Cancer Chemother Pharmacol (1982) 7:81–85

Cancer Chemotherapy and Pharmacology

Review

VP16-213 (Etoposide)

A Critical Review of its Activity

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Introduction

Medicinal properties have been recognized for many years in the plant Podophyllum peltatum, commonly known as the American mandrake or May apple. Podophyllotoxin, a crystalline extract of those plants, shows antimitotic properties, which have led to the development of many cytotoxic agents. Among them, SPI and SPG underwent clinical trials with rather inconclusive results [38]. More recently two semisynthetic derivatives of Podophyllotoxin were produced, which have renewed interest in this group of compounds: VM26 and VP16-213. Since their initial clinical trials, an abundant amount of information has accumulated on these two structurally related compounds. This commentary will highlight phase-I-II trials with VP16-213: since these data have been recently and extensively well-summarized [1, 24, 32–33], this paper will focus on some peculiar aspects of the available information. Emphasis will mainly be concentrated on the methodological problems, which in the past have most probably hampered a rapid evaluation of the clinical usefulness of this new cytotoxic drug.

Phase-I Studies and Dose Schedules

The six main phase-I studies are shown in Table 1 [12, 15, 19, 26, 29–30]. No one schedule or route of administration has clearly emerged as superior from these trials. This uncertainty is partly due to the availability of different and somewhat poorly defined formulations. In an early attempt to compare the biologic activity of VP16-213 given IV and PO both as capsules or drinking ampoules, Brunner et al. [3] randomised patients to receive either 300 mg/m^2 IV or 600 mg/m^2 orally as capsules or drinking ampoules over 3 days. Activity was evaluated chiefly by modifications in the blood values. The study incorporated a cross-over design between drinking ampoules and capsules. The drinking ampoules and the IV administration were found to be roughly equitoxic, suggesting therefore a 50% absorption. In this trial capsules with the old lipophilic suspension were used: their haematologic toxicity and therefore most probably their absorption were found to be erratic. Later a new formulation of the gelatin capsules incorporating an hydrophilic solution was developed: the absorption and bioavailability were considered to be similar to those of the drinking ampoules [2, 26]. But all these data were generated in pharmacokinetic studies measuring ^{3}H-VP16-213.

However in this issue D'Incalci et al. [13] using determinations by HPLC suggest that even the absorption of the drinking ampoules is more erratic than previously thought and dependent upon the intestinal function of the patients. Moreover based on their data the ampoules seem to still be better absorbed than the capsules. This and other new information tends to demonstrate that our knowlege of the pharmacokinetic properties of this compound is still far from being complete.

It is therefore easily understandable, but nevertheless disturbing, that the data provided by the phase-I studies were rather unprecise. In some trials the maximum tolerated dose (MTD) was clearly not reached. In other instances the dose proposed for starting phase-II studies was questionable. Probably the wide variety of different schedules used in these phase-I trials is a further explanation for this uncertainty. Most of the varying schedules were in turn possibly prompted by the early awareness of the marked schedule dependency of the antitumor activity of VP16-213 in experimental tumors [14]. All this

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0344-5704/82/0007/0081/$01.00

Table 1. Phase-I studies with VP16-213

Author	Formulation	Proposed schedule for PH-II	MTD	Toxicity (limiting)
Nissen et al. [29] CCR 59:769 (1972)	i.v.	45 mg/m^2/d × 7 q? 69–86 mg/m^2 2 × wk. q 3 wks.	54 mg/m^2/d × 7 Not reached	Leukopenia
Creavan et al. [12] CCR 58:901 (1974	i.v.	290 mg/m^2 weekly	290 mg/m^2	Leukopenia
Eagan et al. [15] AACR 16:55 (1975)	i.v.	125 mg/m^2 d, d 1, 3, 5 q 3 wks.	140 mg/m^2/d × 3	Leukopenia
Falkson et al. [19] Cancer 35:1141 (1975)	p.o.[a] capsules	300–400 mg/m^2 over 5 d	?	Leukopenia + GI
Nissen et al. [30] CTR 60:943 (1976)	p.o. drinking ampoules	120 mg/m^2/d × 5 d q 3 wks.	Not clearly reached	Leukopenia GI
Lau et al. [26] CTR 63:485 (1979)	p.o.[b] capsules	100–130 mg/m^2/d × 5 d q 3 wks.	150 mg/m^2/d × 5 d	Leukopenia

[a] Lipophylic suspension
[b] Hydrophylic solution

underlines once more the urgent need for a more stringent and standardized methodology for starting and conducting the clinical evaluation of new drugs.

Phase-II Studies

Early, classic "broad" phase-II studies were carried out by the EORTC [18] and Jungi et al. [25]. Already at that stage myelo-monocytic acute leukemia [18] and small cell lung cancer [25] were recognized as neoplasms where VP16-213 displays a pronounced antitumor activity. Many disease-oriented studies have since been carried out and the data are summarized in Tables 2–4. However these tabulations give an inprecise impression about the exact degree of efficacy of VP16-213 in each tumor type, since the dose, schedule, route of administration and the patient population differ widely from one study to an other.Of course the activity of the drug is somewhat more likely to be reproducible when a large number of patients with a certain tumor type have been treated and observed. But even this assumption is only of limited value: the data reported in the literature as regards non-Hodgkin's lymphoma exemplifies this point. In fact among the 220 reported patients the cumulative response rate is 21%: but this rate varies between 0–55%. Therefore, and at least in tumors which are as heterogeneous as NHL, only an accurate analysis of the treated populations might generate useful data. In contrast, data in ovarian cancer (101 patients) are consistently negative, allowing therefore a final assessment.

Table 2. Tumors with a response rate greater than 20%

Tumor	Number evaluated	Response
Small cell lung cancer	197	43%
Acute myelomonocytic leukemia	18	39%
Non-seminomatous testicular cancer	56	34%
Non-Hodgkin's lymphoma	220	21%
Hepatocellular carcinoma	30	20%
Squamous cell lung cancer	25	20%

Table 3. Tumors with response rate less than 20%

Tumor type	Number evaluated	Response
Hodgkin's disease	75	19%
AML	32	18%
Adenocarcinoma of lung	30	13%
Ovary	101	10%
Soft-tissue sarcoma	36	8%
Endometrium	17	8%
Breast	180	5%
Head and neck	31	3%
Colorectal	140	3%
Melanoma	61	2%
Kidney	40	0%
Cervix	30	0%

Adapted from Arnold [1]

The Methodological Problems of Phase-II-Studies

Phase-II trials are today the most difficult step in the clinical evaluation of new drugs generally and particularly in case of analogues [5, 28]. This fact is

Table 4. Tumors for which less than 14 patients have been treated

Tumor type	Number evaluated	Number responding
ALL	12	0
Bladder	9	1
Cerebral	2	0
Large cell lung cancer	8	0
Mesothelioma	5	0
Oesophagus	6	1
Osteosarcoma	7	0
Prostate	7	1
Stomach	9	0

Adapted from Arnold [1]

chiefly related to the increasingly extensive prior chemotherapy of the patients, who are eligible for phase-II trials.

Furthermore, the methodology of such studies has rapidly evolved in the last decade and the compliance with the new rules is quite variable from one study to an other. In order to generate comparable results, the methodology of phase-II studies should at present be standardized at least in five points: the selection of the patients, the study design, the definition of the antitumor result, the assessment of the antitumor result and of the toxicity, the way of reporting data [28]. The following review of some of the phase-II data generated with VP16-213 aims at emphasizing at least the methodological problems, which are more often encountered.

Pretreatment

It is well known, that many tumors become resistant to cytotoxic drugs after first line chemotherapy: this applies mainly to neoplasms which are not very sensitive to chemotherapy. It is therefore possible that in neoplasms like, e.g., stomach cancer, VP16-213 could still display an higher antitumor activity than presently assumed. In these tumors phase-II studies with new drugs should be generally done only in previously untreated patients or at least the results analysed separately according to the previous treatment. But even in tumors sensitive to cytotoxic drugs, pretreatment is of paramount importance in the evaluation of the exact degree of antitumor activity. One might assume, that the wide range in the response rate registered with VP16-213 in NHL (0–55%) is probably mainly related to the different intensity of the previous treatment. The same fact accounts at least partially for some of the inconsistencies, which will be discussed later.

Assessment of Response

Toxicity is the main parameter in phase-I trials and survival might correct some inaccurate clinical assessments registered in phase-III trials. Phase-II studies however look solely at the response rate: therefore the definition of response and the way of assessing it are of paramount importance. So the inconsistency of the results registered in two studies, where patients with squamous cell carcinoma of the lung [17, 23] were treated with VP16-213, may be partially related to different criteria in evaluating the response: in the former report 40% of the patients had only evaluable tumors, in the latter all lesions were clearly measurable.

Non-seminomatous testicular tumors are highly chemosensitive neoplasms and VP16-213 has emerged as one of the most active drugs in the treatment of these diseases. However the two major phase-II trials report a response rate of respectively 20% and 45% [10, 20]. In the former study the oral form and a more (too?) aggressive schedule were used, in the latter trial the IV formulation and a less aggressive treatment were evaluated. The characteristics of the patients were also quite dissimilar for both populations. But the main reason explaining the difference in the response rate has probably to be seen in the different criteria for evaluating tumor response: in the second study raised markers alone were accepted as evidence of a lesion, which was not the fact for the other trial.

Schedule

The problem of the schedule is probably crucial for a drug like VP16-213, which has been proven to have a marked schedule-dependency for its antitumor activity in experimental tumors [14] as well as in man [6]. In our randomized trial [8] using three different and roughly equitoxic schedules, the response rates varied from 20% to 62%. It is therefore conceivable that some of the inconsistencies registered in the literature are primarly related to differences in the treatment schedule. In a "broad" phase-II trial performed by the CALGB and only recently published, an overall response rate of only 8% out of 382 patients was registered [31]. Even in small cell lung cancer only 10% of the patients responded. The explanation of these disappointing results must be sought, as stated by the authors, in the type of schedule and also in an insufficient dosage.

VP16-213 has clearly emerged as the most active drug in the treatment of small cell lung cancer [1, 16, 24, 32, 33]. However at present there are conflicting

data, and some are presented in this issue [22] as regards its efficacy in previously treated patients. Differences in the drug scheduling as well as the variable intensity of the treatment administered in each series might explain this further inconsistency.

Formulation

In the case of VP16-213 the formulation used in a particular trial might also be of importance: sometimes different formulations prompted also the use of dissimilar schedules, adding a further element of uncertainty. In a pilot study we have previously reported a striking antitumor activity of this drug given IV in the treatment of hepatocellular carcinoma [7]. Based on these data the Early Clinical Trial Group of the EORTC decided to start a disease-oriented phase-II trial using the oral formulation. The results of this confirmatory trial were slightly disappointing, since only three PR out of 24 treated patients were registered [11]. Recent pharmacokinetic findings [13] and the lack of correlation in our trial between the degre of impairment of the liver function and the grade of myelosuppression observed, seem to hint at a decreased absorption of the drug in the presence of an impaired liver function. We might therefore speculate, that the inconsistent results registered in our two subsequent studies with VP16-213 in the treatment of hepatocellular carcinoma are probably related to the different formulations used.

Study Design

The principal aim of phase-II trials is to obtain a qualitative answer: is the drug active or not [4, 28]? The threshold for a clinically useful response rate has been set at 20% of the treated patients. Therefore a two step design is presently recommended: if no response is registered among the first 14 treated patients or less than three responses are seen in the first 30 cases, than one might assume, that the drug is unable to reach the limit of 20% ($P < 0.05$). If more responses than outlined above ar observed during this first step, than further cases must be accrued clearly to assess the exact degree of antitumor activity. However even this elaborate methodology does not avoid possibilities of error [27, 37]. It is therefore possible, that the results of some trials were influenced by the study design itself. So in a randomized comparison between the IV and the PO formulation of VP16-213 we treated in each arm 14 patients with advanced breast cancer without registring a PR: the drug was therefore declared as being fully negative [9]. At another institution however, where more sophisticated study design is regularly implemented, 72 patients were treated with the drug either as IV bolus or as continuous infusion: a response rate averaging 18% was registered [35].

Conclusion

VP16-213 is a new semisynthetic podophyllotoxin derivative, which appears to have a unique mode of action. Early suggestive data of activity in small cell lung cancer [21, 25] have ben confirmed and the single-agent response rate remains at over 40% with well more than 200 patients studied. It also shows a pronounced antitumor activity in the treatment of testicular cancer, monocytic or myelomonocytic leukemia, non-Hodgkin's lymphomas and hepatocellular carcinoma. Its role in some other neoplasms, like non-small cell lung cancer and breast cancer, has still to be ascertained.

New data on its pharmacokinetic properties are being rapidly accumulated. Based on this knowledge a more optimal schedule of administration can be expected. New modes of administration, which like, e.g., continuous infusions in the past were only occasionally used [6, 36], are presently being thoroughly investigated. One might therefore reasonably hope, that in the next few years all potentialities of the drug will be more exactly defined.

Retrospectively the phase-I-II trials with VP16-213 might be viewed as an example of the methodological difficulties encountered in the clinical evaluation of new agents. Some pitfalls can probably be avoided by implementing a more stringent and standardized methodology. Other difficulties seem on the contrary to represent inherent drawbacks of our current approach. Hopefully the "stem cell clonogenic assay" will in future turn out to be a useful tool for the solution of some of these remaining problems [34].

Acknowledgements. To Ms. O. Kraitrova for having typed this manuscript.

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Accepted July, 1981