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Review

Current Development of Podophyllotoxins

Renzo Canetta[1], Peter Hilgard[2], Sylvia Florentine[1], Paolo Bedogni[2], and Luigi Lenaz[1]

[1] Bristol-Myers Company, International Division, Clinical Anti-Cancer Research, 345 Park Avenue, New York, NY 10154, USA
[2] Bristol-Myers International Corporation, Chaussée de la Hulpe 185, B-1170, Brussels, Belgium

Summary. *The unique biological properties and therapeutic efficacy of the podophyllotoxin derivatives, Vumon (VM26, teniposide) and Vepesid (VP16-213, etoposide), are stimulating the interest of both laboratory and clinical researchers. Investigations on new pharmaceutical formulations, pharmacokinetics and metabolism are providing more appropriate information on drug administration; experimental chemotherapy indicates that, among others, cytosine arabinoside and cisplatin are highly synergistic with podophyllotoxins; single agent and combination treatment clinical trials are defining the respective role of Vumon and Vepesid in cancer chemotherapy.*

Introduction

The podophyllotoxin's semi-synthetic derivatives, teniposide (VM26, Vumon) and etoposide (VP16-213, Vepesid) were reported to display experimental anti-tumor activity since the early 70's by the Sandoz research group [55–56]. In 1978 both drugs were included in the clinical anti-cancer program of Bristol-Myers Company. Rather than present an extensive review, this report proposes to discuss the current status of these compounds emphasizing the recent progress achieved and future developments.

Pharmaceutical Formulation

The interest raised by the laboratory and clinical activity of both drugs has warranted subsequent interventions in the formulation, especially for Vepesid, in order to facilitate the availability as well as the acceptability of a compound with potential for oral administration.

Historically the first formulation adopted in clinical trials was the ampule for intravenous use [20, 38]. This was followed a few years later by an oral formulation (lipophilic capsules containing etoposide suspension) whose bioavailability appeared to be somewhat variable because of erratic absorption [39]. To resolve the initial problem, a so called drinking ampule, quite similar in comparison to the original parenteral ampule and capable of inducing predictable dose-related side effects was introduced [10, 40].

Because of the unpleasant taste of the latter, not ameliorated in the experience with an experimental flavored drinking ampule [15], additional work has been done on the oral formulation with the introduction of a new soft gelatin capsule containing etoposide in solution. This was able to reach a comparable maximum tolerated dose (MTD) in a Phase I trial conducted the same group responsible for early testing [32]. Table 1 lists the Vepesid formulation development trail.

Stability Studies

Together with the work on the new capsule, further tests have been done in order to assess the stability of the Vepesid ampule content when administered orally in different fluids to increase palatability. The drug proved to be stable for at least 3 h when diluted in orange juice, lemonade and dextrose water [3].

Additional investigations were also performed on the parenteral administration. Since the old clinical brochure suggested instability of the drug in 5% dextrose water, laboratory tests have been repeated,

Send offprint requests to L. Lenaz at the above address

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Table 1. Vepesid formulation development

Year	Form	Comment	Reference
1972	I.V. ampule	MTD: 45 mg/m^2 d × 7	[38]
1975	Lipophilic capsule (suspension)	Absorption problems	[39]
1976	Drinking ampule	MTD: 120 mg/m^2 d × 5	[40]
1978	Flavored drinking ampule	Palatability problems	[15]
1979	Hydrophilic capsule (solution)	MTD: 100–130 mg/m^2 d × 5	[32]

Table 2. Lack of cross-resistance between i.v. epipodophyllotoxins: cases reported in the literature

Diagnosis	Failure to	Response to	Type and duration	Reference
ALL	VP16 75 mg/m^2 twice weekly	VM26 75 mg/m^2 daily × 3	CR, 13 days	[46b]
ALL	VP16 150 mg/m^2 twice weekly	VM26 100 mg/m^2 twice weekly	PR, 60 days	[46b]
ANLL	VP16 100–150 mg/m^2 daily × 5	VM26 130 mg/m^2 weekly	CR, 42 days	[7, 8]
Ewing's sarcoma	VM26 130–180 mg/m^2 weekly	VP16 15 mg/m^2 daily × 5	PR, unspecified	[7, 16]

either in the latter or in normal saline, showing the same concentration-related stability as follows:

- solution 0.25 mg/ml: stable up to 72 h,
- solution 0.40 mg/ml: stable up to 4 h,
- solution 1 mg/ml: crystal formation by 5–30 min.

The administration of 250 ml 5% dextrose or 0.9% NaCl for each 100 mg Vepesid ampule is therefore recommended for short-term therapy; prolonged infusions will require appropriate dilution.

Pharmacokinetics

The initial investigations on teniposide and etoposide pharmacokinetics were conducted in animals and in man using tritium-labelled drugs [6, 18, 19]. Only recently a high performance liquid chromatography (HPLC) procedure has been introduced [57] and many interesting preliminary communications on podophyllotoxins kinetics and metabolism assessed through this method have been presented [5, 21, 26, 44, 53].

These studies are still ongoing but important observations such as the existence of active metabolites, the lack of kinetic intereference with other commonly combined agents and the bioavailability differences among the various formulations have already provided valuable information for clinicians and warrant further investigations.

Single Agent Activity

According to the most recent literature reviews [4, 30, 41, 45], the single-agent activity of Vepesid and Vumon is already defined in malignant lymphomas and, respectively, in small-cell lung cancer, acute non-lymphoblastic leukemia, testicular cancer and choriocarcinoma for the former and bladder cancer, brain tumors and neuroblastoma for the latter. Nevertheless, several tumor types still deserve adequate investigations particularly in situations where preliminary experiences have suggested hints of activity (as in hepatoma, upper G.I. tract cancers and thyroid cancer for Vepesid) or where contrasting data require clarification (as in ovarian and small-cell lung cancer for Vumon) [48, 60].

An accurate definition of the respective spectra of action is not currently provided by the available clinical data. Only slight differences can be postulated through cumulative and non-randomized series [7]. Perhaps new laboratory research methods such as the stem-cell assay test [31] will offer new insights. Also, the cross resistance between the two drugs remains controversial. A few cases (listed in Table 2) have

been described in the literature as responding to one podophyllotoxin after developing definite resistance to the other (e.g., objective response to one after progression under single-agent therapy with the other). Again basic research, such as the selection of drug-resistant tumor cell lines [51] could help resolve the problem.

Therapeutic Synergism

Because of their relatively low and predictable toxicity and their unique mechanism of action, podophyllotoxins offer attractive possibilities for combination chemotherapy.

Many laboratory tests have been carried out in order to find the best potential combinations. Table 3 lists those compounds which have shown a more than additive effect against murine tumors. In addition, it must be noted that in these models the toxicity of Vepesid when combined either with cyclophosphamide, BCNU or cisplatin was less than the sum of the two components [22, 50]. On the other hand, drugs such as actinomycin D, daunorubicin, fluorouracil, mercaptopurine and methotrexate did not provide benefit when combined with VP16-213 [22].

Moreover, in an in vitro test neither VP16-213 nor VM26 were found to potentiate the effect of concomitant radiation therapy [33].

Interestingly enough the only combination of Vumon tested in mice (the one with cytosine arabinoside) after being transferred into clinical trials by the same St. Jude group showed very promising results [46, 47]. The most extensive and favorable experience on therapeutic synergism in laboratory testing has been made with the combination of Vepesid and cisplatin (Table 4). Results obtained independently by several authors in several tumor models came to the same conclusion, so that the clinical investigation of the potential of such combination sounds very attractive. Preliminary results reported in oat [52] and non-oat cell lung [28, 34] cancer as well as in testicular cancer [59] seem to substantiate the experimental hypothesis and to warrant further trials, particularly in malignant lymphomas and choriocarcinoma, where single agent activity of both drugs has been demonstrated.

If an analogous synergism between Vumon and cisplatin being currently investigated is be confirmed, clinical trials in tumours such as neuroblastoma, bladder, ovarian and brain tumors would become more attractive. Further development along this way could eventually involve tumors where one of the two components of the combination is less active or has previously failed.

Table 3. Combinations including podophyllotoxins found to be synergistic against intraperitoneally implanted mouse leukemias

Treatment	Model	Reference
Vepesid + AAFC[a]	P388	[11]
Vepesid + BCNU	L1210	[22]
Vepesid + cyclophosphamide	L1210	[22]
Vepesid + cytosine-arabinoside	L1210	[46]
Vepesid + vincristine[b]	P388	[17]
Vumon + cytosine-arabinoside	L1210	[46]

[a] 2-2′-anhydro-1-β-D-arabinofuranosyl-5-fluorocytosine
[b] given 96 h before vepesid

Table 4. Effect of combining vepesid and cisplatin in laboratory tumours

Model	Effect	Reference
Human T-lymphoma cells (in vitro)	Additive	[23]
I.P. P388 leukemia	Synergistic	[11, 35, 50]
I.P. L1210 leukemia	Synergistic[a]	[11]
I.P. B16 melanoma	Synergistic	[35]
FANFT-induced bladder cancer	Synergistic	[54]

[a] Carboxyphtalato platinum (NSC-271674)

Other Combination Chemotherapies

In addition to the results being obtained through this parallel laboratory-clinical experience other combinations including podophyllotoxins have been introduced along four main lines of development:

a) Substition for a Vinca Alkaloid in an Established Regimen. This rationale relies on the resemblance of the mitosis-blocking mechanisms and the potential lack of neurotoxicity of combinations containing podophyllum instead of vinca derivatives. Despite the influence of such an hypothesis in designing new studies, only one randomized trial has been so far published [25] comparing Vumon or Vincristine in combination with procarbazine and prednisolone in Hodgkin's disease.

At the present time further randomized studies are in progress in testicular cancer comparing cisplatin, bleomycin and vinblastine or Vepesid (Indiana University); in non-Hodgkin's lymphomas comparing cyclophosphamide, prednisolone and vincristine or Vumon (New Zealand-Australia Cooperative Group) and in non-oat cell lung cancer comparing cisplatin and vindesine or Vepesid (Holsti, Finland). Several controlled trials are also ongoing in the U.S. in small cell lung cancer comparing cyclophosphamide, adriamycin and vincristine or Vepesid.

Table 5. Example of development of combinations including podophyllotoxin in oat-cell lung cancer

Modifications	Regimen	Author	No. of patients	CR rate %	CR + PR rate %	Reference
Original	CAV	Holoye	24	29	63	[29]
Substitutive	CAVp	Pendergrass	12	42	83	[43]
Additive	CAVVp	Valdivieso	22	73	95	[58]
Alternative (CAV failures)	PVp	Osoba	20	10	50	[42]
Alternative (first line)	PVp	Sierocki	32	53	97	[52]
Sequential	CAV/PVp	Natale	44	63	96	[37]

C = cyclophosphamide; A = adriamycin; V = vincristine; Vp = Vepesid; P = cisplatin

b) Addition of one Podophyllotoxin to an Active Combination. When it became clear that podophyllotoxins toxicity was predictable and manageable and their mechanism of action could not mandatorily imply cross-resistance with vinca alkaloids, many investigators simply added one of these drugs to their best regimen. This has been the case especially in oat-cell lung cancer [14, 24, 36, 58] where Vepesid is the most active single agent available.

c) Designing of New Non-cross Resistant Combinations. This development originated first as an attempt to investigate active combinations for patients with advanced disease, relapsed after initial treatment. In the above mentioned studies of Rivera [47] in acute lymphocytic leukemia and Williams [59] in testicular cancer this approach led to results so impressive, when considering the history of patients being treated, to allow the use of the term "salvage therapy".

Very promising preliminary results have also been reported in malignant lymphomas where the response rates obtained with non-cross resistant combinations (iphosphamide, methotrexate, and Vepesid in non-Hodgkin; CCNU, Vepesid and prednimustine in Hodgkin's disease respectively) suggest the possibility of valuable reinductions even in patients relapsing after highly active treatments such as CHOP, MOPP or ABVD [13, 49].

d) Cyclic Sequential Combination Chemotherapy. As a conceptual implication of the preceeding point this modality is being currently actively pursued in first-line therapy. The exposure of the tumor cell population to many different effective weapons before developing drug resistance has been frequently applied in oat-cell lung cancer [1, 2, 9, 37] and in non-Hodgkin's lymphomas [12, 27]. Long term results are needed to clarify the actual validity of this approach.

In Table 5 is presented an example of the development of podophyllotoxin-containing combinations as realized, along the lines indicated, in oat-cell lung cancer.

More controlled clinical trials in additional indications will contribute to better delineate the potential of Vepesid and Vumon in cancer chemotherapy.

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