4. Carmichael J, Cornbleet MA, MacDougall RH, *et al.* Cisplatin and methotrexate in the treatment of transitional cell carcinoma of the urinary tract. *Br J Urol* 1985, 57, 299–302.
5. Hermann GG, Geertsen PF, von der Maase H, *et al.* Recombinant interleukin-2 and LAK-cell treatment of advanced bladder cancer: Clinical results and immunological effects. *Cancer Res* 1992, 52, 726–733.
6. Miller AB, Hoogstaten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, 47, 207–214.
7. Hillcoat BL, Raghavan D, Matthews J, *et al.* A randomised trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. *J Clin Oncol* 1989, 7, 706–709.
8. Oliver RTD, Kwok HK, Highman WJ, Waxman J. Methotrexate, cisplatin and carboplatin as single agents and in combination for metastatic bladder cancer. *Br J Urol* 1986, 58, 31–35.
9. Stoter G, Splinter TAW, Child JA, *et al.* Combination chemotherapy with cisplatin and methotrexate in advanced transitional cell cancer of the bladder. *J Urol* 1987, 137, 663–667.
10. Harker WG, Meyers FJ, Freiha FS, *et al.* Cisplatin, methotrexate, and vinblastine (CMV): An effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract—A Northern California Oncology Group Study. *J Clin Oncol* 1985, 3, 1463–1470.
11. Logothetis CJ, Dexeus FH, Finn L, *et al.* A prospective randomised trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990, 8, 1050–1055.
12. Sternberg CN, Yagoda A, Scher HI, *et al.* M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988, 139, 461–469.
13. Waxman J, Abel P, Farah JN, *et al.* New combination chemotherapy programme for bladder cancer. *Br J Urol* 1989, 63, 68–71.

Eur J Cancer, Vol. 29A, No. 3, pp. 350–354, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Phase II Study of Pirarubicin (THP) in Patients with Cervical, Endometrial and Ovarian Cancer: Study of the Clinical Screening Group of the European Organization for Research and Treatment of Cancer (EORTC)

J. Chauvergne, P. Fumoleau, P. Cappelaere, R. Metz, J. P. Armand, B. Chevallier, P. Kerbrat, M. de Forni, C. Lhommé, H. Roche, Ph. Chollet, A. Goupil, N. Guiochet, P. Herait and M.A. Lentz

From 1986 to 1990, a multicentric phase II study was conducted with pirarubicin, a new semi-synthetic anthracyclin [4′-*O*-tetrahydropyranyl-adriamycin (THP)]. 87 patients with advanced gynaecological cancers were treated: epidermoid cervical carcinoma (n = 31), adenocarcinoma of the endometrium (n = 28) and ovarian adenocarcinoma (n = 28). THP was administered by short intravenous infusion, for 3 consecutive days, every 3 weeks. The initial dose of THP was 25 mg/m² day (25% of patients) which was then reduced to 20 mg/m² day. The average number of courses was 3.7 (range 1–10). The cumulative THP dose was 180 mg/m² (range 56–594) in cervix and endometrial tumours and 121 mg/m² (range 58–425) in ovarian tumours. Myelosuppression was the major observed toxicity with grade 3–4 leukopenia and thrombocytopenia in 62 and 19% of the patients, respectively. Severe general complications occurred in 6% of the patients with three fatalities due to infections. Gastro-intestinal side-effects were frequent and usually mild (7% of grade 3 vomiting). 48% of the patients showed alopecia, which was complete in 9 cases (10%). 3 patients experienced cardiac events. No significant antitumoral activity was observed in patients who had failed to respond to previous chemotherapy. Promising antitumoral activity was noticed in untreated cervico–uterine carcinomas with 19% partial responses and 12% complete responses (CR). THP activity was lower in endometrial carcinomas (9.5% CR). Results were found to be negligible in ovarian cancer patients, most of them being refractory to previous chemotherapy containing an anthracyclin compound. On the basis of these results, the definite role of THP in gynaecological cancers deserves to be studied in more favourable programmes (e.g. in combined protocols as first-line chemotherapy).
Eur J Cancer, Vol. 29A, No. 3, pp. 350–354, 1993.

INTRODUCTION

PIRARUBICIN [4′-*O*-tetrahydropyranyl-adriamycin (THP)] is a semi-synthetic analogue of doxorubicin and chemically resembles other anthracyclins [1, 2]. It acts by inhibiting DNA synthesis via intercalation or direct interaction with DNA polymerase and topoisomerase II. It also acts by generating free radicals and modifying membraneous phospholipids [3]. THP blocks the cell cycle in phase G2. In experimental models, THP antitumoral activity was found to be at least equivalent to that of doxorubicin [4] and showed a higher and faster intracellular uptake [5, 6] and less pronounced myocardial, capillary [7] and biological [8] toxicities.

THP pharmacokinetics in humans showed brief tissular distribution [8] and high intracellular—especially intratumoral—concentrations [6]. THP half life is short with the main metabolite being doxorubicin, which is detected after active metabolites such as glycosyl compounds. Doxorubicin accumulates in the plasma when THP is administered by short intravenous injections over 3 consecutive days [9]. The main pathway of THP elimination is by the biliary tract [10, 11], with high hepatic clearance.

Initial phase I studies showed THP to be of mild toxicity, particularly in relation to the heart and the gastro-intestinal tract. Myelosuppression was dose-limiting (mainly neutropenia). THP antitumoral activity was close to that of doxorubicin and was observed in non-Hodgkin lymphoma [objective response 36%; objective response (OR) = partial response (PR) + complete responses (CR)] [12] in solid tumours, in particular in pretreated (OR 20–30%) or untreated (OR 40%) breast carcinomas [13, 14]. Several phase II studies had been carried out in various countries in order to define THP activity and give recommendations for further development.

The phase II studies by the Clinical Screening Group of EORTC were conducted from October 1986 to October 1990 and included 233 patients (220 evaluable) with eight different tumour types including soft tissue sarcoma, malignant melanoma, renal adenocarcinoma, head and neck, colorectal, ovarian, endometrial and uterine cervix cancers. Of the 95 patients with gynaecological cancers, 8 were deemed ineligible with regard to inclusion criteria: no measurable lesions (4 patients: 2 cervical, 2 ovarian), hyper-creatinaemia prior to study entry (1 cervix, 1 ovarian), two concomitant cancers (1 patient), misleading interpretation of pathological type (1 patient; no primary ovarian cancer but ovarian metastasis).

The present study reports the results of the remaining 87 evaluable patients, who were treated in 18 different European institutions (15 French centres).

MATERIALS AND METHODS

Patient selection

Patients with advanced, histologically proven, gynaecological malignancies were included in this phase II study. Tumour type distribution was: 31 epidermoid cervical cancers, 28 endometrial adenocarcinomas and 29 ovarian adenocarcinomas. Additional entry requirements included: age < 70 years, exclusion from conventional therapy, evidence of disease progression within 1 month prior to study entry and at least one site of evaluable or measurable disease. Patients had to have adequate bone marrow, renal and hepatic functions [white blood cell (WBC) count > 4000/mm^3, granulocytes > 2000/mm^3, platelets > 100 000/mm^3, bilirubin < 35 μmol/l, creatinine < 135 μmol/l) and WHO performance status < 2.

Patients with unique brain metastasis, with prior cardiac history or previous cancer, were not eligible for the study. Sociopsychological conditions compromising the patient's ability to complete the study were considered as an exclusion criterion.

Patients' characteristics are summarised in Table 1, with respect to the primary tumour type.

Treatment

THP was administered by bolus injection intravenously by washing of the venous line with isotonic glucose infusion. The initial schedule was 25 mg/m^2/day, for 3 consecutive days, every 4 weeks and was applied in 25% of the patients. Because of haematotoxicity, treatment protocol was modified from March 1987 as follows: 20 mg/m^2 day, for 3 consecutive days, every 3 weeks.

The planned maximum cumulative dose of THP was 550 mg/m^2 (calculated in mg anthracyclin equivalent) unless early drug discontinuation was recommended due to disease progression, disease stabilisation (after a maximum of three courses) or cardiac or haematological toxicities which had required immediate drug stoppage or drug delay > 3 weeks).

Follow-up

Antitumoral response was assessed after two completed courses (6 weeks) unless there was evidence of early disease progression. Regular work-ups were carried out in order to evaluate both tolerance and efficacy prior to each course of THP. These consisted of a physical examination, measurement of

Table 1. Patients' characteristics

	Site of cancer			
	Uterine cervix	Endometrium	Ovary	Total
Number of patients	31	28	28	87
Age (years)				
Median	55	64	60	
Range	34–70	47–70	31–69	
Performance status (WHO)				
0	4	7	14	25
1	15	7	10	32
2	12	14	4	30
Previous treatment				
Surgery	18	23	26	67
(curative)	(17)	(22)	(14)	
Radiotherapy	30	27	4	61
(R)*	(16)	(12)	(2)	
Chemotherapy	15	7	27	49
(R)	(2)	(3)	(11)	
With anthracyclin	0	4	19	23
(R)		(2)	(7)	
Hormonotherapy	0	13	2	15

*Number of responders.

Correspondence to J. Chauvergne at the Fondation Bergonié, 180, rue de Saint-Genès-F-33076, Bordeaux, Cedex, France.
P. Fumoleau is at the Centre René-Gauducheau, Nantes; P. Cappelaere is at the Centre Oscar-Lambret, Lille; R. Metz is at the Centre Alexis-Vautrin, Vandoeuvre-les-Nancy; J.P. Armand, M. de Forni and C. Lhomme are at the Institut Gustave-Roussy, Villejuif; B. Chevallier is at the Centre Henri-Becquerel, Rouen; P. Kerbrat is at the Centre Eugène-Marquis, Rennes; H. Roche is at the Centre Claudius Régaud, Toulouse; Ph. Chollet is at the Centre Jean-Perrin, Clermont-Ferrand; A. Goupil is at the Centre René Hugenin, Saint-Cloud; N. Guiochet is at the Hospices Civils, Strasbourg; P. Herait is at the Laboratoire Roger Bellon, Neuilly sur Seine, France; and M.A. Lentz is at the EORTC Data Center, Bruxelles.
Contributions were also received from the Hôpital Universitaire Saint-Pierre, Bruxelles; the I.P.O. Facultade de Medicina, Coimbra, Portugal; the Centre Léon-Bérard, Lyon; the Institut Paoli-Calmettes, Marseille; the Centre Catherine-de-Sienne, Nantes; the Institut Jean-Godinot, Reims, France; and the Rotterdam Cancer Institute, Rotterdam, The Netherlands.
Revised 2 July 1992; accepted 20 July 1992.

Table 2. Dose adaptation as a function of bilirubin value

Leucocytes (10^9/l)	Platelets (10^9/l)	Bilirubin (μmol/l)	Doses (%) THP-ADM*
⩾ 4	⩾ 120	< 26	100
3.0–3.9	⩾ 75	25–50	75
2.0–2.9	⩾ 50	—	50
		> 50	25
< 2	< 50	—	0†

THP-ADM = 4′-*O*-tetrahydropyranyl-adriamycin.
*Percentage of optimal calculated dose/m².
†Treatment delayed for 1 week until leucocytes ⩾ 3 and platelets ⩾ 75.

tumour lesions, complete blood cell count, bilirubin and creatinine evaluations and electrocardiogram (ECG) investigations.

Chest X-rays, ultrasonograms or computer tomography (CT) scans were repeated every 2 months and complete haematological and biochemical counts every 3 months. Above a cumulative THP dose of 300 mg/m², the left ventricular ejectional fraction (LVEF) was assessed by echocardiography every 3 months. Other investigations were performed as clinically indicated.

Treatment was discontinued when significant changes in ECG and/or LVEF (result < 40% or decrease by 15% with respect to the baseline value) occurred. In the event of haematotoxicity, the dose of THP was reduced or the treatment discontinued, as indicated in Table 2. Table 2 also details the dose modifications as a function of bilirubin value.

Toxicity and antitumoral responses were assessed according to standard WHO criteria [15, 16]. An objective response had to be maintained for > 4 weeks. The duration of an objective response was calculated from the time of diagnosis in complete responders and from the first day of treatment until evidence of disease progression in partial responders.

RESULTS

The median duration of treatment was four courses over 12 weeks in endometrial and cervical cancers and three courses over 9 weeks in ovarian cancers. The number of administered courses ranged from one to 10.

38 patients received less than three courses, 40 patients received three to six courses and 9 patients received more than six courses (treatment duration > 4 months).

Cumulative dose of THP ranged from 58 to 594 mg/m², with a median of 180 mg/m² in cervical and endometrial cancers and 121 mg/m² in ovarian cancers. Daily dose was escalated in 3 patients (1 cervical, 2 endometrial) and was reduced in 37 patients (12 cervical, 15 endometrial, 10 ovarian).

Treatment was delayed at least once in 42 patients (48%): 13 cervical (38%), 10 endometrial (36%), 19 ovarian (57%).

All 87 eligible patients were assessed for toxicity. 8 patients were not evaluable for tumour response, owing to 6 early deaths (3 drug-related; 1 cervical, 1 endometrial, 1 ovarian) and 2 treatment refusals (1 endometrial, 1 cervical). Overall response rate was calculated on the 87 eligible patients according to the WHO guidelines.

Toxicity

THP-induced myelosuppression was the predominant toxicity. Non-haematological complications were also observed, as detailed in Table 3, and were pooled together since no significant differences emerged with respect to the tumour type.

Haematological toxicity. THP-induced haematotoxicity consisted of myelosuppression with predominant leukopenia (71 patients, 81.6%) and less frequent thrombopenia (32 patients, 37%). Grades 3–4 WBC nadir values (i.e. < 2000/m³) were observed in 65% of the patients; 25% were grade 4 (i.e. < 1000/m³) (median 1300, range 0.1–8000; median time of onset: day 14). Granulocyte nadir count was < 0.5/mm³ in 34% of the patients (median 0.5, range 0–6400). Platelet nadir count was < 25 000/mm³ in 9% of the patients (median 118 000, range 5000–595 000). Severe (grade 3–4) leuko- and thrombocytopenia were associated in 17 patients (19.5%): 5 cervical (4 pretreated, 1 drug-related death due to sepsis in a patient who had previously received mitomycin), 4 endometrial (3 pretreated, 1 drug-related death due to aplasia, day 17, in a patient who had previously received carboplatin), 8 ovarian (all heavily pretreated). Haematological recovery occurred within normal delays in all courses, except 1.

Haematological complications were fatal in 2 cases (2.3%). THP myelosuppression was found to be dose-dependent (75 or 60 mg/m² day). The comparative analysis of the haematological nadir values showed significant differences ($P < 0.05$) in cervical cancer with respect to platelet count (3 grades 3–4 at 75 mg/m²/day, 2 grade 3 at 60 mg/m²/day) and in endometrial cancer with respect to white blood cell count (2 grade 3 at 75 mg/m²/day, no grade 3 at 60 mg/m²), but these results are not significant because of the limited sample of patients in each group studied.

Non-haematological toxicities. Nausea/vomiting occurred in 60 (69%) of the courses; 6% were grade 3 and required antiemetic therapy (no difference with regard to the tumour type).

5 patients showed mucositis (associated with dysphagia in 1 patient) and 11 patients experienced diarrhoea (cervical and ovarian tumours), which was prolonged in 1 case. 23 patients developed infections (26%), 6 of major gravity (3 sepsis, three toxic-infectious syndromes, two of them unrelated to concomi-

Table 3. Toxicity

Side-effects	WHO grade (no. of patients) 1	2	3	4
Fever	0	2	0	0
Haemorrhage	4	1	0	1
Infection	10 (21%)	8	2 (6%)	3*
Nausea/vomiting	39 (62%)	15	6 (7%)	0
Stomatitis	2	2	1	0
Diarrhoea	8	2	1	0
Cardiotoxicity	2	0	1	0
Hepatotoxicity	0	1	0	0
Nephrotoxicity	0	1	0	0
Alopecia	24 (39%)	10	9 (9%)	0
Hematological toxicity				
Leukocytopenia	3 (16%)	11	35 (65.5%)	22
Neutropenia	5 (15%)	8	24 (62.0%)	30
Thrombocytopenia	8 (17%)	7	9 (19.5%)	8

*Three deaths with toxic infectious syndrome (cervical cancer: two, endometrial cancer: one).

tant haematoxicity), which occurred after the first cycle and were fatal in three instances. 1 patient, suffering from progressive cervical cancer, showed severe and early haematuria after one course.

3 patients (3.5%) showed cardiac events: ECG ischaemia (grade 1) after the first course (1 patient), asymptomatic LVEF decrease (down to 47%, grade 1) after 10 courses (1 patient) and rhythmic disorders (tachycardia, extrasystoles grade 3, 1 patient) associated with blood pressure paroxyms and malaise. Mild side-effects (< grade 2) included asthaenia (3 patients), headaches (2 patients) and conjunctivitis (2 patients). 1 patient showed renal toxicity (haematuria after one course) and another patient showed hepatotoxicity (bilirubin elevation after six cycles). These were the only cases reported in the 220 patients who received THP within CSG-EORTC phase II studies.

Efficacy

Antitumoral responses were reported separately, taking into account histological differences relative to each tumour type, differently sensitive to anthracyclin compounds (Table 4).

Cervcal carcinoma. Of the 31 patients included, 3 were inevaluable due to early death (1 sepsis, 1 toxic infectious syndrome) or treatment refusal (1 patient). 28 patients were evaluable for response. There were 6 OR (19%) and 2 CR (6.5%). Untreated patients showed a higher response rate than those previously treated: 31.2% [confidence interval (C.I.): 11–58], vs. 6.6% (CI: 0.2–32%). The first CR consisted of supraclavicular lymph nodes regression (after two courses) and lasted 14 weeks. The second CR was on two pulmonary metastasis (after three courses) and lasted 4 weeks.

Partial response sites were: lymph nodes (2 patients), pulmonary (1 patient), locoregional recurrence (1 patient). All PR occurred early (after two courses) with an average duration of 29 weeks (range 20–47).

Cancer of the endometrium. Of the 28 patients treated, 4 were inevaluable due to early death (3 patients: 1 drug-related, 2 intercurrent diseases) or protocol violation (change of drug). Of the 21 pretreated patients, 2 CR occurred (9.5%, C.I. 1.2–30.4%) in axillary lymph nodes (1 patient, after one course) and pulmonary metastasis (1 patient, after five courses) and lasted 18 and 38 weeks, respectively.

No response was observed in the 7 previously treated patients.

Ovarian cancers. Of the 28 patients treated, 3 were not evaluable: early drug discontinuation due to toxicity (1 patient), early death due to disease progression (2 patients). All patients, except 1, had received previous treatment. 1 pretreated patient showed PR. She had previously responded to anthracyclin-containing chemotherapy (epirubicin). She presented a large tumour burden (15 cm in diameter) and ascitis. After four cycles, tumour regression was observed and CA 125 concomitantly decreased (from 10000 to 4300 U/ml). The response duration was 17 weeks.

DISCUSSION

The present study focused on the efficacy and tolerance of THP in three gynaecological cancers. Treated patients who present with advanced diseases and previously received radiotherapy (75%), chemotherapy (> 50%) or both, are a particularly refractory and vulnerable population. Haematological toxicity observed in our series was dose-limiting and similar to data reported for doxuribicin. Nevertheless, THP at the dose of 60 mg/m^2 in patients not previously treated was better tolerated.

An excessive initial dose of THP (75 mg/m^2) was an additional cause underlying the frequent and severe complications that we observed, 3% of them being fatal. Myelosuppression was frequent with predominant leukopenia (65% grades 3–4) and less pronounced thrombocytopenia; 6% of the patients presented life-threatening complications. Although frequent gastro-intes-

Table 4. Treatment responses

	No. of patients					
	Complete response	Partial response	No change	Disease progression	Total*	Response (%)
Uterine cervix						
No prior therapy	2	3	4	6	16	31.25
Prior therapy	0	1	4	8	15	6.67
Total	2	4	8	14	31	19.35
Total (%)	6.45	12.90	25.81	45.16		
Endometrium						
No prior therapy	2	0	9	8	21	9.52
Prior therapy† A	0	0	1	3	4	0
B	0	0	0	1	3	0
Total	2	0	10	12	28	7.14
Total (%)	7.14	0	35.71	42.86		
Ovary						
No prior therapy	0	0	0	1	1	0
Prior therapy† A	0	1	5	11	19	5.26
B	0	0	4	3	8	0
Total	0	1	9	15	28	3.57
Total (%)	0	3.57	32.14	53.57		

*All patients (evaluable or not).

†Treatment with anthracyclin (A) or without (B).

tinal side-effects were not severe (less than 10% of grade 3) cardiotoxicity—which is dose-limiting for doxorubicin—occurred in this relatively elderly population (55–64 years) which had received previous anthracyclin chemotherapy in 25% of the cases. 2 patients showed dysrythmia and 1 patient LVEF decrease, which was easily manageable and non-progressive. Other extrahaematological side-effects of THP were mild (especially alopecia), like epirubicin.

Although conducted on a limited series of 31 patients, the present study showed THP to be active in untreated cervical carcinomas with more than 30% of OR (C.I. 11–58%) and 6% of CR (C.I. 0.2–32%). This response rate compared with that reported for drugs known to be active in cervical carcinomas, and was higher than that of anthracyclin, which averaged at 20% depending on the dose [17, 18]. Multidrug protocols gave an increased OR from 30 to 50%. Contrary to mitomycin, the integration of an anthracyclin compound did not improve the antitumoral efficacy significantly. The definite role of THP deserves to be studied in multidrug combinations as palliative or neoadjuvant settings.

The poor response rate (< 10%) that we observed in our series of endometrial cancers did not agree with the reported results of anthracyclin in this tumour type. Indeed, anthracyclins are considered as some of the most active drugs (OR: 20–35% as single agent) which compare to platinum or alkylating agents [19–21]. Improved efficacy was observed by cisplatin–anthracyclin combinations with overall OR increasing from 35 to 57% ($P < 0.01$). In fact, the major problem did not really consist of poor chemosensitivity, but poor treatment compliance in those patients with poor general conditions due to age or associated diseases. A less cardiotoxic anthracyclin compound is needed which might allow its safe administration in combined protocols, mainly as induction chemotherapy.

In the patients treated for ovarian cancer, THP showed minimal activity (OR < 5%). These results were not consistent with those reported for other anthracyclin compounds whose activity averaged 30% in first line therapy, or with a previous study of THP (OR: 25%) [22]. Since pretreatment favours an acquired pleitropic resistance, the low response rate in ovarian cancer is not surprising.

A high response rate can be obtained by the integration of an anthracyclin compound into a multidrug combination [23–25]. Nevertheless, the definite role of these compounds remains controversial because of associated toxicity and the lack of significant results, both in terms of histopathological response rate and survival (no change of median survival). A higher dose intensity due to better tolerance could result in a higher response rate or better long-term results, as reported for other anthracyclins [26].

CONCLUSION

THP seems to be of interest for the treatment of gynaecological cancers in patients previously untreated. The limiting toxicity is haematological: neutropenia was sometimes severe at the initial dose of 75 mg/m^2, which was too high, particularly in pretreated patients. Other systemic side-effects were moderate as compared with other anthracyclin compounds (especially infrequent alopecia and low cardiotoxicity). THP's optimal use has to be defined either in palliative protocols or in intensive induction chemotherapy.

1. Umezawa H, Takahashi Y, Kinoshita M, *et al.* Tetrahydropyranyl derivatives of daunomycin and adriamycin. *J Antibiot* 1979, **32**, 1082–1084.
2. Umezawa H, Yamada K, Oki T. Comparative experimental studies on 4'-O-tetrahydropyranyl-adriamycin and adriamycin. In Mathé G, Maral R, De Jager R, ed. *Anthracyclines Current Status and Future Developments*. Masson Publishing USA. 1981, 183–188.
3. Lavelle F. Structure et activité des anthracyclines. *Path Biol* 1987, **35**, 11–19.
4. Tsuruo T, Lida H, Tsukagoshi S, Sakurai Y. 4'-O-Tetrahydropyranyl-adriamycin as a potential new antitumor agent. *Cancer Res* 1982, **42**, 1462–1467.
5. Kunimoto S, Miura K, Takahashi Y, Takeuchi T, Umezawa H. Rapid uptake by cultured tumor cells and intracellular behavior of 4'-O-tetrahydropyranyl-adriamycin. *J Antibiot* 1983, **36**, 312–317.
6. Munck JN, Fourcade A, Bennoun M, Tapiero H. Relationship between the intracellular level and growth inhibition of a new anthracyclin 4'-O-tetrahydropyranyl-adriamycin in Friend leukemia cell variants. *Leuk Res* 1985, **9**, 289–296.
7. Dantchev D, Paintrand M, Hayat M, Bourut C, Mathé G. Low heart and skin toxicity of a tetrahydropyranyl derivative of adriamycin as observed by electron and light microscopy. *J Antibiot* 1979, **32**, 1085–1086.
8. Miller AA, Schmidt CG. Clinical pharmacology and toxicity of 4'-O-tetrahydropyranyl-adriamycin. *Cancer Res* 1987, **47**, 1461–1465.
9. Robert J, David M, Huet S. Chauvergne J. Pharmacokinetics and metabolism of pirarubicin in advanced cancer patients. *Eur J Cancer Clin Oncol* 1988, **24**, 1289–1294.
10. Majima H, Iguchi H, Tone H. Pharmacokinetic studies of tetrahydropyranyl-adriamycin. *Jap J Cancer Chemother* 1986, **13**, 542–548.
11. Robert J, David M, Huet S, Chauvergne J, Monnier A. Pharmacocinétique de la pirarubicine (THP-doxorubicine) chez des malades cancéreux. *Bull Cancer* 1989, **76**, 889–892.
12. Ogawa M, Miyamoto H, Inigari J. Phase I clinical trial of a new anthracycline: 4'-O-tetrahydropyranyl-adriamycine. *Invest New Drugs* 1983, **1**, 169–172.
13. Samonigg H, Kasparek AK, Sröger H, *et al.* 4'-O-Tetrahydropyranyl-doxorubicin in advanced breast cancer: a phase II study. *Cancer Chemother Pharmacol* 1990, **26**, 293–296.
14. Spielmann M, Kerbrat P, Delozier R, *et al.* Pirarubicin in advanced breast cancer: a French cooperative phase II study. *Eur J Cancer* 1990, **26**, 821–824.
15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
16. WHO (World Health Organization). *WHO Handbook for Reporting Results of Cancer Treatment*. Offset Publication No. 48, Geneva, 1979.
17. Muscato MS, Perry MC, Yarbro JW. Chemotherapy of cervical carcinoma. *Semin Oncol* 1982, **9**, 373–387.
18. Wong LC, Choy DTK, Ngan HYS, Sham JST, Ma HK. 4-épidoxorubicin in recurrent cervical cancer. *Cancer* 1989, **63**, 1279–1282.
19. Cappelaere P, Horner-Vallet D, Demaille A. Chemotherapy of endometrial adenocarcinomas. In Bolla M, Racinet G, Vrousos C, eds. *Endometrial Cancers*. Basel, Karger. 1986, 177–182.
20. Chauvergne J, Avril A, Pigneux J, Mage P, Granger C. Place actuelle de la chimiothérapie dans le traitement des adénocarcinomes de l'endomètre. *Bull Cancer* 1986, **73**, 675–679.
21. Moore TD, Phillips PH, Nerenstone SR, Cheson BD. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *J Clin Oncol* 1991, **9**, 1071–1088.
22. Kato T, Nishimura H, Umezu J, *et al.* Phase II study of 4'-O-tetrahydropyranyl adriamycin (THP-ADM) in patients with gynecological cancer. *Jap J Cancer Chemother* 1985, **12**, 1962–1967.
23. Bertelsen K, Jackobsen A. Andersen JE, *et al.* A randomized study of cyclophosphamide and cisplatinum with or without doxorubicin in advanced ovarian carcinoma. *Gynecol Oncol* 1987, **28**, 161–169.
24. Levi F, Benavides M, Chevelle C, *et al.* Chemotherapy of advanced ovarian cancer with 4'-O-tetrahydropyranyl doxorubicin and cisplatin: a randomized phase II trial with an evaluation of circadian timing and dose-intensity. *J Clin Oncol* 1990, **8**, 705–714.
25. Omura GA, Bundy BN, Berck JS, Curry S, Delgado G, Mortel R. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol* 1989, **7**, 457–465.
26. Bezwoda WR. Treatment of advanced ovarian cancer: a randomized trial comparing adriamycin or epi-adriamycin in combination with cisplatin and cyclophosphamide. *Med Pediatr Oncol* 1986, **14**, 26–34.