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A PHASE I TRIAL OF TRANS-1-DIAMINO-CYCLOHEXANE OXALATO-PLATINUM (l-OHP)

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ABSTRACT

Oxalato-platinum in a new platinum derivative which was found to be active in experimental tumors and devoid of nephrotoxicity. A phase I study was conducted in cancer patients according to a new design following the recommendations of our Institution's ethical committee to avoid the major drawback of classical phase I studies in which many patients receive the experimental drug at doses far under the potentially active dose extrapolated from experimental studies. The potentially active dose of l-OHP was determined from the Maximally Efficient Dose Range (MEDR) to be between 45 mg/m² (subcurative dose) and 67 mg/m² (subtoxic dose). The patients in this study received with increasing intervals 1/100, 1/10, 1/5, 1/3, 1/2, 2/3, 3/4, 1, of the low dose of the MEDR, this dose being reached after 90 to 120 days on study. 23 evaluable patients have entered the trial of which 19 reached the low dose of MEDR (45 mg/m²). Gastro-intestinal toxicity, nausea and vomiting, similar to those with CDDP occurred in all patients at or above the dose of 30 mg/m². Renal toxicity was monitored with creatinine level and did not occur in any patient at any dose nor did significant hematologic toxicity occur. Thus nausea and vomiting appear to be the limiting toxicity of the drug. Responses were observed in this phase I study in lung cancer (1), breast cancer (1), melanoma (1) and perhaps hepatoma (major decrease in αFP levels) (1). The proposed starting dose for phase II studies is 45 mg/m² but we plan to continue dose escalation during the phase II according to the design of Jones and Holland. This new study design allows each patient entering a phase I study to be treated with a potentially active dose of the drug studied.

ABRÉGÉ

L'oxatalo-platinum (l-OHP) est un nouveau dérivé du platine doué d'une forte activité antitumorale sur les modèles expérimentaux et dénué de néphrotoxicité. Nous avons réalisé un essai phase I chez des patients cancéreux en utilisant un nouveau modèle d'augmentation progressive des doses chez chaque malade, selon les recommandations de notre comité d'éthique, pour éviter que de nombreux malades ne reçoivent le médicament à des doses très inférieures aux doses potentiellement actives extrapolées de l'expérimentation animale. La dose potentiellement active à l-OHP a été déterminée à partir de l'intervalle de doses maximalement efficaces (MEDR) chez les souris, c'est-à-dire entre 45 mg/m² (dose subcurative) et 67 mg/m² (dose subtoxique). Les patients de notre étude ont reçu à des intervalles de temps croissants, 1/100, 1/10, 1/5, 1/3, 1/2, 2/3, 3/4, 1 de la dose basse du MEDR, cette dernière étant atteinte après 90 à 120 jours. 23 patients ont été inclus dans cette étude dont 19 ont atteint la dose basse du MEDR; la toxicité digestive, faite de nausées et de vomissements, semblable à celle du cis-diamino-dichloro-platinum a été observée chez tous les patients à partir de la dose de 30 mg/m². Il n'y a eu aucun cas d'insuffisance rénale et aucune toxicité hématologique significative. La toxicité digestive paraît être la toxicité limitante du médicament. Une efficacité antitumorale a été observée, dans un cas de cancer du poumon, dans un cas de cancer du sein, dans un cas de mélanome malin et dans un cas de carcinome hépatocellulaire. La dose basse du MEDR, 45 mg/m² est une dose sans danger et est proposée comme dose de départ de l'essai de phase II durant lequel nous prévoyons de continuer l'escalade des doses selon le modèle de Jones et Holland. Ce nouveau modèle d'essai de phase I permet à chaque patient inclus de recevoir des doses potentiellement actives du médicament étudié.

Cis-diamino-dichloro-platinum (CDDP) introduced by Rosenberg (1) in 1969, is a powerful cytostatic agent that is frequently and successfully used in clinical cancer chemotherapy (2). It has however significant side effects among which in the short term nausea and vomiting are the most feared, and in the long term renal toxicity, otovestibular toxicity and allergic reactions.

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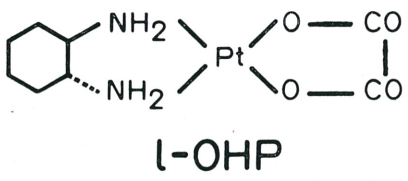
To try to avoid this toxicity, other Pt(II) complexes have been prepared, including the oxalato-Pt(II) complex of diamino-cyclohexane (DACH) obtained as isomeric mixtures, and which is active on several murine tumors (3-6).

Kidani *et al.* (7) succeeded in separating DACH into geometric isomers, cis and trans, and then separated the trans into 2 optical isomers: trans-d and trans-l. Among the complexes they prepared, the oxalato Pt(II) complex of the trans-l-DACH (Fig. 1) appeared to have the maximal T/C (treated/control) values on L1210 leukemia.



l-OHP

FIG. 1.

We have used l-OHP on our murine tumor screening system and found it more active than CDDP on L1210 leukemia. On AKR leukemia, l-OHP was as active as CDDP but less toxic. Moreover, in murine large cell lymphoma and L1210 grafted intracerebrally l'OHP increased the life span while CDDP was inactive (7).

As compared to CDDP on the basis of toxicity, the tolerance superiority of l-OHP was remarkable over the latter. The absence of nephro-toxicity was histologically confirmed in mice and also observed in baboons.

We present in this paper the preliminary results of a phase I clinical trial of l-OHP employing a new method of intra-patient escalation conducted from June 84 in the « Service des Maladies Sanguines et Tumorales ».

PATIENTS AND METHODS

Twenty-three patients with histologically confirmed malignancy were evaluated in this study. Most patients had exhausted all standard therapy and in the two patients with no previous treatment the disease was the one for which no therapy of proven benefit was available. All but one had never received cisplatin before (Table I).

Patients were asked for informed consent and on entry all had a performance status of at least 50 % (on Karnofsky scale) and a minimum of life expectancy of 2 months. All the pretreated patients have been off previous chemotherapy or irradiation for a period of 4 weeks.

Prior to beginning l-OHP treatment, patients were required to have an adequate renal function, WBC $>$ 4,000/mm^3, platelet count $>$ 100,000/mm^3 and Hb $>$ 10 g/dl. Some liver dysfunctions were not considered as contra-indications in patients with hepato-carcinoma or those with confirmed hepatic metastases.

Baseline and follow up studies for tolerance included weekly evaluation of body-weight and surface, performance status, complete blood cells counts with differential, renal function: blood urea and creatinin, electrolytes, blood proteins, liver function tests and enzymes, electrocardiogram, and monthly chest X ray and tumor measurement if applicable including tumor markers such as CEA, alphafetoprotein, lipid-bound sialic acid, according to each particular case. Toxicity as well as anti-tumor activity were evaluated and graded according to W. H. O. criteria (8).

Patients characteristics and tumors are shown in Table I.

Drug and schedule of administration

L-OHP was kindly supplied by R. Bellon Laboratory, as a formulation in

1 ml vials containing 1 mg
10 ml vials containing 10 mg

and 100 ml vials containing 100 mg of 1,2-diamino-cyclohexane (trans-1) oxalato-platine II (Fig. 1).

TABLEAU I

Patients characteristics.

Number of patients evaluated		23
Sex ratio male/female		14/9
Age range in years		21-77
Average		51
Prior therapy		
	None	2
	Chemotherapy only	12
	Chemotherapy and hormonotherapy	1
	Chemotherapy and immunotherapy	3 (*)
	Radiotherapy only	2
	Chemotherapy and radiotherapy	4
Previous CDDP		1
Tumors:	Unknown primary	2
	Breast cancer	3
	Intraocular melanoma	1
	Lung cancer	1
	Malignant melanoma	9
	Primary liver tumor	3
	Prostate cancer	1
	Cholangiocarcinoma	1
	Small bowel carcinoma	1
	Schwanoma	1

(*) 1 patient received chemotherapy, radiotherapy and immunotherapy.

The doses and schedule of administration of the drug were chosen according to the new ethical rules of phase I trials (9) with a dose escalation scheme in each patient so that every patient entering the trial would have a chance to benefit from the drug. The starting and escalation doses were determined from the MEDR (10) doses in mice (7) ranging from 45 mg/m^2 (subcurative dose) to 67 mg/m^2 (subtoxic dose).

Despite the low toxicity of l-OHP observed in animal models (namely in mice and baboons) we have chosen as the starting dose the 1/100 of the Maximally Efficient Dose Range in mice in order to detect any reaction of anaphylaxis or hypersensitivity of the patient to the drug. Because of the reported risk of nephrotoxicity for most derivatives of platine known up to date, prior to l-OHP administration patients were hydrated with 1 l of

IV fluids (containing 5 % dextrose in 0.4 % saline with 2 g KCl) and mannitol given as previously described. The use of antiemetics was not indicated for the first three dose levels.

Table II shows dosage escalation in each patient and the day of administration. The high dose of Maximally Efficient Dose Range (MEDR) is reached by day 120 of treatment if all intermediate doses are given. When all the doses of the schema have been given without adverse effects in the first patients, some intermediate doses may be omitted in the following ones to reach more quickly the potentially active dose supposed to be similar to MEDR in mice.

TABLE II

Dose escalation table.
Modality of Administration: IV infusion.

0.45	Day 1	
4.5	Day 1	afternoon
9	4	
15	11	
22.5		3 weeks interval
30		
45		
56		
67		

RESULTS

Twenty-three patients were available for evaluation of toxicity during the period from June 84 to February 1986.

There was no treatment related death nor any disruption of the drug consecutive to unacceptable toxic effects during the study. No reaction of anaphylaxis or hypersensitivity to the drug was observed. 20 patients were treated at least at three dose levels namely 1/100-1/10 and the subcurative dose extrapolated from the MEDR (Maximally Efficient Dose Range) established in mice, that is 45 mg/m^2. The other 3 patients were withdrawn from protocol for early rapid disease progression. Eleven out of the 23 evaluated patients have reached the subtoxic dose level established in mice, that is 67 mg/m^2. Patients received from 3 to 14 cycles with an average of 7-8 cycles, Table IV indicates the number of patients having been treated at each dose level and the main toxic effects observed in this study.

The total dose range extended from 78 mg to 1,002 mg. The patient with 78 mg was accepted for evaluation for toxicity because was already treated at the three dose levels *i. e.* 1/100, 1/10 and 45 mg/m^2 with one cycle at each dose level, and by the moment of this writting this patient was still on study. The median total dose was approximately 500 mg.

Hematologic toxicity

Anemia was observed in three patients during this study but only one of these patients was assessable for hematologic toxicity evaluation. The other two patients are not considered evaluable for the following reasons:

1. one patient had a positive bone marrow biopsy,
2. the second patient presented anemia and mild thrombocytopenia grade I on WHO scale (Hb 9.7 g/dl and 124,000/mm^3 platelets) only after six months of treatment at the same time the disease was progressive and for this reason l-OHP therapy was discontinued. It may be more likely to consider these symptoms as consecutive to progressive disease rather than due to toxicity. Unfortunately bone marrow biopsy was not performed in this patient. In the patient available for evaluation anemia appeared on day 40 of treatment, lasted approximately 4 weeks with stable value of Hb between 9.9 g/dl and 9.5 g/dl which is evaluated as grade I on WHO scale. Neutropenia was not observed in this patient and in none of the patients of this study.

Non-hematologic toxicity

Non-hematologic toxicity was confined to nausea and vomiting. Nephrotoxicity was not observed on the basis of increase of serum creatinine or by urea dosage. No alopecia was reported by any of the patients nor mucositis. Modification of liver enzymes was limited to one patient. Out of the 22 evaluated patients only one presented increase of serum alkaline phosphatase with absence of hepatic metastasis confirmed by hepatic echography and scanning. This disturbance of hepatic function consecutive to l-OHP treatment was transient and evaluated as grade I on WHO scale.

Although the use of antiemetics made it difficult to evaluate adequately this side effect, nausea and vomiting were first encountered at 30 mg/m^2 in one out of the 9 patients and by 45 mg/m^2 up, in all patients intered in this study. The intensity of the symptom was dose dependent but did not prevent the continuation of therapy although it might be a cause of considerable anxiety for the patient. The failure to continue l-OHP treatment in these evaluated patients was due to progressive disease rather than to limiting toxicity of any kind.

The preliminary results of this first clinical trial confirmed the encouraging data obtained from previous studies on animal models and provided additional evidence for the better tolerance to l-OHP than to other derivatives of platine and namely CDDP because of the absence of nephrotoxicity and the relative lack of myelosuppression which is in contrast with the significant hemotologic toxicity observed with other analogs of platinum such as Ipro-

TABLE III

Tolerance.

Dose level	No. patients N = 23	Toxicity							
		Nausea vomiting	Lung	Heart	Liver	Kidney	Hematopoiesis: Hb	Hematopoiesis: WBC	Hematopoiesis: Platelet
0.45	21	—	—	—	—	—	—	—	—
4.5	21	—	—	—	—	—	—	—	—
9	9	—	—	—	—	—	—	—	—
15	12	—	—	—	—	—	—	—	—
22.5	8	—	—	—	—	—	—	—	—
30	9	1/9	—	—	—	—	—	—	—
45	19	19/19	—	—	—	—	1/19 Gr1	—	—
56	15	15/15	—	—	1/15	—	1/15 Gr1	—	—
67	11	11/11	—	—	—	—	1/11 Gr2	—	1/11 Gr1

Parameters evaluated:
Liver: transaminases, alkaline phosphatase.
Kidney: urea, creatinine.
Gr : grade according to WHO (8).

TABLE IV

Antitumor activity.

Response	No. patients	Tumor + target	Total dose received	Imaging
Progressive disease	16/23			
Stabilisation	3/23	1 prostate + liver and bone metastasis	798 mg	Echo + PAP
		2 liver	843 mg	
		3 liver	943 mg	αFP
Minor response	1/23	Lung	740 mg	Tomo-scan
Partial response	1/23	Breast carcinoma + bone metastasis	473 mg	Scintigraphy
Complete response	1/23	Melanoma + metastases of the lung and parotid	297 mg *	Scan (of the head and lung)

* *N. B.:* This patient is still on study. Although he has reached only a low level (45 mg/m²) at the time of this report the results as evidenced by scan of the and the head confirmed a complete disappearance of the metastases of the lung and the parotide seen before treatment.

platin or SHIP (11). The recommended starting doses for phase II trial will be 67 mg/m² but higher doses may be reached in a dose escalation phase II design, according to Norton's model (12). Toxicity results are presented in Table IV.

Response data

Evaluation of efficacy was not the principal aim of this first clinical trial but some very interesting and encouraging responses were observed.

Data are summarised in Table IV.

The preliminary results of the present paper demonstrate the good tolerance of l-OHP in man at the higher dose of the MEDR established in mice and suggests that subtantial antitumor activity of l-OHP might be obtained principally in hepatocarcinoma and colorectal carcinoma. Nevertheless these encouraging data must be confirmed by further phase II clinical study.

CONCLUSION

In conclusion we confirm the safety of l'OHP at the dose extrapolated from the MEDR in mice, dose at which antitumor responses have been observed. The fact that we did not reach a dose limiting toxicity is inherent to the new design of this phase I study, the objective of which was to confirm the tolerance of the high dose of MEDR. Further dose escalations are planned within the phase II study according to the Norton's model.

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AN ORIENTED PHASE II TRIAL OF THP-ADRIAMYCIN IN BREAST CARCINOMA

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ABSTRACT

THP-ADM is a new anthracyclin with broad antitumor activity without cardiac toxicity or alopecia in experimental models. Phase I studies had established a proposed dose for phase II trials of 50 mg/m² every three weeks. This modality gave an insignificant result in breast carcinoma. Cellular pharmacokinetics suggested that a longer time of administration could be more efficient. In this phase II trial oriented to advanced breast cancer, we have used 3 consecutive daily doses of 20 mg/m²/day in monthly cycles with dose escalation in each patient. We have observed 28 % partial remissions (PR). Two patients previously treated with adriamycin had PR. Significantly less alopecia and no cardiac toxicity were observed.

ABRÉGÉ

La tétrahydropyranyl adriamycine, THP-ADM est une nouvelle anthracycline dotée d'une large activité antitumorale et dépourvue de cardiotoxicité sur les modèles expérimentaux. Les études de phase I avaient établi une dose initiale de 50 mg/m² chaque trois semaines pour les essais de phase II. Cette modalité n'a pas donné de résultats appréciables dans le cancer du sein. Les résultats de la pharmacocinétique cellulaire du médicament ont suggéré qu'une administration plus prolongée pourrait être plus efficace. Dans l'essai phase II présenté ci-dessous dans les cancers du sein, nous avons administré trois doses quotidiennes consécutives de 20 mg/m² chaque mois avec escalade des doses chez un même malade. Nous avons observé 9 réponses partielles (28 %). Deux patients ayant préalablement reçu de l'Adriamycine à titre adjuvant ont obtenu une rémission partielle. Nous n'avons pas observé de toxicité cardiaque et une alopécie significativement moindre qu'avec l'Adriamycine.

Adriamycin (ADM) is one of the most efficient agents to induce complete and partial remissions (CR and PR) in advanced breast carcinoma (2). It induced CR + PR in 36 out of 121 patients (30 %) according to Blum and Carter (1). Toxicity of anthracyclins affecting the hair and heart (4, 5) are however stumbling blocks to some uses (2). Among all available anthracyclins that we studied experimentally for hair and cardiac toxicity (4, 5), (4'-0-tetra-hydropyranyl-adriamycin-hydrochloride) or THP-Adriamycin proved to be one of the two least toxic analogues while highly active on experimental tumors such as P388, L1210 and Lewis tumor (14).

Majima (8) concluded a phase I study by recommending, for phase II trials, to use THP-ADM in a

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