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Cell Cycle Modifications of Breast Cancers During Neoadjuvant Chemotherapy: a Flow Cytometry Study on Fine Needle Aspirates

Y. Remvikos, M. Jouve, P. Beuzeboc, P. Viehl, H. Magdelenat and P. Pouillart

Breast cancer cells from 92 patients were obtained by repeated fine needle sampling and analysed by flow cytometry for cell cycle modifications during neoadjuvant chemotherapy. Modifications of the histograms were observed for 47 of the 71 informative cases (66%), the most frequent concerning S-phase (increase or decrease) and G_2M accumulation. These modifications correlated well with the efficacy of cytotoxic chemotherapy ($P < 0.0001$). A significant relationship between clinical regression and pretreatment proliferative activity was also observed, with 31/35 (89%) responders in the high proliferation group (S-phase fraction > 5% or BrdU labelling index > 3.3%) compared to 20/36 (56%) in the low proliferation group ($P < 0.002$). For patients undergoing chemotherapy including doxorubicin, a high incidence of G_2M accumulation was observed (33%), a modification which was rare (4.5%) for a regimen with no anthracycline, for which S-phase was the most frequently modified cell cycle compartment (64%). The measurement of the pretreatment tumour proliferative activity as well as the early kinetic modifications, as indicators of response, may prove interesting parameters for the future management of neoadjuvant chemotherapy.
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INTRODUCTION

NEOADJUVANT CHEMOTHERAPY was first proposed as part of multimodality treatments for locally advanced breast cancer [1–3], but was soon extended to operable tumours [4]. Unfortunately, up until now there have been no results from randomised trials demonstrating an advantage of the chemotherapy-first sequence, although it has been claimed to improve breast conservation [5].

The systematic research for prognostic factors led us and others to develop a method for DNA flow cytometric analysis on fine needle samples without aspiration [6, 7] at the time of diagnosis. Thus we were able to show that pretreatment proliferative activity, expressed in terms of S-phase fractions (SPF), was highly correlated with response to neoadjuvant chemotherapy [8].

In the present study, we applied sequential fine needle sampling to follow the course of breast cancers during neoadjuvant chemotherapy. All samples were analysed by flow cytometry for DNA content and the more recent ones for BrdU incorporation [9] in an attempt to achieve early prediction of the efficacy of treatment in individual patients.

PATIENTS AND METHODS

Fine needle cytological samples (FNS) of breast cancers were obtained from 92 patients before and during neoadjuvant chemotherapy, with their informed consent. The patients were treated for stage II or IIIA disease. All were premenopausal. FNS were performed before the first injection (day 0), after the last injection of the first cycle (day 8) and before starting the second cycle (normally day 28).

Flow cytometry

DNA histograms for ploidy or spectrofluorometry analysis and BrdU labelling indices (BLI) were obtained as previously

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described [9]. The median values of each distribution were used for the purpose of classification of the tumours into high or low proliferation groups. It was previously shown that cases with discordant values represent approximately 6% of the total [9]. In the present study there were 4 out of 46 (9%) cases with discordant indicators of proliferative activity for which the highest value was used for classification. Because the precision is much higher as the measured values of SPF or BLI increase, modifications in the S (SPF and/or BLI) or G_2M phases of the cell cycle were arbitrarily chosen to be significant if a variation by a factor greater than or equal to 2 was observed in any one of the repeated samplings. For the purpose of simplicity, subpopulation changes including the reduction of the proportion of non-diploid cells or the appearance of a new peak outside the range of the expected G_2M, were considered as histogram modifications.

The corresponding cytological smears were inspected for the presence of cancer cells. The cases for which the malignant cells disappeared during treatment were excluded from the analysis.

Treatment and response

All patients received 4 monthly cycles of chemotherapy. Two different protocols were used:

—5-fluorouracil (5FU) 500 mg/m^2 on days 1, 3, 5 and 8, cyclophosphamide, 500 mg/m^2 on days 1 and 8, and doxorubicin 25 mg/m^2 on days 1 and 8 (CFA).

—Thiotepa at a dose of 10 mg/m^2 replaced doxorubicin in the TFC regimen, while the dose of cyclophosphamide was increased to 700 mg/m^2.

Response to treatment was assessed according to UICC criteria, using the product of the two axes reported on the patients' files. Patients with less than 50% regression of the tumour were included in the no change group.

RESULTS

21 cases were excluded from the analysis, because of non-interpretable histograms during treatment (9 cases), a low proportion of tumour cells in the samples (4 cases) or insufficient cells for the analysis (8 cases). 71 patients were thus considered informative. When comparing the initial histograms to those during treatment, two different types of modifications were observed.

(1) Subpopulation changes, typically consisting of a progressive reduction in the proportion of the aneuploid cells as shown in Fig. 1. Cytological smears of the three FNS confirmed the presence of a majority of tumour cells. However, additional subpopulations (excluding peaks that could be interpreted as an increased G_2M) were also observed in 4 cases (not shown). In all the other cases DI values before and during treatment were in good agreement (less than 5% variation).

(2) Changes in the cell cycle distribution were quantified both on the DNA histograms and by BrdU incorporation analysis. Thus one of the most frequent kinetic modifications was early accumulation in the G_2M phase observed at day 8, often associated with a modification of the S-phase, as shown in Fig. 2. In this particular case, there was a considerable drop in the BLI from 17.4% at day 0, to 9.5% at day 8, while the G_2M increased from 10 to 24%. In some cases, BLI analysis revealed modifications of DNA synthesis that were not visible by DNA content analysis (results not shown). Transient increases in SPF and BLI were also observed.

The incidence of the various patterns is summarised in Table 1. 47 of the 71 cases presented modifications (66%), the most frequent concerning S-phase (33%) or G_2M (23%).

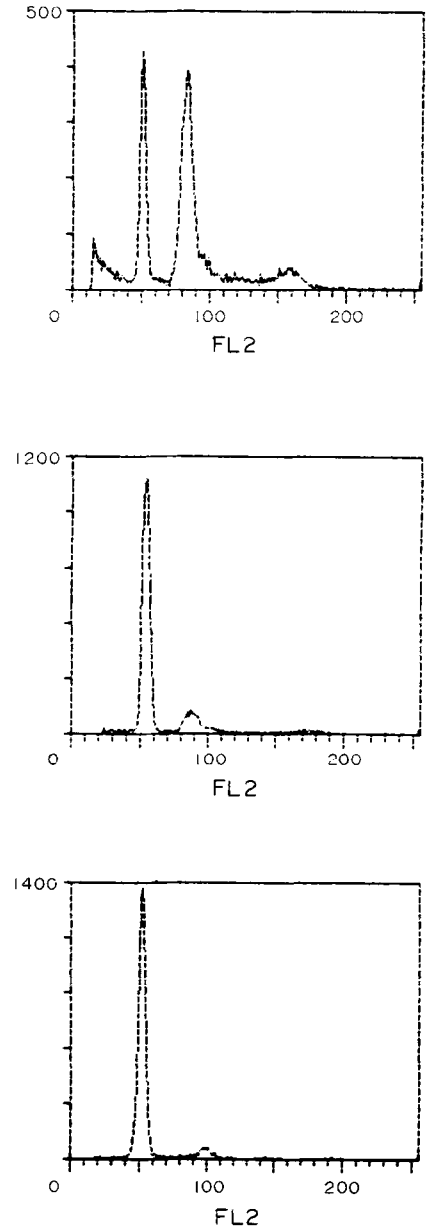

Fig. 1. DNA histograms obtained from FNS performed on day 0 (upper panel), day 8 (middle panel) and day 28 (lower panel) on the same lesion, showing the progressive disappearance of the aneuploid cells. The corresponding smears were found to contain a majority of tumour cells, suggesting the existence of diploid cancer cells.

All patients were evaluated for clinical response after completion of the four cycles. There were 72% major responses. As shown in Table 2, the kinetic modifications were highly correlated to clinical response (χ^2 test after regrouping the different kinetic modifications or considering overall response, $P < 0.0001$).

Four cases for which the modifications were considered to be significant did not respond clinically. In 2 of the 4 cases there were only significant subpopulation changes. An example is shown in Fig. 3, in which an important reduction of the aneuploid cells occurred on day 28. Clinically, despite a small reduction after one cycle, the tumour mass remained stable thereafter. Figure 4 shows the biparametric representations of BrdU/DNA distribution of the tumour at day 0 and after

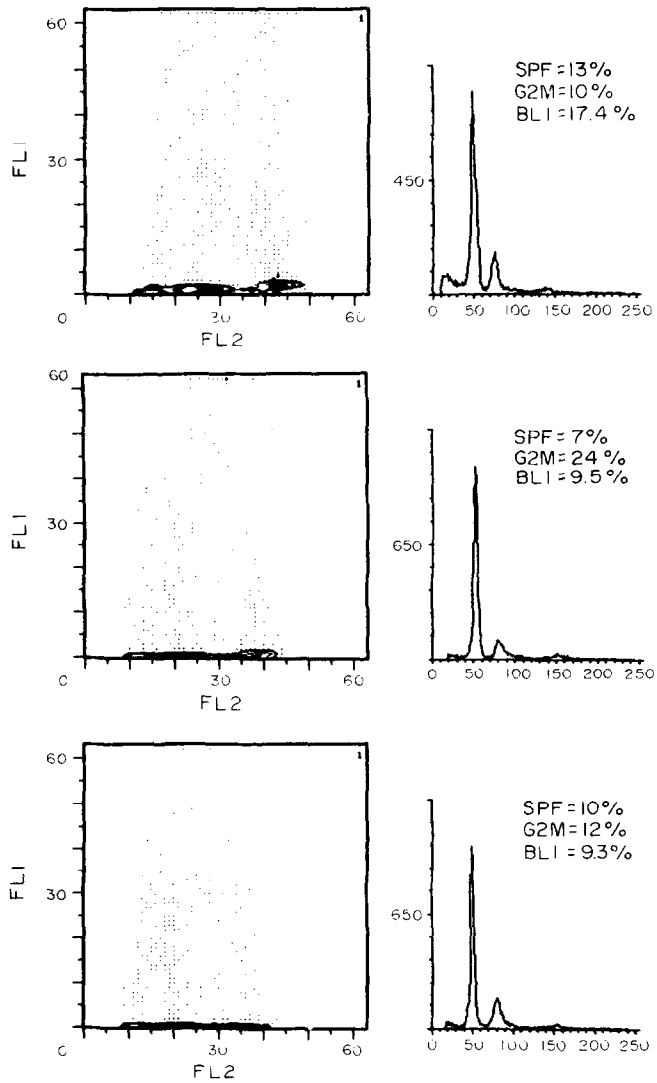

Fig. 2. DNA histograms of a highly proliferating tumour obtained sequentially. The percentages of cells in S-phase (SPF and BLI) and G_2M are shown for each one.

completion of three cycles. The total BLI were equivalent, 4 and 4.5% respectively, suggesting continuing growth of the tumour.

Conversely, 8 responders to treatment showed no significant modification. The most striking example concerned a tumour for which a slight increase in labelling index, from 6 to 8.5%, occurred between day 0 and day 28. However, after three cycles of chemotherapy, the tumour cells displayed a BLI of 6.8%, comparable to the one before treatment. After surgery, despite the significant reduction of the tumour mass, histological examination revealed an active lesion in the breast and a massive nodal involvement, with 20/30 positive axillary nodes. It must be noted that 6/8 "false negatives" were observed for cancers with low proliferative activity.

Table 1. Frequencies of the different cytokinetic modifications

Kinetic modification type	Count
None	24 (34%)
S-decrease	7 (10%)
S-increase	16 (23%)
G_2M accumulation	6 (8%)
Modified $S+G_2M$	11 (15%)
Subpopulation change	7 (10%)

Table 2. Correlation between the kinetic modifications and the response to chemotherapy

Kinetic modification	No response	PR	CR	PR+CR
None	16	8	0	8
S	2	14	7	21
G_2	0	11	6	17
Subpopulation change	2	3	2	5
Total modified	4	28	15	43

PR, partial response; CR, complete response.

Since all patients had proliferative activity assayed before treatment, we also tested the relationship of this parameter to response to treatment. Using the median values of the respective

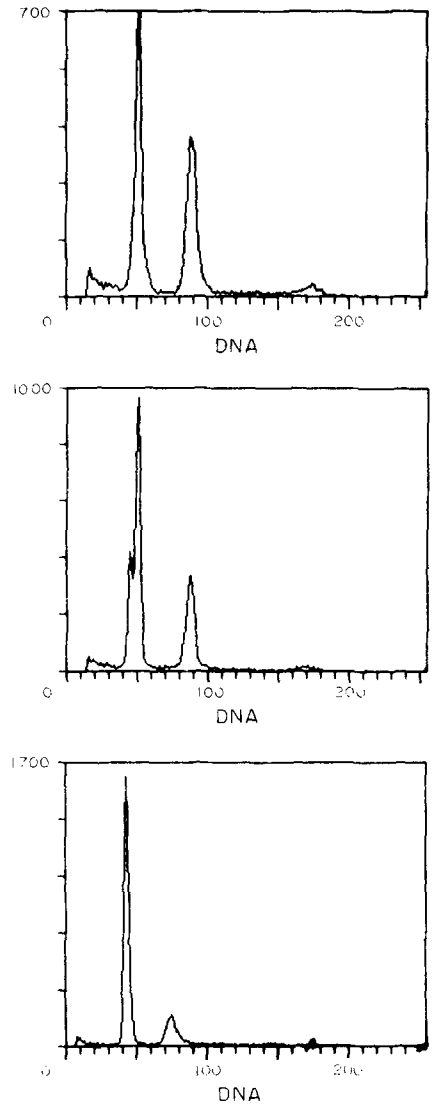

Fig. 3. DNA histograms corresponding to FNS on days 0 (upper panel), 8 (middle panel) and 28 (lower panel), showing a significant reduction of the aneuploid cells only in the last sample.

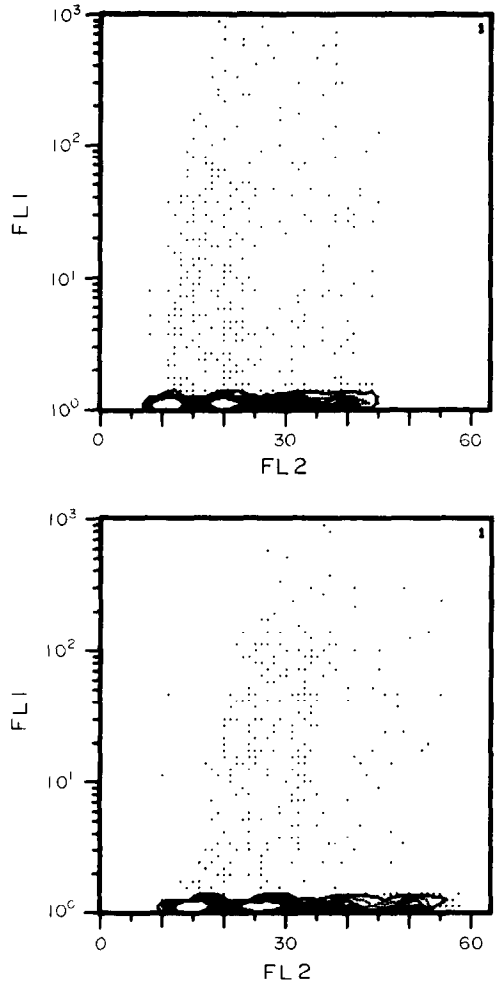

Fig. 4. Biparametric BrdU/DNA cytograms obtained from FNS on day 0 (upper panel) and after completion of three cycles of the CFA regimen (lower panel). Total BLI (including the diploid cells) were equivalent (4 and 4.5%, respectively).

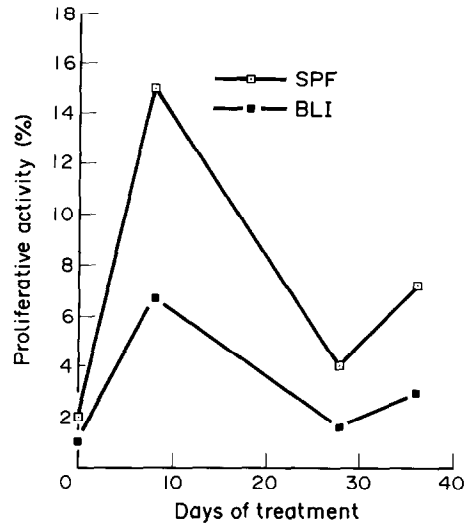

Fig. 5. Course of the cytokinetic parameters (SPF and BLI) during the first two cycles of TFC. Despite the low initial values, a substantial increase was observed between day 0 and 8, followed by a reduction on day 28 and a second less pronounced increase on day 36.

distributions as cutoff for both SPF (5%) and BLI (3.3%), the relationship was found to be significant ($P < 0.002$) with 56% of responders (20/36) in the low proliferation group and 89% in the high proliferation group (31/35). A detailed analysis revealed that the difference was more significant when the extent of the response was analysed separately (Table 3, $P < 0.0001$).

Despite this relationship, some tumours with pretreatment low proliferative activity exhibited very important kinetic modifications during treatment. As shown in Fig. 5, the SPF increased from 2% at day 0 to 17% at day 8, as did the BLI from 1 to 6.5%. The SPF and BLI decreased at day 28, while a less marked increase was observed during the second cycle.

The 71 patients of our series were treated by two different protocols, one including doxorubicin (CFA) the other not (TFC). As can be seen in Table 4, kinetic modifications during TFC treatment consisted almost exclusively in changes of the S-phase compartment (14 out of 22), typically consisting of an increase already observed on day 8 (11 out of 14), G_2M accumulation being rare (1 out of 22). On the contrary, tumours of patients receiving CFA frequently showed an increase in the G_2M peak (16 out of 49), some of which were associated with a modified S-phase (10 out of 16).

Table 3. Correlation between the pretreatment proliferative activity and response to chemotherapy

Response	SPF:low	SPF:high	Statistics
None	16 (44%)	4 (11%)	$\chi^2 = 9.56$
PR+CR	20 (56%)	31 (89%)	$P < 0.002$
PR>50%	19 (53%)	17 (49%)	$\chi^2 = 18.57$
CR	1 (3%)	14 (40%)	$P < 0.0001$

PR, partial response; CR, complete response.

DISCUSSION

The cytokinetic effects of most of the currently used cytotoxic agents in clinical oncology have been studied in model systems and flow cytometry (FCM) has proved to be a useful tool to monitor these cell cycle modifications *in vitro* (reviewed in [10]). Some of these modifications have been found to be compatible with the known mechanism of action of the drugs. For instance, vinca alkaloids which are known to interfere with the mitotic spindle block cells in mitosis [11], provoking an accumulation of events in the G_2M region of the DNA histograms.

Only a few *in vivo* studies have been reported, monitoring the cell cycle distribution during chemotherapy and correlating the

Table 4. Cytokinetic modifications in the two different chemotherapeutic protocols

Kinetic modification	CFA	TFC
None	18 (37%)	6 (27%)
S	9 (18%)	14 (64%)
G_2	16 (33%)	1 (4.5%)
Subpopulation change	6 (12%)	1 (4.5%)

changes to the treatment efficacy [12–14], and another study on repetitive FNS analysis of breast lesions, described only morphological changes [15].

The present report is the first to our knowledge including both SPF and BrdU incorporation analyses, although the latter was performed only on 58 of the 71 patients included in our series. Because our instrument is equipped with a pulse processor, a relatively fine analysis of the cell cycle distribution was possible, mainly as a result of the exclusion of aggregates which may bias the estimation of the G_2M cells.

71 of the 92 patients (77%) included in the study were considered informative, mostly because of the difficulty in obtaining a sufficient number of cells in all three FNS and sometimes because of the complexity or the poor quality of the histograms. Modifications were frequent (66%) and consisted of an increase or decrease of the S-phase compartment (both using DNA content and BrdU incorporation), G_2M accumulation or subpopulation changes. These were highly significantly related to tumour regression, although some exceptions were noted. In order to facilitate the analysis of our data, changes in the subpopulations present on the DNA histograms (reduction or appearance of a new one, not corresponding to double the value of the G_1 peak) were considered at an equal level with cytokinetic modifications. However, subpopulation changes may be less specific, since they could also reflect tumour heterogeneity [9]. It must also be stressed that only cases for which the corresponding cytological smears throughout the first cycle showed roughly equivalent proportions of cancer cells were included. This is particularly important for the understanding of the case shown in Fig. 1.

On the other hand, few cases presenting unchanged kinetic parameters throughout the study were found to respond clinically. This group consisted essentially of tumours with low proliferation (6/8), for which all measurements are less precise. But it is significant that for the case with persistently high BLI throughout three cycles of chemotherapy, a local recurrence occurred 20 months later. One interpretation could be that the unmodified proliferative activity corresponded to an authentically resistant subpopulation.

In the low proliferation group there were fewer cytokinetic modifications. However, some cases with very low initial values of BLI and/or SPF did show substantial changes in the subsequent samplings. In these instances, it might be hypothesised that other parameters such as cell cycle phase duration may come into play. Indeed, substantial variations of the duration of DNA synthesis have been reported in a study using *in vivo* BrdU incorporation [23]. A more pronounced cell cycle effect can be expected for a tumour with short cell cycle duration, despite a relatively low initial SPF or BLI, both only providing a measurement of the S-phase.

As stated previously, all cytotoxic agents do not produce the same changes in the cell cycle distribution as defined by FCM. Of the 71 patients in our series, 49 had received a protocol including doxorubicin and 22 one with no anthracycline. Interestingly, different patterns of cell cycle perturbations were observed in the two groups. In the TFC group, there was practically no observation of G_2M accumulation (1/22) while this phenomenon seemed to be frequent in the CFA group (16/49). Thiotepa and cyclophosphamide are both alkylating agents which have been shown to provoke S-phase accumulation [16]. 5-FU is an inhibitor of the S-phase through its interaction with the thymidilate synthase enzyme [17]. On the other hand, doxorubicin has been reported to induce a G_2M block in various model systems [18, 19]. Therefore, our results seem to correspond to the expected cell cycle modifications, although caution should be used in comparing the single agent effects *in vitro* to those of multidrug protocols *in vivo*. Another source of potential bias might have been the choice of the timing of the sequential samplings. These were chosen in accordance with the schedule of treatment for outpatients, and no indication can be given as to the optimal moments for obtaining maximal kinetic modifications.

We also confirmed the results of a previous study concerning the relationship between the pretreatment proliferative activity and the response to neoadjuvant chemotherapy [8]. The increase in the frequency of overall and complete response when one of the proliferation-related parameters was elevated may prove to be important, since in many studies on breast cancer these have been shown to correlate with poor prognosis [20–22].

In conclusion, the accessibility of breast cancers to serial fine needle cytological sampling, combined with the powerful FCM-based cell cycle analysis, should allow a better understanding of the cellular events during chemotherapy and help to identify subsets of patients who fail to respond to treatment or who respond suboptimally. We can at present speculate that the analysis of early cytokinetic modifications during neoadjuvant chemotherapy can be used to identify the biologically non-responding tumours with above median proliferation indices. This can have a considerable impact on the therapeutic decision since we have shown that within this subgroup less than 30% of patients remain disease-free at 24 months [24].

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MICE: a New Active Combination for Non-small Cell Lung Cancer

Giuseppina Arcangeli, Alberto Zaniboni, Salvatore Milano, Fausto Meriggi, Edda Simoncini, Patrizia Marpicati and Giovanni Marini

We have treated 38 patients with stage III/IV non-small cell lung cancer with the following regimen: mitomycin-C = 6 mg/m², ifosfamide = 3 g/m², cisplatin = 75 mg/m², vindesine = 3 mg/m² (MICE), intravenously (i.v.) on day 1, every 3 weeks. Among 26 patients with stage IV disease, 15 obtained a partial remission (PR) (response rate = 57%, 95% confidence interval = 38–76), with a median time to disease progression and a median survival of 4.9 and 7.1 months, respectively. 6 out 7 patients with stage IIIA disease were documented as PR and 5 of them underwent radical surgery with two pathologically confirmed complete remissions. Overall toxicity was substantial but manageable: 3 patients had grade III/IV leucopenia (although 5 patients had neutropenic fever) whereas 13 patients experienced grade II/III anaemia. In conclusion we believe that MICE regimen is an interesting combination and warrants further evaluations both for palliation and in a neoadjuvant setting.
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INTRODUCTION

THE HIGH incidence, the elevated mortality rate and the low curability of non-small cell lung cancer (NSCLC) represent a frustrating challenge for the oncologist.

A number of cytotoxic drugs have been studied alone or in combination to improve the results, but at present the response rate for this tumour ranges between 5 and 50% and median survival approximates 20–30 weeks in stage IV patients [1].

In an attempt to contribute to this challenge, we began a phase II study using the four most active drugs in NSCLC: mitomycin C, ifosfamide, cisplatin and vindesine (MICE) [2]. We based our experience on the Cullen's MIC regimen [3] by increasing the cisplatin dose and adding vindesine.

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PATIENTS AND METHODS

Patients

Between September 1989 and January 1992, 38 consecutive patients (36 males, 2 females) with advanced histologically proven NSCLC entered into the study according to the following elegibility criteria: performance status (ECOG) 0–3; age less than 70 years; histologically confirmed NSCLC; measurable disease; no prior chemotherapy; total white blood cell count $> 4000/mm^3$; platelet count $> 100000/mm^3$; bilirubin < 1.5 mg/dl; creatinine < 1.2 mg/dl; oral informed consent. 15 patients had adenocarcinomas, 21 squamous cell carcinomas, 2 large cell carcinomas. 5 patients had been previously resected for primary tumour and then they relapsed before entering into this study. All patients were chemo-naive. There were 26 stage IV, 7 stage III A and 5 stage III B patients. Sites of disease