, pathological stage and residual disease had similar ^{3}H-dT LI values. Only a trend in favour of a direct relation between ^{3}H-dT LI and histological grade was observed (P = 0.10).

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Table 2. Complete response rate (%) as a function of ^{3}H-dT LI and treatment

	No. of cases	Complete response rate (%) Overall series	Low LI tumours	High LI tumours
Monochemotherapy	39	23	27	21
Polychemotherapy	46	39	45	33

Table 3. Survival (%) as a function of ^{3}H-dT LI and treatment

	Survival (%) at 3 years Overall series Low LI	High LI	Non responders Low LI	High LI
Monochemotherapy	63	21	61	11
Polychemotherapy	46	51	9	42
P value	ns	0.04	0.008	0.08

The role of ^{3}H-dT LI on objective clinical response was analysed in patients treated with monochemotherapy or polychemotherapy as first-line treatment. The clinical response was surgically documented by second-look laparotomy. A slightly higher complete response rate was observed for patients treated with polychemotherapy than for patients treated with monochemotherapy, but no difference was observed for the two kinetic subgroups within the same clinical protocol (Table 2).

In patients treated with monochemotherapy, survival was inversely related to ^{3}H-dT LI of the primary tumour (Fig. 1). In fact, the probability to survive at 3 years was three times higher for patients with slowly proliferating than for patients with rapidly proliferating cancers (low LI, 63%; high LI, 21%; $P = 0.013$). The better prognosis for patients with slowly proliferating tumours was generally independent of tumour grade and residual disease. A breakdown analysis as a function of clinical response (Fig. 2) showed that the probability of survival for the two kinetic subgroups was significantly different in patients who did not reach complete remission (low LI, 61%; high LI,11%; $P = 0.005$) but not in clinically responsive patients (low LI, 75%; high LI, 50%).

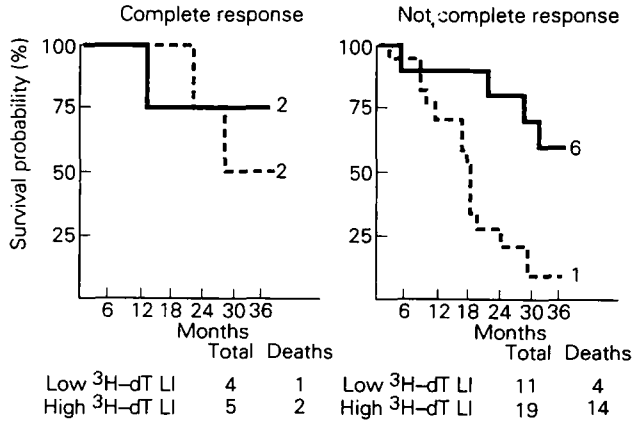

Fig. 2. Probability of survival according to ^{3}H-dT LI and clinical response complete (left), incomplete (right) in patients treated with monochemotherapy. —— lowLI; --- high LI. Right curve, $P = 0.005$.

In patients treated with polychemotherapy, the 3-year probability of survival for the two kinetic subgroups was similar for the overall series (Fig. 3) as well as for the two analysed subgroups of responsive and non-responsive patients (Fig. 4), except for a late and inverse trend of diversification of the survival curves in the latter group (high LI, 42%; low LI, 9%).

The survival of patients with slowly or rapidly proliferating tumours was also analysed as a function of treatment (Table 3). Overall, in patients with slowly proliferating tumours, survival was higher following monochemotherapy (63%) than polychemotherapy (46%), but not significantly different. This finding was amplified and reached statistical significance in the subgroup of patients who did not achieve complete remission (monochemotherapy, 61%; polychemotherapy, 9%; $P = 0.008$). For these patients with clinically resistant, slowly proliferating tumours, survival following monochemotherapy was 6-fold greater than that following polychemotherapy. Conversely, in patients with rapidly proliferating tumours, survival was significantly higher following polychemotherapy (51%) than

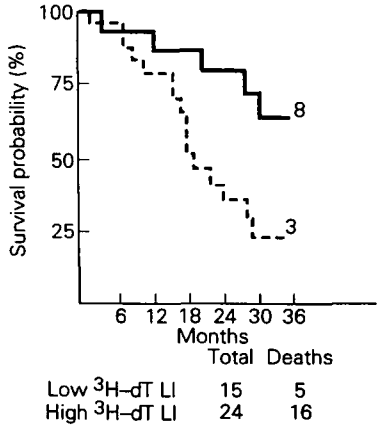

Fig. 1. Probability of survival according to ^{3}H-dT LI in patients treated with monochemotherapy. —— low LI; ---- high LI. $P = 0.013$.

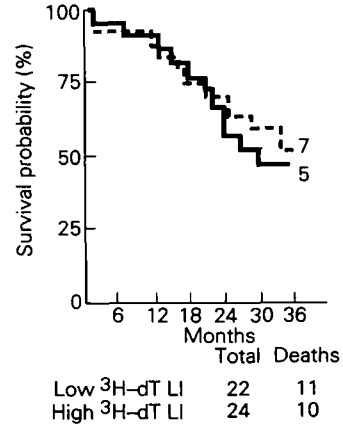

Fig. 3. Probability of survival according to ^{3}H-dT LI in patients treated with polychemotherapy. —— low LI; --- high LI.

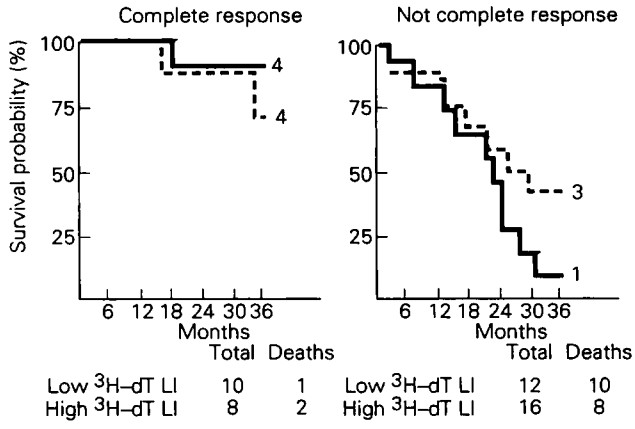

Fig. 4. Probability of survival according to ^{3}H-dT LI and clinical response in patients treated with polychemotherapy. —— low LI; --- high LI. Right curve, $P = 0.16$.

monochemotherapy (21%). Again this finding was amplified within the subgroup of patients who did not achieve complete remission after first-line chemotherapy (polychemotherapy, 42%; monochemotherapy, 11%; $P = 0.08$).

DISCUSSION

Among the biological variables that have provided reliable information for the long-term prognosis of solid and systemic tumours, cell kinetics has gained a prominent role. In fact, its prognostic contribution was evident in operable diseases treated with local-regional therapy alone and also emerged in advanced diseases submitted to systemic treatments. Such findings, consistently observed for several tumour types [18–21], are not consistent in ovarian cancers. In fact, in a first study we observed an inverse relation between cell proliferation rate and survival duration [16]. However, this result was not confirmed by the data of Conte *et al.* [17], who failed to find any prognostic role of cell kinetics. The main difference between the two studies is the type of treatment, i.e. monochemotherapy in the first and polychemotherapy in the second. Therefore, the inconsistent results can be explained by an impact of the two treatments on the natural history of the disease.

In the present study, the availability of biological and clinical information for patients with ovarian cancers treated with monochemotherapy or polychemotherapy has made it possible, for the first time, to define the impact of the two regimens as a function of pretreatment cell kinetics. Our data show that ^{3}H-dT LI maintains its prognostic role on survival in patients submitted to monochemotherapy with platinum compounds as first-line treatment, thus confirming at a longer follow-up our preliminary findings [16].

In contrast, in patients who received polychemotherapy, survival at 3 years as well as complete remission rate appear independent of pretreatment ^{3}H-dT LI, in agreement with the results of Conte *et al.* [17]. A probable explanation is that the prognostic role of a biological marker can be nullified when an effective and intensive treatment is given. In fact, polychemotherapy regimens seem adequate to control more aggressive, rapidly proliferating cancers, even those not completely responding to first-line treatment. Conversely, a monochemotherapy treatment with platinum compounds seems to be more suitable than polychemotherapy to control disease progression in indolent, slowly proliferating tumours. As regards polychemotherapy, it is hypothetically reasonable to assume an eventual expansion of drug-resistant clones following the killing of sensitive clones, or that one or more of the drugs included in polychemotherapy regimens can induce a proliferation recruitment of cells from the unstable G_0 phase through DNA repair mechanisms. In any case, the inherent drug resistance of recruited proliferating cells prevents any benefit from further chemotherapy, and the stimulation of cell proliferation negatively prevails, as already observed for other tumour types [24–26].

Our results on the varying efficacy of different treatments as a function of biological tumour characteristics are supported by other evidence according to which more aggressive aneuploid ovarian cancers do not benefit from radiotherapy alone and more indolent diploid tumours have an excellent prognosis when treated with radiotherapy alone or with a single alkylating agent [11]. Moreover, Friedlander *et al.* [10] have shown that polychemotherapy was superior to chlorambucil alone in prolonging time to first relapse for patients with aneuploid tumours.

The potentially interesting relation between cell kinetics and response to different treatment regimens needs to be confirmed on larger, prospectively recruited case series. Cell kinetics should therefore be incorporated with other biological and clinical factors of prognostic importance to identify subsets at different risk and to provide a sounder basis for therapeutic decision making, which is usually planned on the basis of stage alone.

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Chemotherapy with or without High-dose Medroxyprogesterone Acetate in Oestrogen-receptor-negative Advanced Breast Cancer

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In a randomised study 142 patients with advanced oestrogen-receptor-negative breast cancer in the tumour tissue received chemotherapy alone or chemotherapy combined with high doses (1000 mg daily) of oral medroxyprogesterone acetate (HD-MPA). Of the 126 fully evaluable for response, the response rates were 46% for chemotherapy alone and 73% for chemotherapy with HD-MPA ($P = 0.005$). There was no significant difference with regard to duration of response. Of the 138 patients evaluable for survival and toxicity, survival was shorter in the combined treatment group; median survival of 9 versus 13 months ($P < 0.05$). Considerable toxicity was seen from HD-MPA, especially weight gain and fluid retention. The present study provides evidence that in concordance with preclinical studies an interaction between chemotherapy and HD-MPA may exist in breast cancer normally resistant to hormone therapy. The side-effects from MPA were substantial, however, and the survival data are of great concern.
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INTRODUCTION

SEVERAL STUDIES have indicated an increased response rate in advanced breast cancer when chemotherapy is combined with high doses of medroxyprogesterone acetate (HD-MPA) [1]. Receptor assays were not reported in these publications, and the response could merely reflect an additive effect, with some patients responding to chemotherapy and some to hormone therapy. Preclinical experimental data for a true interaction between chemotherapy and HD-MPA were been provided by Formelli *et al.* [2] who found that MPA could potentiate the effect of chemotherapy on a hormone insensitive subline of 13762 mammary adenocarcinoma in rats. This hypothesis can only be tested in a clinical setting by treating patients that are normally resistant to hormone therapy. There is abundant data demonstrating that breast cancer patients with oestrogen receptor contents <10 pmol/g protein (ER-) in the primary