Haematologica 2000; 85:502-507
original paper

Phase II study of 3-hour infusion of high dose paclitaxel in refractory and relapsed aggressive non-Hodgkin's lymphomas

RENÉ-OLIVIER CASASNOVAS, CORINNE HAIOUN, CHARLES DUMONTET, JEAN GABARRE, BRUNO RICHARD, PIERRE LEDERLIN, DENIS CAILLOT, ASPASIA STAMATOULLAS, PIERRE MOREL, BRUNO QUESNEL, JEAN-YVES BLAY, KAMEL BOUABDALLAH, CHRISTIAN GISSELBRECHT FOR THE GROUPE D'ETUDE DES LYMPHOMES DE L'ADULTE
Centre Hospitalier Universitaire Le Bocage, Dijon; Hôpital Henri Mondor, Créteil; Centre Hospitalier Lyon-Sud, Pierre Bénite; Hôpital Pitié-Salpétrière, Paris; Centre Hospitalier Universitaire Nimes; Centre Hospitalier Universitaire Brabois, Nancy; Centre Henri Becquerel, Rouen; Centre Hospitalier Schaffner, Lens; Centre Hospitalier Universitaire Huriez, Lille; Centre Léon Bérard, Lyon; Centre Hospitalier Libourne; Hôpital St Louis, Paris, France

ABSTRACT

Background and Objectives. **The first clinical studies of paclitaxel as a single agent for the treatment of relapsed or refractory low or intermediate grade non-Hodgkin's lymphomas (NHL) yielded controversial results regarding the response rates observed, mainly related to the dose and schedule of administration used. To obtain additional data concerning the efficacy and toxicity of paclitaxel in intermediate and high grade NHL we initiated a phase II study using a 3-hour infusion of high doses of paclitaxel.**

Design and Methods**. The eligibility criteria included patients with relapsed or refractory aggressive NHL, a performance status ≤ 2 (WHO index), a platelet count ≥ 100,000 / µL, a neutrophil count ≥ 2,000 / µL, measurable disease, and adequate hepatic function. Patients were excluded if they were infected with HIV, had a left ventricular ejection fraction < 50%, or prior peripheral neuropathy. Paclitaxel was administered as a 3-hour infusion at a dose of 250 mg / m² every 3 weeks for a maximum of 6 courses.**

Results. **Of 45 eligible patients, 42 received a total 73 courses of paclitaxel. Forty patients were assessable for response (89%), and 42 for toxicity (93%). Six patients (15%) achieved a partial (n = 4) or a complete remission (n = 2). Responses were observed in intermediate grade (n = 4) as well as in high grade lymphoma (n = 2). The main factor influencing the response to paclitaxel was the median duration of response to previous chemotherapy regimens which was 3 times longer in patients who responded to paclitaxel (16.3 months) than in patients who did not respond to paclitaxel (5.2 months) ($p < 0.05$). The most common serious side effects were related to the hematologic toxicity of paclitaxel, and included grade IV granulocytopenia in 20 cases (48%), grade III / IV thrombocytopenia in 14 cases (33%) and grade III-IV anemia in 13 cases (31%).**

Interpretation and Conclusions. **Despite frequent manageable hematologic toxicity, paclitaxel is usually well tolerated at a dose of 250 mg / m² given by a 3-hour infusion. However, the clinical efficiency as a single therapy seems modest in relapsed or refractory aggressive lymphoma.**

Key words: lymphoma, paclitaxel, phase II

Correspondence: R.O. Casasnovas, MD, Hématologie Clinique, Hôpital Le Bocage CHU Dijon, 2104 Dijon Cedex, France. Phone: international +33.3.80293306 - Fax: international +33.3.80293605 – E-mail: hemato.clinique@planetb.fr

Although non-Hodgkin's lymphoma (NHL) appears to be a chemosensitive malignancy, only half of patients with intermediate- and high-grade lymphomas achieve long-term disease free survival. Paclitaxel, a recently available drug, has proven to be one of the most promising antimicrotubule agents against various human cancers, especially ovarian, breast and lung carcinomas.[1] Previous studies of paclitaxel as single agent treatment of relapsed or refractory lymphomas yielded heterogeneous results which have been mainly related to differences in the doses and the schedule of administration of this molecule.[2-6] The best overall response rate published reached 25%, including 11% complete responses, and were reported for a 3-hour 200 mg/m² infusion schedules of paclitaxel.[5] Two previous studies using continuous infusions had found no more than a 17% response rate with few complete responses.[2,6] These studies were performed on patients with low grade as well as intermediate grade lymphomas.

To address the question of efficiency and tolerance of paclitaxel in intermediate and high grade lymphoma specifically, we designed a phase II study using a high dose of paclitaxel (250 mg/m²) infused over 3 hours.

Design and Methods

Patients

From May 1995 to February 1997, 45 patients were assigned to receive paclitaxel in a phase II study approved by the institutional review board from the university hospital of Dijon (CCPPRB). All patients had a histologically confirmed intermediate or high grade lymphoma including, diffuse large B-cell, Burkitt's, lymphoblastic, follicular center cell grade III, anaplastic, or peripheral large T-cell lymphoma subgroups of the REAL classification. All patients had relapsed or refractory disease after having

received at least one standard regimen, with an identical histologic type at diagnosis and at relapse, were considered to be incurable, and signed informed consent to the study. The staging of disease, performed less than 3 weeks before entry into the study, required a complete physical examination, computed tomography of the chest, abdomen, and pelvis, bone marrow biopsy, serum lactate dehydrogenase and β_2 microglobulin levels, and complete blood cell count. The eligibility criteria included a performance status ≤ 2 according to the WHO index, a platelet count $\geq 100{,}000/\mu L$, a neutrophil count $\geq 2{,}000/\mu L$ (unless lower counts were due to bone marrow involvement by lymphoma), two-dimensionally measurable tumors, and adequate hepatic function (bilirubin level <1.5 mg/dL, and serum glutamate-pyruvate transaminase level < double the normal value). Patients were excluded if they were infected with human immunodeficiency virus, had previous cardiac arrhythmias, had had a recent myocardial infarction, had a left ventricular ejection fraction less than 50%, or prior peripheral neuropathy of grade ≥ 2. All low grade NHL or transformed lymphomas were also excluded from this study.

Chemotherapy

All patients were premedicated and received 130 mg of prednisone orally 12 and 6 hours before paclitaxel infusion. Thirty minutes before the infusion, the patients were given an intravenous injection of 5 mg of dexchlorpheniramine, and 300 mg of cimetidine. Paclitaxel was infused intravenously over 3 hours at a dose of 250 mg/m^2 and the treatment cycle was repeated every 3 weeks.

The dose was adjusted for hematopoietic toxicities: the dose of paclitaxel was reduced by 20% in patients who had nadir neutrophil or platelet counts below 900/μL or 50,000/μL respectively for a period of at least seven days, or in patients who developed neutropenic fever. The use of granulocyte growth factor was restricted to patients who developed neutropenic fever.

Definition of response

Complete response (CR) was defined as the disappearance of all evidence of disease for at least one month. Partial response (PR) and minor response (MR) were defined as at least a 50% and a 25% reduction respectively in the sum of the products of the greatest diameters of the measurable lesions without evidence of new lesions for at least one month.

Response to treatment was evaluated after each course and specifically after the first two courses of paclitaxel, except for patients whose tumors progressed after one course of paclitaxel, and who were removed from the study. Patients continued the treatment for a maximum of six courses only if they reached at least a partial response after two courses of paclitaxel.

Results

Patients

Of 45 patients who were registered for the study, 42 (93%) received at least one course of paclitaxel and were assessable for toxicity. Three patients (7%) were excluded because they withdrew from the study after signing the consent form but before receiving paclitaxel. Two patients died early after the first course of paclitaxel, and were not assessable for response. Of 40 patients assessable for response, 36 (90%) had advanced disease, with extranodal involvement in 28 cases (70%). Lactate dehydrogenase and β_2 microglobulin levels were elevated in most cases (Table 1). Ten (25%) had a primary refractory lymphoma, the remaining had disease that had been sensitive to at least one previous chemotherapy regimen (Table 1). About half the patients had already received more than 2 chemotherapy regimens, and 9 patients (22.5%) had previously received high dose chemotherapy with autologous hematopoietic stem cell (HSC) transplantation, before receiving paclitaxel.

Treatment response

The overall response rate was 15% in the 40 assessable patients including 4 PR (10%) and 2 CR (5%) (Table 2). The sensitivity of the disease to paclitaxel was observed early during the treatment course. After the first course of paclitaxel, 23 patients (57.5%) had progressive disease and discontinued the treatment, 8 had stable disease (20%) and 9 (22.5%) achieved either a minor (n = 3) or a partial response (n = 6). The 6 patients in PR, remained in PR with further courses of paclitaxel in 4 cases, and achieved a complete response in two cases. Conversely, none of the patients without significant response after the first course of paclitaxel went on to achieve an objective response. The responses were of short duration, with a median time to disease progression of 3.2 months (range, 2.7 to 11).

At entry into the study there was no difference in the initial parameters, clinical presentation (Ann Arbor staging, number of extra nodal sites involved, B symptoms, performance status), or biological data (LDH, β_2 microglobulin), between responding and non-responding patients (Table 1). The responses were observed in all types of histologic subgroups including two high grade lymphomas.

The response was not influenced by the number or the kind of previous treatments received including prior autologous HSC transplantation. Conversely, the occurrence and the duration of a previous response to the first line treatments influenced the response to paclitaxel. So, the median duration between the first diagnosis of lymphoma and inclusion in the trial was significantly longer in patients responding to paclitaxel (median: 24.4 months; range: 2.9 to 52), than those not responding (median: 13.9 month; range: 1.9 to 51.5) (Mann-Whitney test: $p = 0.05$). As well, the overall median duration of response to first line treatments tended to be longer in patients responding to paclitaxel (median: 16.3 months; range: 0 to 40) than in patients not responding to paclitaxel (median: 5.2 months; range: 0 to 37) (Mann-Whitney test: $p < 0.05$). However, while the response rate was also slightly higher in relapsing patients (5/30: 17%), than in patients with refractory disease (i.e. patients who had not achieved a prior CR) (1/10: 10%), this was not statistically significant.

Table 1. Characteristics of 40 assessable patients with relapsed or refractory aggressive lymphoma.

Characteristics of patients	*Total (n = 40) n (%)*	*Response to paclitaxel*		*p*
		Yes (n = 6) n (%)	*No (n = 34) n (%)*	
Age (years)				
Median	63	62.5	63	NS
Range	18-75	47-74	18-75	
Sex				
Male	23 (57.5)	5 (80)	18 (53)	NS
Female	17 (42.5)	1 (20)	16 (47)	
Histology				
B phenotype	35 (87.5)	5 (83)	30 (88)	
Diffuse large B cell				
Centroblastic	28 (70)	2 (33)	26 (76)	
Immunoblastic	4 (10)	2 (33)	2 (6)	
Follicular center cell grade III	2 (5)	1 (17)	1 (3)	
Burkitt's	1 (2.5)	0	1 (3)	NS*
T phenotype	*5 (12.5)*	*1 (17)*	*4 (12)*	
Precursor T-lymphoblastic	1 (2.5)	0	1 (3)	
Anaplastic T-cell	2 (5)	1 (17)	1 (3)	
Peripheral T-cell	2 (5)	0	2 (6)	
Ann Arbor stage				
II	4 (10)	1 (17)	3 (9)	
III	8 (20)	0	8 (23)	NS
IV	28 (70)	5 (83)	23 (68)	
Extranodal sites				
1	13 (46)	3 (60)	10 (43)	NS
32	15 (54)	2 (40)	13 (57)	
B symptoms	20 (50)	1 (17)	19 (56)	NS
Elevated lactate dehydrogenase	28 (70)	4 (67)	24 (71)	NS
Elevated β_2 microglobulin	34 (85)	5 (83)	29 (85)	NS
Disease status				
Primary refractory	10 (25)	1 (17)	9 (26)	
First or second relapse	19 (47.5)	4 (67)	15 (44)	NS°
> second relapse	11 (27.5)	1 (17)	10 (29)	
Prior treatment				
No. of prior chemotherapy regimens				
One	6 (15)	1 (17)	5 (14)	
Two	15 (37.5)	1 (17)	14 (41)	NS
>2	19 (47.5)	4 (67)	15 (44)	
Previous HSC transplantation				
Yes	9 (22.5)	1 (17)	8 (24)	NS
No	31 (77.5)	5 (83)	26 (76)	
Duration of response (months)				
Median	7.1	16.3	5.2	< 0.05
Range	0-40	0-40	0-37	
Duration between initial disease diagnosis and entry into the study				
Median	14.9	24.4	13.9	0.05
Range	1.9-52	2.9-52	1.9-51.5	

**Intermediate vs high grade lymphomas; °relapsing vs refractory lymphomas.*

Toxicity

Forty-two patients received a total of 73 courses at a mean total dose of 460 ± 337 mg/m^2 of paclitaxel. Twenty-three patients received only one course (57.5%), ten received two courses (25%), two received three courses (5%), and five received more than three courses (12.5%) of paclitaxel. The administered dose intensity of paclitaxel calculated at 81.5±7.2 mg/m^2/week, was similar for patients who received either one course or more than one course of paclitaxel, and reached 97.8% of the planned dose.

None of the 42 patients experienced hypersensitivity reactions or cardiac toxicity while receiving paclitaxel (Table 3). Overall, the non-hematologic side effects related to paclitaxel were mild. Nausea and vomiting were infrequent and a stomatitis ≥ grade 2 was observed in only two cases. A peripheral neuropathy ≥ grade 2 was observed after the first course of paclitaxel in 2 cases, and after the third course in 1 case while arthralgias and myalgias ≥ grade 2 occurred in only 1 case.

A neutrophil nadir below 500/μL occurred in 20 patients (48%), and was associated with fever in 17 cases (40%) requiring use of G-CSF. Three patients, including two neutropenic patients, developed a documented sepsis. A *Campylobacter jejuni* septicemia occurred in one case, an *Escherichia coli* infection of the upper urinary tract was diagnosed in another case.

Table 2. Characteristics of the 6 patients responding to the paclitaxel treatment.

Pts	Histology	At entry to the trial					Prior treatment	Response to paclitaxel	Response duration to paclitaxel (months)
		Age (yrs)	Stage	Extranodal sites involved	B symptoms	LDH			
1	DLBCL	47	IV	Stomach, esophagus	No	AN	(1) ACVBP, (2) ESHAP, (3) MINE	PR	3.2
2	DLBCL	74	IV	Rectum	No	AN	(1) ACVBP, (2) MIV, (3) IVAM / AHSCT	CR	8.7
3	DLBCL	62	IV	Pleura	Yes	AN	(1) CHOP	PR	3
4	DLBCL	61	IV	Bone marrow	No	AN	(1) CHOP, (2) MIV, (3) VAD	PR	3
5	Anaplastic T-cell lymphoma	66	II	–	No	N	(1) CHOP, (2) MIV	CR	11
6	Follicular B-cell lymphoma	63	IV	Bone marrow, pleura, liver	No	N	(1) ACVBP, (2) DHAP, (3) IVAM	PR	2.7

Abbreviations: DLBCL, diffuse large B-cell lymphoma, ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, CHOP, doxorubicin, cyclophosphamide, vincristine, and prednisone, DHAP, dexamethasone, high dose cytarabine, and platinum, ESHAP, DHAP + etoposide, MIV, mitoxantrone, ifosfamide, etoposide, MINE, MIV + vinorelbine, IVAM, ifosfamide, vepeside, doxorubicin, methotrexate, VAD, vincristine, doxorubicin, dexamethasone, AHSCT, autologous hematopoietic stem cell transplantation. CR: complete response; PR: partial response.

Table 3. Toxicities in 42 patients treated with paclitaxel.

	Grade of toxicity according to WHO scale							
	0	1	2	3	4	5		
Neutropenia	6	11	8	5	12	0	G-CSF requiring:	17/42 (40%)
Thrombocytopenia	25	2	1	3	10	1	Platelet transfusion:	10/42 (24%)
Anemia	5	11	13	9	4	0	RBC transfusion:	16/42 (38%)
Infection	23	5	11	1	2	0		
Sensory neuropathy	29	10	1	2	0	0		
Arthralgia/myalgia	37	4	0	1	0	0		
Nausea/vomiting	39	2	1	0	0	0		
Diarrhea	35	3	2	1	0	1		
Constipation	40	1	1	0	0	0		
Stomatitis	38	2	1	1	0	0		
Allergic reaction	42	0	0	0	0	0		

Table 4. Published trials including relapsed intermediate or high grade NHL treated with paclitaxel.

	Patients n	Paclitaxel dose	Administration	PR n (%)	CR n (%)	Overall Response Rate	Median duration of response (months)
Wilson	20	140 mg/m^2	96 h continuous infusion	4 (20%)	0	20%	NA
Younes	44	200 mg/m^2	3 h infusion	6 (14%)	7 (16%)	30%	NA
Press	44	175 mg/m^2	24 h continuous infusion	6 (14%)	1 (2%)	16%	3
Goss	35	175 to 210 mg/m^2	3 h infusion	3 (9%)	0	9%	2
Casasnovas	40	250 mg/m^2	3 h infusion	4 (10%)	2 (5%)	15%	3.2

The last patient developed extensive thoracic *Herpes zoster* manifestations. Platelet and hemoglobin nadirs below 50,000/µL and 8 g/100 mL occurred respectively in 33% (14/42) and 31% (13/42) of patients, requiring platelet transfusions in 10 cases (24%) and red blood cell transfusions in 16 cases (38%).

Two deaths related to treatment occurred (4.8%), both due to bleeding complications: one patient who had a lymphoblastic lymphoma with bone marrow involvement developed disseminated intravascular coagulation and died with refractory thrombocytopenia of cerebral bleeding; the second patient who had an intestinal localization of an intermediate grade lymphoma died from gut bleeding 8 days after the first course of paclitaxel.

Discussion

This phase II study demonstrates that high dose paclitaxel, administered by a 3-hour infusion every 3 weeks as single therapy, has a modest activity in refractory and relapsed, intermediate or high grade lymphoma.

The disappointing 15% overall response rate, including only a 5% CR rate, was not related to compliance to the paclitaxel treatment since the administered dose intensity reached about 98% of the planned dose. Consistent with a previous report,[3] the responses occurred early during the courses of paclitaxel. Conversely, 57% of patients were excluded from the trial after the first course because of progressive disease.

The two factors found to be predictive of disease sensitivity to paclitaxel were the median duration passed between the initial diagnosis of lymphoma and inclusion in the trial and consequently, the median duration of response reached with previous chemotherapy regimens. So, the median duration of response to previous treatments was found to be three times longer in patients responding to paclitaxel than those not responding to paclitaxel. Since the number of previous chemotherapy courses and regimens did not differ between the two groups, it appears that alone, the duration of the disease sensitivity to prior chemotherapy influences the occurrence of a clinical response to paclitaxel. However, although the response rate to paclitaxel was higher in relapsed than in refractory patients, the numbers are too small to be significant.

The response rate observed in this study was significantly lower than that reported in a prior phase II trial using the same schedule of infusion but at a lower fixed dose[3,5,7] (Table 1). The discrepancies between these two trials could be partially explained by differences in the populations of patients studied. In our trial, patients were older, more heavily pretreated, particularly with more frequent prior high dose chemotherapy and some had received an autologous hematopoietic stem cell transplantation before paclitaxel. More aggressive disease was also entered in the present study with 15% (6/40) of high grade lymphomas including immunoblastic, lymphoblastic and Burkitt's lymphomas not having been enrolled in the MD Anderson Cancer Center trial.[7] Conversely, our results were very similar to those reported in a recently published escalating dose trial using a 3-hour infusion schedule,[8] and in two previous studies using a continuous infusion of lower doses of paclitaxel[2,6] (Table 4). As observed in breast cancer, for an equal dose of 250 mg/m^2, 24-hour continuous infusions gave better results than 3-hour administrations,[9] and a 140 mg/m^2 96-hour continuous infusion could be equivalent to a 250 mg/m^2 3-hour administration.[10] So altogether, these results suggest that the clinical efficiency of paclitaxel at 140 mg/m^2 by a 96-hour infusion, 175 mg/m^2 by 24-hour infusion and 250 mg/m^2 by a 3-hour infusion is very similar. Moreover, attempts to overcome the resistance of lymphoma to a 3-hour infusion of paclitaxel by using a longer infusion duration,[11,12] based on the increased cytotoxicity of the molecule induced by prolonged exposure of tumor cell lines,[13] failed to improve the clinical response rate to paclitaxel. Modulators of multidrug resistance were no more successful.[14,15]

Overall, whatever the schedule of administration used, the results of the five studies now available, including 183 patients with relapsed or refractory agressive NHL treated with paclitaxel show an overall response rate of 18%, including 23 PR (13 %) and 10 CR (5%). These response rates are very close to those observed with docetaxel, an other agent of the taxan family.[16] In the two studies in which data were available for intermediate and high grade lymphomas (Table 4), the median duration of response was short, not exceeding 4 months and was significantly shorter than in low grade lymphoma.[6] Despite the mild efficiency of paclitaxel as a single agent paclitaxel could be more useful in combination with other drugs in the management of relapsed or refractory NHL. Preliminary data from patients with aggressive NHL who had received a maximum of two previous chemotherapy regimens, and who were treated with a combination of a 3-hour infusion of 200 mg/m^2 paclitaxel with a 30-minute infusion of 1 mg/m^2 topotecan on day 1 through to 5, show a 72% (13 of 18) and a 27% (4 of 15) response rate in relapsed and refractory disease respectively.[17] The combination of high dose cyclophosphamide (900 mg/m^2/day, days 1 to 3) associated with a 3-day continuous infusion of paclitaxel (50 mg/m^2/day) also gave similar results with a 73% response rate in relapsing patients.[18] These promising results from patients with relapsing aggressive NHL need to be confirmed on larger series, and the place of paclitaxel in such a setting remains to be determined.

The side effects observed in this trial were mainly related to the hematologic toxicity of paclitaxel, in agreement with previous published data.[2-6,8] The incidence of neutropenia and thrombocytopenia > grade 3 was slightly higher (40% and 33% respectively) than that observed by either Younes[5] (23% and 21% respectively) or Goss[8] (21% and 5 % respectively) in previous trials using a 3-hour infusion schedule and was probably related to the higher dose of paclitaxel used in our study. Thrombocytopenia was associated with clinical bleeding in one case in the context of disseminated intravascular coagulation and led to the death of the patient. Despite a high incidence of neutropenic fever, no patient died of septic complications. The non-hematologic toxicities were mild

and using appropriate premedication, no serious hypersensitivity reactions occurred.

Our results demonstrate that high dose paclitaxel infused by a 3-hour schedule has a modest activity in relapsed or refractory intermediate or high grade NHL. Paclitaxel remains active and offers brief palliation to patients with relapsed aggressive NHL who have a history of sensitivity to previous lines of treatment.

Contributions and Acknowledgments

All the co-authors enrolled patients in the trial and collected their data. ROC and CG conceived and designed the study. The analysis and the interpretation of data were discussed between the co-authors before the first draft was written by ROC. The manuscript was critically revised by each author, and submitted for approval to the scientific committee of the GELA group. Each co-author approved the final version, and the order of authorship, which was determined according to either the role in the conception of the study, for the first and the last author, or the number of patients included in the study for the remaining co-authors.

We thank the following clinicians who also participated in this study: R. Bouabdallah, S. Caillère, B. Coiffier, P. Collin, E. Jourdan, G. Lepeu, F. Morvan, B. Peault, P. Solal-Celigny, A. Thyss, H. Tilly.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received September 21, 1999; accepted December 30, 1999.

Potential implications for clinical practice

- As a single agent, paclitaxel can offer brief palliation in patients with relapsed aggressive non-Hodgkin lymphomas who have a history of sensitivity to previous lines of treatment.

References

1. Long HJ. Paclitaxel (taxol): a novel anticancer chemotherapeutic drug. Mayo Clin Proc 1994; 69:341-5.
2. Wilson WH, Chabner BA, Bryant G, et al. Phase II study of paclitaxel in relapsed non-Hodgkin's lymphomas. J Clin Oncol 1995; 13:381-6.
3. Younes A, Sarris A, Melnyk A, et al. Three-hour paclitaxel infusion in patients with refractory and relapsed non-Hodgkin's lymphoma. J Clin Oncol 1995; 13: 583-7.
4. Younes A, Cabanillas F, McLaughlin PW, et al. Preliminary experience with paclitaxel for the treatment of relapsed and refractory Hodgkin's disease. Ann Oncol 1996; 7:1083-5.
5. Younes A, Ayoub JP, Sarris A, et al. Paclitaxel (Taxol) for the treatment of lymphoma. Ann Oncol 1997; 8: 129-31.
6. Press OW, LeBlanc M, O'Rourke TJ, et al. Phase II trial of paclitaxel by 24-hour continuous infusion for relapsed non-Hodgkin's lymphomas: Southwest Oncology Group trial 9246. J Clin Oncol 1998; 16: 574-8.
7. Younes A, Ayoub JP, Sarris A, et al. Paclitaxel activity for the treatment of non-Hodgkin's lymphoma: final report of a phase II trial. Br J Haematol 1997; 96:328-32.
8. Goss P, Stewart AK, Couture F, et al. Combined results of two phase II studies of Taxol (paclitaxel) in patients with relapsed or refractory lymphomas. Leuk Lymphoma 1999; 34:295-304.
9. Mamounas E, Brown A, Smith R, et al. Effect of taxol duration of infusion in advanced breast cancer (ABC): results from NSABP B-26 trail comparing 3- to 24hr infusion of high dose taxol. Thirty-fourth Annual Meeting of the American Society of Clinical Oncology. Los Angeles, 1998.
10. Holmes FA, Valero V, Buzdar AU, et al. Final results: randomized phase III trial of paclitaxel by 3-hr versus 96-hr infusion in patients (pt) with metastatic breast cancer (MBC). The long and short of it. Thirty-Fourth Annual Meeting of the American Society of Clinical Oncology. Los Angeles, 1998.
11. Chang AY, Boros L, Garrow G, Asbury R. Paclitaxel by 3-hour infusion followed by 96-hour infusion on failure in patients with refractory malignant disease. Semin Oncol 1995; 22:124-7.
12. Younes A, Ayoub JP, Hagemeister FB, et al. No effect of 96-hour paclitaxel infusion in patients with relapsed non-Hodgkin's lymphoma refractory to a 3-hour infusion schedule. J Clin Oncol 1996; 14:543-8.
13. Liebmann JE, Cook JA, Lipschultz C, Teague D, Fisher J, Mitchell JB. Cytotoxic studies of paclitaxel (Taxol) in human tumour cell lines. Br J Cancer 1993; 68: 1104-9.
14. Miller TP, Chase EM, Dorr R, Dalton WS, Lam KS, Salmon SE. A phase I/II trial of paclitaxel for non-Hodgkin's lymphoma followed by paclitaxel plus quinine in drug-resistant disease. Anticancer Drugs 1998; 9:135-40.
15. Sarris AH, Younes A, McLaughlin P, et al. Cyclosporin A does not reverse clinical resistance to paclitaxel in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol 1996; 14:233-9.
16. Budman DR, Petroni GR, Johnson JL, et al. Phase II trial of docetaxel in non-Hodgkin's lymphomas: a study of the Cancer and Leukemia Group B. J Clin Oncol 1997; 15:3275-9.
17. Younes A, Rahman D, Hagemeister F, Romaguera J, McLaughlin P, Cabanillas F. Phase II study of paclitaxel plus topotecan with G-CSF support for the treatmet of relapsed and refractory aggressive non-Hodgkin's lymphoma. Fourty Annual Meeting of the American Society of Hematology. Miami Beach, 1998.
18. Younes A, Romaguera J, Mesina O, et al. Paclitaxel plus high-dose cyclophosphamide with G-CSF support in patients with relapsed and refractory aggressive non-Hodgkin's lymphoma. Br J Haematol 1998; 103: 678-83.