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Editorial

Phase I Trials in Clinical Oncostatic Pharmacology*

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Every clinical oncostatic, pharmacologic, and therapeutic researcher uses the term 'phase I therapeutic trials' to describe those studies involving toxicology, tolerance, and pharmacologic and therapeutic effects that are carried out for the first time on patients [15].

The rules for conducting this kind of trial can be satisfactorily defined as far as theoretical methodology is concerned. In practice, the clinical researchers meet many difficulties when they try to follow the perfect ethical and scientific methodologies. The result is a long delay in performance of the required preclinical studies and a long duration of the trial.

We have established a compromise between the perfect theoretical requirement and the practical possibilities, without depriving our patients of the maximum security.

Phase I trials can only be attempted with compounds or therapeutic techniques or methods that have been fully explored by means of *preclinical studies in animals*. In our practice, we attempt to: (a) find out the LD_{50} and LD_{10} in mice; (b) demonstrate an oncostatic effect in animals, especially in the most widely used experimental murine grafted tumours (the correlation between their sensitivity and that of at least some human neoplasias being good) [19]; (c) study the therapeutic index, which, in our experience, means looking for the maximally efficient dose interval (MEDI) [10, 12]; (d) conduct an experimental study of both the pharmacokinetics and the organ and/or tissue distribution of the compound or the degradation product(s) that might carry the activity for some agents that are not active by themselves [3, 5]; (e) conduct macroscopic and microscopic studies, and even electron microscopic examination, of some organs or tissues [7] to determine the different organ and tissue toxicities in mice or other animals that have received either the minimal dose of the MEDI or the optimal dose for common tumour models; (f) determine the clinical, functional, and biochemical tolerance of this dose extrapolated from rodents to monkeys (which, in our practice, are baboons) [6, 18], and the possible pharmacokinetic data obtained in monkeys according to different modalities of administration of different doses.

If there is no difference in the side effects between rodents and monkeys, one is justified in passing on to patients. If there is a difference, a study on a third species (e.g., dogs) is required: we consider that 'primates... should be regarded not as anthropocentric or as little men, but as any other laboratory animals' [8].

The human phase I trial consists in bridging the gap between the preclinical studies and the so-called phase II study to determine the optimal clinical efficiency, i.e., maximum efficacy at the minimum toxicological cost.

Certain ethical rules are respected by our team:

a) No compound is used in normal subjects at any dose [13].

b) As in phase II trials, only patients who are resistant to all available treatments receive the new compounds: they must have 'nothing to lose and something to gain' from the trial, about which they should be fully informed [14]. Each doctor is responsible for each patient [1] even if the protocol has been accepted by an Ethical Committee, which has no legal authority for judges [13] and no moral authority for moral doctors.

c) The same gallenic preparation is administered to man and monkey, its effect having been checked in the rodent model initially used.

d) The route of administration must also be the same as the one already tolerated in one of the experimental models.

e) The patients who receive the new compounds, even if they had received other oncostatic therapy in the past, do not receive any further therapy during this

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phase I trial, and the period separating this trial and any other oncostatic treatment is as long as possible. In any case patients should have recovered, at least apparently, from all side effects of previous treatments.

f) Initially, only one patient is given the compound, so that if an unpredictable accident occurs, the number of patients at risk will be limited as much as possible. A sufficiently long time is maintained between the successive patients. Consequently, we think that pharmaceutical companies or chemists of public institutions should agree to give their new agents to *only one* clinical pharmacological research team for a phase I trial [14]. We once received a new compound with no note of neurological toxicity either in rodents or in larger animals; we administered it to one patient, who developed a delayed cerebellar toxicity; we learned afterward that the same drug had been given to two other teams, who by that time had administered it to patients, and several of their patients developed the same delayed neurological toxicity.

g) The dose administered to the first patient should not exceed one-third of the LD_{10} for mice [17], and the extrapolation unit chosen should be the square meter of body surface area: the correlation between tissue distribution and the chemotherapeutic component dose has been shown to be quite similar in the different species if the doses are expressed in this unit [11], whereas it varies much more when it is expressed in kilograms of body weight.

Obviously, the first patient very often does not show any positive oncostatic or secondary effect. After a given period of time, during which the possibility of any latent effect can be eliminated, a second patient receives the double dose. The increase for the next patients is developed according to an adapted Fibonacci diagram (see [4]; Table 1) until it reaches the maximal dose (md) of the MEDI (expressed per square metre of body surface area), which must previously have been shown to be tolerated in monkeys, or the maximal dose tolerated in monkey, if this md of the MEDI is toxic.

Table 1. Dose increase in Phase I trials according to Fibonacci diagram [4]

Dose n = dose given to the first patients (mg/m²)	Percentage increase above initial dose
2 n	100
3.3 n	67
5 n	50
7 n	40
9 n	30–35
12 n	30–35
16 n	30–35

The value of the data concerning toxicology in mice, compared with that of larger animals, has been shown for 12 compounds by Penta et al. [17].

The combined use of these data, to allow us to start with the smallest doses in a phase I trial in man, and of the detailed biochemical toxicity data obtained with higher doses in monkeys (the corresponding dose of the md of the MEDI in mice) seemed to us the best way of giving the maximum security to patients while saving much work and materials in large animals.

h) All information relating to the patient, to the disease, and to his past history concerning any other disease(s) and any specific or nonspecific treatment is recorded [21].

i) Any information concerning the period following the trial is also recorded, and follow-up observation of the patient and of the disease after the end of this trial continues for as long as is permitted by the condition of the patient: delayed side effects or beneficial actions are possible.

j) All possible clinical information, that reported by doctors as well as that noted by the nurses, the families, or the patients themselves is precisely recorded, whether it concerns side effects or beneficial effects.

k) All paraclinical (laboratory, radiological, isotopical, etc.) information must be collected before, during, or after the trial.

l) The treatment application modalities should be fully described in detail:

1. The protocol must a priori be written very precisely;

2. The report of the application modalities must record any difference between the written protocol and the modalities used. The proportion of planned doses, courses, and cycles actually given must be noted. The reasons for any dosage modification or delays in administration of the compound must be explained;

3. All symptomatic therapies applied systematically or to correct any pathological event must be qualitatively and quantitatively recorded;

4. All events occurring during the administration cycle, and between the cycles of administration must be noted by doctors, nurses, or families or by the patients themselves.

m) As phase I trials are devoted mainly to toxicity and tolerance studies, and as the side effects may appear at a certain dosage and be correlated with dosage, grading of acute and subacute toxicity is necessary. Gradings have been proposed by the EORTC Clinical Screening Group [9] and by the WHO/EORTC/NCI Committee on Standardization of Reporting of Results of Cancer Treatments [21]. We recommend the use of one of these.

n) Samples of blood, urine, and even CSF are taken when laid down in the protocol for pharmacokinetics

studies [23] if the methods of measurement and logistics are available.

o) As phase I trials are devoted not only to toxicity and tolerance, but also to determination of the dose(s) and modalities of administration yielding a favourable effect with the lowest possible toxicity, any favourable effect observed must also be evaluated qualitatively and quantitatively, and subjectively and objectively recorded. We also recommend clinical pharmacologists to follow the rules of the EORTC Clinical Screening Group [9] or NCOG [16], or those described in more detail by the WHO/EORTC/NCI Committee [21]; we recommend the use of international terminology: the WHO International Classification of Tumours [22] for microscopical classifications and UICC staging categorizations [20].

p) Finally, phase I trials are not only devoted to single-drug trials. Every recommendation mentioned above must be equally observed for toxicity and tolerance in trials of any combined therapy [2]. Any detail to be recorded for a single drug is recorded for each compound or method included in any combination therapy; and it is necessary, whether the combination is concurrent or sequential, to record any detail that might help to attribute any side effect or favourable action to one of the components of this combination or to their interaction(s).

References

1. Arpaillange, P., Gaston-Mathé, J. L.: Therapeutic trials and the applicable principles of law. Biomedicine **28,** 57 (1978)
2. Breast Cancer Task Force Treatment Committee: National Cancer Institute Report from the Combination Chemotherapy Trials Working Group, p. 10. DHEW Publication No. (NIH) 77-1192: DHEW 1977
3. Borck, N., Hohorst, H. J.: Metabolism of cyclophosphamide. Cancer **20,** 900 (1967)
4. Carter, S. K.: Study design principles for the clinical evaluation of new drugs as developed by the chemotherapy programme of the NCI. In: The design of clinical trials in cancer therapy. Staquet, M. (ed.), p. 242. Bruxelles: Sc. Europ. 1972
5. Chen, H. S. G., Gross, J. F.: Physiologically based pharmacokinetic models for anticancer drugs. Cancer Chemother. Pharmacol. **2,** 85 (1979)
6. Colloque International sur les Animaux de Laboratoire, Lyon, Septembre 1978
7. Dantchev, D., Slioussartchouk, V., Paintrand, M., Hayat, M., Bourut, C., Mathé, G.: Electron microscopic studies of the heart and light microscopic studies of the skin after treatment of golden hamsters with adriamycin, detorubicin, AD-32 and aclacinomycin. Cancer Treat. Rep. **63,** 875 (1979)
8. Dayan, A. D.: Uses and limitations of primates in the evaluation of drug efficacy and safety. J. R. Soc. Med. **71,** 691 (1978)
9. EORTC Clinical Screening Group: Proposal for the introduction of uniformity in the expression of evaluation criteria in therapeutic responses. EORTC Newsletter n° 29, 1973
10. Hayat, M., Bourut, C., Chenu, E., Montero, J. L., Imbach, J. L., MacDonald, J. S., Mathé, G.: Comparative pharmacology of three new nitrosourea analogues: RFCNU, RPCNU, and chlorozotocin. I. Oncostatic effects in mice. Cancer Chemother. Pharmacol. (in press, 1979)
11. Homan, E. R.: Quantitative relationship between toxic doses of antitumor chemotherapeutic agents in animals and man. Cancer Chemother. Rep. **3** (3), 13 (1972)
12. Imbach, J. L., Montero, J. L., Moruzzi, A., Serrou, B., Chenu, E., Hayat, M., Mathé, G.: The oncostatic and immunosuppressive action of new nitrosourea derivatives containing sugar radicals. Biomedicine **23,** 410 (1975)
13. Lortat-Jacob, J. L., Mathé, G., Servier, J. (eds.): Proceedings of the International Meeting on Comparative Therapeutic Trials, Paris, January 1978. Biomedicine **28,** special issue (1978)
14. Mathé, G.: Les essais thérapeutiques cliniques. Bull. Cancer **61,** 191 (1974)
15. Mathé, G., Kenis, Y.: Logistics of therapeutic trials: the example of cancerology. Biomedicine **18,** 181 (1973)
16. NCOG: Proposed NCOG respone criteria. S. K. Carter (Pers. comm.)
17. Penta, J. S., Rozencweig, M., Guarino, A. M., Muggia, F. M.: Mouse and large animal toxicology studies of twelve antitumor agents: relevance to starting dose for phase I clinical trials. Cancer Chemother. Pharmacol. **3,** 97 (1979)
18. Ribaud, P., Alcock, N., Burchenal, J. H., Young, C., Muggia, F., Mathé, G.: Preclinical trial in baboon and phase I–II trials and pharmacokinetics in man of malonato-platinum (MP). Proc. Am. Soc. Clin. Oncol. **20,** 336 (Abstract C-186) (1979)
19. Schepartz, S. A.: Screening. Cancer Chemother. Rep. **2,** 3 (1971)
20. UICC: TNM, Classification of malignant tumors, 2nd ed., Geneva: WHO 1974
21. WHO/EORTC/NCI: Meeting on standardization of reporting of results of cancer treatment
22. WHO: International Histological Classification of Tumors. 13 vol. Geneva: WHO 1967–1975
23. Zahardo, D. S.: Pharmacokinetics. Cancer Chemother. Rep. **3** (3), 21 (1972)

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