Cancer Chemother Pharmacol (2005) 55: 244–250
DOI 10.1007/s00280-004-0858-2

ORIGINAL ARTICLE

Katel Marigny · Fabienne Aubin · Gwenola Burgot
Edouard Le Gall · Virginie Gandemer

Particular cutaneous side effects with etoposide-containing courses: is VP16 or etoposide phosphate responsible?

Received: 21 July 2003 / Accepted: 4 May 2004 / Published online: 4 November 2004

Abstract *Purpose*: Etoposide is commercially available in France in two different pharmaceutical forms: VP16 and its phosphate ester (etoposide phosphate, EP). EP shows better chemical and physical properties, is said to be less toxic but is five times more expensive than VP16. Some criteria were defined for the use of each form in the Paediatric Oncohaematology Department in Hôpital Sud in Rennes. As some particular cutaneous side effects were observed during treatment with etoposide-based course in this department, a retrospective study was initiated. The aims of this work were to determine the side effects (especially cutaneous toxicity), whether the pharmaceutical formulation of etoposide had any influence on the toxicity of the drug, and whether the observed side effects resulted from etoposide alone or from particular antineoplastic drug associations. *Methods*: Five types of etoposide-containing protocols were chosen: NB 97 and NB 99 (neuroblastoma), FRALLE 93 (acute lymphoid leukaemia), LAME 91 (acute myeloid leukaemia), OS 94 (osteosarcoma), Ewing 97 and Euro-Ewing 99 (Ewing sarcoma). The medical files of 36 children (88 EP courses, 25 VP16 courses) included in these protocols were analysed on the basis that if a child showed a side effect during a course, the child had to have recovered from that side effect before the beginning of the next course. *Results*: Apart from classical side effects (haematological and digestive toxicities etc.), two particular cutaneous side effects were observed: (1) palmar–plantar eruptions and nail inflammations, and (2) irritation of the anal area and anal fissures. Those side effects were observed with three of the studied protocols: NB 97, OS 94 and Ewing sarcoma treatments. *Conclusions*: No striking differences in toxicity appeared between the two etoposide formulations, but this retrospective study seemed to confirm the appearance of particular cutaneous and anal side effects especially with two associations: (1) etoposide–ifosfamide (OS 94 and Ewing 97), and (2) etoposide–ifosfamide–Adriamycin–vincristine (VIDE course of the Euro-Ewing 99 protocol).

Keywords Etoposide · Etoposide phosphate · Anal toxicity · Acral erythema · Excipient

K. Marigny (✉) · F. Aubin · G. Burgot
Department of Pharmacy, CHU Hôpital Sud, Bd de Bulgarie, 35000 Rennes, France
E-mail: katel.MARIGNY@chu-rennes.fr
Tel.: +33-299-267130
Fax: +33-299-267148

E. Le Gall
Department of Paediatric, CHU Hôpital Sud, Bd de Bulgarie, 35000 Rennes, France

V. Gandemer
Department of Paediatric Oncohaematology, CHU Hôpital Sud, Bd de Bulgarie, 35000 Rennes, France

Introduction

Discovered in the 1960s, VP16 is an antineoplastic drug, a semisynthetic derivative of podophyllotoxin, a natural substance extracted from the roots and rhizomes of *Podophyllum peltatum* and *Podophyllum emodi* [25]. Commercialized by many pharmaceutical firms, this molecule has shown great effectiveness in the treatment of a variety of neoplasms including small-cell lung cancer, Hodgkin's disease, non-Hodgkin's lymphomas and leukaemia. Haematological and digestive toxicities are the most important side effects observed. According to its physical and chemical properties, VP16 has two disadvantages: a low water solubility [23], which explains the use of many excipients in the injectable solution, and instability that makes it necessary to prepare a solution in the concentration range 0.2–0.4 mg/ml to avoid precipitation [3]. In 1997, Bristol-Myers Squibb (BMS) commercialized a new molecule, a prodrug of VP16: etoposide phosphate (Etopophos, EP). This phosphate ester is characterized by its high water solubility and stability in injectable solutions (up to 20 mg/ml), thus avoiding the use of many excipients for its injectable formulation. BMS presented these two properties

(chemical and physical stability in solution and fewer excipients) as two great advantages of EP over VP16. Nevertheless, the actual cost of the ester phosphate drug compared to that of VP16 may limit its use.

Included in many chemotherapy protocols, etoposide is very often used in the Paediatric Oncohaematology Department of Hôpital Sud in Rennes. Because of the different costs of the two formulations of etoposide, some criteria were defined for the use of EP: patient weight < 20 kg (because of the large dilution volume of VP16), high dose of VP16 (graft pretreatment), administration of etoposide during a weekend (because of the limited stability of VP16), patients who had already been treated with EP.

As some particular cutaneous side effects had been observed during etoposide-containing chemotherapy, we carried out a retrospective analysis of the medical files of patients treated with etoposide—VP16 or EP—in the Paediatric Oncohaematology Department. The aim of this work was to study more particularly these cutaneous toxicities occurring during etoposide-based courses, to determine whether they were linked to a particular formulation of etoposide or to particular associations of chemotherapeutic agents, then to find out if the occurrence of side effects was different between VP16 and EP.

Materials and methods

Our retrospective analysis was based on clinical data collected from patients' medical files. In order to study the involvement of etoposide in the side effects observed during chemotherapy courses and the possible difference between VP16 and EP, five chemotherapy protocols were chosen. These protocols were associated with different pathologies, allowing the study of groups of patients of various ages and associating etoposide with several cytotoxic agents. The criteria used to select these protocols were based on pathologies (haemopathies or solid tumours), doses, administration cycles, total antineoplastic agent dose for a course, and finally association of cytotoxic agents. As a result of this selection, some neuroblastoma treatment protocols (NB 97, NB 97 modified version of May 1999, and NB 99), two leukaemia treatment protocols (FRALLE 93 for acute lymphoid leukaemia, and LAME 91 for acute myeloid leukaemia) and two bone tumour treatment protocols (OS 94 for osteosarcomas, and Ewing 97 and Euro-Ewing 99 for Ewing sarcomas) were studied (Table 1). A list of patients treated with etoposide-based courses between October 1998 and August 2000 was established (data collected from the cytotoxic agents preparation register of the pharmacy). The two key points of this analysis were: to research the side effects (more particularly cutaneous) and the involvement of the etoposide formulation in these toxicities.

All the events noted in the patients' medical files during the hospitalization for the etoposide-containing course and the following hospitalization were collected. Based on the WHO acute and subacute cytotoxic agents side effects scale, haematological toxicities (especially leucopenia and neutropenia), mucositis, digestive toxicities (nausea, vomiting, diarrhoea), immediate allergic reaction (fever after infusion, cutaneous rash) and long-term cutaneous side effects were sought. Side effects were recorded as new toxicities in each course on the basis that if a child had shown a side effect during a course, the child had to have recovered from that side effect before the beginning of the next course. A side effect observed after a course started with one etoposide formulation and finished with another was considered as 0.5 side effect for each formulation. In order to find a possible correlation between the observed toxicities and the formulation of etoposide, the type of etoposide (VP16 or EP) administered during each course was noted.

Results

The medical files of 36 children were analysed. Most of the children under 4 years old were treated for neuroblastoma ($n = 5$) and received a total of 17 etoposide-containing courses. Three 2-year-old children and 17

Table 1 Protocols (*6 TG* 6 thioguanine, *ADR* Adriamycin, *ARA C* cytarabine, *CBDCA* carboplatin, *CDDP* cisplatin, *CPM* cyclophosphamide, *DNR* daunorubicin, *DXM* dexamethasone, *IDA* idarubicin, *IFM* ifosfamide, *VRC* vincristine)

NB 97	Etoposide (600 mg/m^2/course)–CDDP (200 mg/m^2/course)
NB 97 modified in May 1999 (first part)	Etoposide (500 mg/m^2/course)–CDDP (200 mg/m^2/course)
NB 97 modified in May 1999 (second part)	Etoposide (500 mg/m^2/course)–CBDCA (800 mg/m^2/course)
NB 99 (99.1 et 99.3)	Etoposide (450 mg/m^2/course)–CBDCA (594 mg/m^2/course)
Fralle 93 group B & C1: consolidation, intensification, intensification no. 1	Etoposide (450 mg/m^2/course)–ARA C (180 mg/m^2/course)–6 TG (1260 mg/m^2/course)
Fralle 93 group C1: intensification no. 2	Etoposide (300 mg/m^{2}course)–ARA C (120 mg/m^2/course)–6 TG (1260 mg/m^2/course)
Fralle 93 group C2, bloc R3	Etoposide (450 mg/m^2/course)–ARA C (8 g/m^2/course)–DXM (100 mg/m^2/course)
Fralle 93 group C2, CAZED	Etoposide (450 mg/m^2/course)–ARA C (8 g/m^2/course)–DXM (100 mg/m^2/course)–CPM (1.2 g/m^2/course)–IDA (30 mg/m^2/course) or DNR (150 mg/m^2/course)
LAME 91	Etoposide (400 mg/m^{2}course)–ARA C (400 mg/m^2/course)–DNR (160 mg/m^2/course)
OS 94	Etoposide (300 mg/m^2/course)–IFM (12 g/m^2/course)
Ewing 97	Etoposide (500 mg/m^2/course)–IFM (9 g/m^2/course)
Euro-Ewing 99, VIDE	Etoposide (450 mg/m^2/course)–IFM (9 g/m^2/course)–ADR (60 mg/m^2/course)–VCR (1.5 mg/m^2/course)

Table 2 Children's distribution in the studied protocols

Protocol	Number of patients ($n=36$)	Average age	Number of courses ($n=113$)
Neuroblastomas protocols			
NB 97	1	2.3 years (1–4 years)	3
NB 97 modified in May 1999	2		
1st part			4
2nd part			4
NB 99.1 and NB 99.3	2	41 days (22 days and 2 months)	6
FRALLE 93 (four different types of courses)			
Group B	5	5.4 years (4–8 years)	36
Group C1	3	4.3 years (2–7 years)	
Group C2	6	5.8 years (2–11 years)	
LAME 91	6	6.4 years (2–13 years)	6
OS 94	3	13.5 years (11–15 years)	11
Ewing 97	3	16.3 years (15–17 years)	14
Euro-Ewing 99	5	14 years (11–16 years)	29

children aged between 5 and 13 years were treated for leukaemia pathology (42 etoposide-based courses). Among those older than 10 years, 11 received a total of 54 etoposide-containing courses for the treatment of bone tumour (Table 2). Thus, 113 etoposide-containing courses prepared during the studied period, divided into 12 different types of chemotherapies, were analysed, and comprised 25 courses with VP16 and 88 courses with EP.

Apart from the well-documented haematological (often associated with fever) and mucositis toxicities (data not shown), two particular side effects were observed:

1 Irritation of the anal area and anal fissures: ten observations (one WHO grade I, two WHO grade II, seven WHO grade III)
2 Palmar–plantar cutaneous and inflammatory reactions of fingers and toes: 12 observations (two WHO grade I, ten WHO grade II).

These two side effects noted in the patients' medical files are not the usual toxicities caused by cytotoxic agents. The first leads to inflammation and painful reactions of the mucous membrane (WHO grades I and II), a reaction that may get worse and lead to ulceration and anal fissures (WHO grades III). The symptoms of the cutaneous palmar–plantar reaction were erythematous and inflammatory eruption of the palms and/or soles (WHO grades I), without infection, with possible subsequent desquamation (WHO grade II).

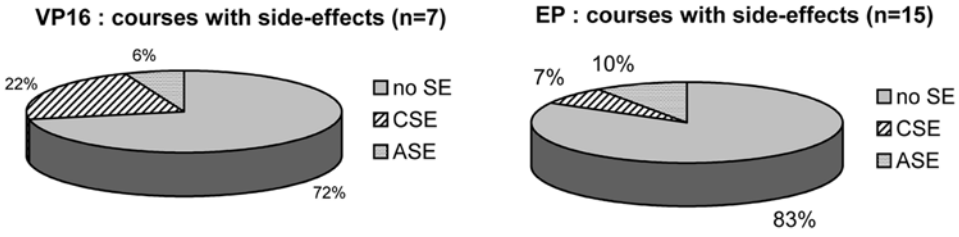
These two types of reactions were observed with both VP16 and EP and were associated with four different chemotherapy protocols: NB 97 modified in May 1999 (first part), OS 94, Ewing 97, and Euro-Ewing 99. Nine patients showed those toxicities (see Table 3). Side effects occurred in 7 of 25 courses (28%) with VP16 and 15 of 88 (17%) with EP (Fig. 1). Of the 11 OS 94 courses and 29 Euro-Ewing 99 courses, 5 and 7 generated cutaneous toxicities, respectively. Anal side effects occurred after 1 of 4 neuroblastoma courses and 1 of 11 OS 94 courses. Ewing 97 courses and Euro-Ewing 99 courses were associated with a higher incidence of anal side effects with (2 of 14 and 6 of 29 courses, respectively; Fig. 2).

In the neuroblastoma treatment protocols, only EP was administered (patients' weight <20 kg). One of five patients showed anal toxicity. In the OS 94 protocol, two of three patients showed side effects with VP16 and/or EP (one treated only with EP showed cutaneous and anal toxicities, the other treated with VP16 and EP showed cutaneous side effects). In the Ewing 97 protocol, one of three patients showed anal toxicity. This child received alternately VP16 and EP. The two other children treated only with EP did not show such side effects. The Euro-Ewing 99 protocol (VIDE course) was associated with a high number of side effects. The five children included in that protocol showed toxicities. Three treated only with EP (and one VP16 course with no particular toxicity) showed cutaneous and/or anal side effects. One child treated with EP without any particular side effects developed cutaneous toxicity after one VP16 course. The last child developed cutaneous toxicity during the third course (the two first courses with VP16

Table 3 Protocols and side effects (anal and cutaneous)

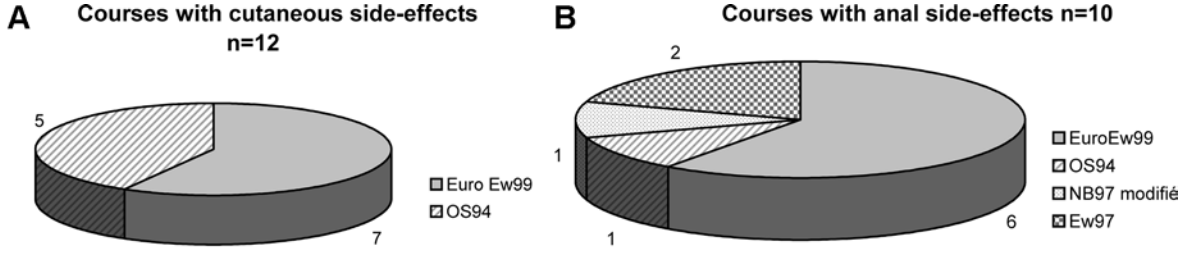
Protocol (total number of patients)	Number of patients with side effects	Cytotoxic agent (overall number of courses)	Number of side effects (cytotoxic agent)	
			Cutaneous	Anal
NB 97 modified in May 1999, first part ($n=2$)	1	EP (4)	0	1 (EP)
OS 94 ($n=3$)	2	VP16 (5), EP (6)	3 (VP16), 2 (EP)	1 (EP)
Ewing 97 ($n=3$)	1	VP16 (2.5), EP (11.5)	0	1 (VP16), 1 (VP16 and EP)
Euro-Ewing 1999 ($n=5$)	5	VP16 (5.5), EP (23.5)	2.5 (VP16), 4.5 (EP)	6 (EP)

Fig. 1 Side effects in relation to etoposide formulation



SE : side-effect, CSE : cutaneous side-effect, ASE : anal side-effect

	Total number of courses	Courses with no side-effects (CSE or ASE)	Courses with CSE	Courses with ASE
VP16	25	18 (72%)	5.5 (22%)	1.5 (6%)
EP	88	73 (83%)	6.5 (7%)	8.5 (10%)



SE : side-effect, CSE : cutaneous side-effect, ASE : anal side-effect

	Total number of courses	Courses with no side-effects (CSE or ASE)	Courses with CSE	Courses with ASE
NB 97 modified in May 99 (first part)	4	3 (75%)	0	1 (25%)
OS 94	11	5 (45.5%)	5 (45.5%)	1 (9%)
Ewing 97	14	12 (86%)	0	2 (14%)
Euro-Ewing 99	29	16 (55%)	7 (24%)	6 (21%)

Fig. 2 Type of side effects in relation to protocol

did not generate any particular side effects). This toxicity reappeared during the fourth course starting with VP16 and finishing with EP, and appeared again during the two last courses with EP. In summary, 2.5 courses with VP16 and 4.5 courses with EP caused cutaneous reactions (out of a total of 5.5 and 23.5 courses, respectively), and six EP courses (out of 23.5) caused anal reactions (see Table 3).

In contrast, FRALLE 93, LAME 91, NB 97, NB 97 modified in May 1999 (second part), and NB 99 did not produce such toxicities. The children included in these protocols received either VP16 (total of 12 courses) or EP (total of 43 courses).

Discussion

Etoposide is an antineoplastic agent widely used in adult and paediatric chemotherapeutic protocols. When EP was commercialized, the pharmaceutical firm insisted on two properties: stability at high concentrations and no toxic solvent (particularly polysorbate 80) in its formulation.

As cutaneous side effects were observed after etoposide-containing courses in the Paediatric Oncohaematology Department of Hospital Sud in Rennes, and considering the important difference in cost between VP16 and EP, we carried out a retrospective study, completed with bibliographic research. This work had two main objectives: to record side effects (particularly cutaneous symptoms) observed during etoposide-based chemotherapies and to establish a causal link between those side effects and the use of VP16 or EP.

Except for cutaneous rashes linked to hypersensitivity reactions, the toxic effects of antineoplastic agents are observed mainly in rapidly growing cellular tissues, such as haematopoietic, cutaneous and mucous tissues. Alopecia, mucositis or stomatitis are the most frequent toxicities. Diffuse or localized cutaneous hyperpigmentation, and the appearance of inflammatory signs in cutaneous areas irradiated months or years before have been described with many antineoplastic agents [5, 22].

A particular cutaneous reaction localized on the hands and feet has also often been described and many names have been given to this syndrome (acral erythema, palmar–plantar erythema, hand–foot syndrome, Burgdorf reaction). Many molecules may generate, alone or in combination, dose-dependent acral erythema, the most commonly quoted being fluorouracil, Adriamycin, cytarabine, methotrexate, hydroxyurea and cyclophosphamide [2, 22]. The onset of these reactions is usually rapid (24 h to 2–3 weeks) and more severe with bolus or short-term chemotherapy than with low-dose continuous infusion (the reaction occurring then within 2–10 months) [2].

The palmar–plantar eruption starts typically with a tingling in the hands and feet, progressively evolving over the next 3–4 days into a painful, oedematous erythema of the extremities with the occasional formation of blisters. This phenomenon may extend to the back of the hands and feet and appear in other areas of the body. Desquamation and a re-epithelialization process usually indicate healing. Symptoms can reappear with reintroduction of the drug. Histological observation of the lesions reveals a vacuolar degeneration of the basal cell layer, necrotic and dyskeratotic keratinocytes, dermal oedema and a mild perivascular lymphohistiocytic infiltrate [2, 9]. The origin of this phenomenon is unknown and many mechanisms have been proposed [2, 9]: the particular anatomical characteristics of acral areas (vascular anatomy, rapid epidermis cell division, numerous eccrine glands), the toxicity of the drug in the epidermis, immune factors (the acral erythema appears in conditions such as neutropenia and immune deficiency). This kind of reaction is also observed in acute graft versus host reaction (aGVHR) and it can be extremely difficult to differentiate toxic acral erythema from acral erythema indicating aGVHR when this syndrome appears soon after grafting [9, 26].

Cutaneous reactions observed during etoposide-based chemotherapies are often described in the literature. These reactions have frequently been observed when etoposide is associated with ifosfamide and carboplatin [4, 19], Adriamycin and methotrexate [18], cyclophosphamide and vincristine [18], Adriamycin and cyclophosphamide [26], methotrexate and hexamethylmelamine [26], and daunorubicin and hydrocortisone [26]. Authors have often attributed the cutaneous toxicities observed to etoposide for different reasons (for example, histological analysis shows cells closely resembling those treated with topical podophyllin, a VP16-related compound, in condyloma acuminata [26]). But it is important to note that some other etoposide-containing associations, cited by these authors, never generated any of these cutaneous toxicities when administered to the same patients. Therefore, considering this information, it seems that these reactions must result from some particular associations of chemotherapeutic agents and not from etoposide or its formulation alone. Among the above-cited associations, etoposide is frequently associated with nitrogenous mustards (cyclophosphamide and ifosfamide), and with anthracyclines (Adriamycin and daunorubicin).

Although the origin of the anal toxicity is unknown, the same kind of complex biological process as the one occurring in mucositis may explain the observed reactions. This process can be divided into four phases: inflammatory and vascular, epithelial, ulcerative and bacteriological, and a final recovery phase. This phenomenon usually appears in rapidly growing cells. The cytotoxic agents used in our study, well-known to generate high-grade mucositis, are probably toxic to the digestive tract and, considering the anal localization, the ulcerative and bacteriological phase may be more important, leading to ulceration.

Concerning excipients, VP16 and EP formulations are notably different (Table 4). Due to its low water solubility, many additives were introduced into the injectable VP16 formulation. Some of these excipients, especially polysorbate 80, are frequently thought to be responsible for the immediate side effects observed after VP16 administration including hypotension or hypertension, tachycardia, dyspnoea, bronchospasm, flushing and exanthema [10, 16, 25]. The EP formulation, less complex than that of VP16, contains only dextran 40 and sodium citrate bringing the pH of the reconstituted solution to 4.5 [25]. Nevertheless, some authors have reported hypersensitivity reactions after EP administration [21, 25]. Only limited information on the toxicity of excipients is available in the literature, most from studies carried out in animals. Cardiovascular, neurological and/or respiratory side effects are more frequently associated with ethanol [8, 15], benzyl alcohol [8, 15], polysorbate 80 [14, 24] and polyethyleneglycol [12, 15], and allergic reactions are often associated with dextrans [6, 17, 20]. Except for ''greasy'' lower extremities observed in monkeys after PEG administration [12], no particular cutaneous or anal side effects were noted in those studies.

In our retrospective study, two particular side effects (apart from the classical mucositis and haematological toxicities) were noted: palmar–plantar eruptions or nail inflammation and irritation of the anal area or anal fissures. These two side effects occurred with both the EP and VP16 formulations. It is interesting to note that, in our retrospective study, palmar–plantar desquamation occurred more frequently than anal side effects when VP16 was administered (22% vs 7% with EP, see Fig. 1). This may have resulted from a particular mechanism of interaction of PEG with acral areas (palmar–plantar desquamation is also often described with pegylated liposomal Adriamycin [1, 13]). Nevertheless, this finding must be viewed with caution as cutaneous toxicity after VP16 courses was seen in only three children. Occurrence of anal side effects was similar with both formulations (6% with VP16 and 10% with EP, see Fig. 1). Otherwise, no immediate allergic reactions were reported in our patients' medical files (with either VP16 or EP), but no particular survey was done during the administration of these drugs.

Because few children were enrolled in this study, a particular sensitivity of the children could explain the side effects observed with the NB 97 modified in May 1999 (first part), Ewing 97 and OS 94 protocols. For the last of these protocols, high doses of methotrexate, which is known to generate cutaneous and mucosal toxicities [2, 7, 11], are used alternately with etoposide–ifosfamide courses. Nevertheless, if we consider both Ewing 97 and OS 94, a particular toxicity of the association etoposide–ifosfamide, cannot be ruled out.

On the other hand, the involvement of VIDE courses (Euro-Ewing 99) in the observed side effects is major; indeed nearly 45% of them led to cutaneous or anal toxicity. As the five patients included in this protocol showed cutaneous and/or anal toxicities, hypersensitivity of children is unlikely. It is interesting to note that anal side effects appeared more often during the first VIDE courses, the palmoplantar lesions being more often observed after the third course.

Finally, despite a similar dose of etoposide (300–500 mg/m^2 per course), none of the acute leukaemia treatment protocols (FRALLE 93 and LAME 91) or neuroblastomas treatment protocols—except NB 97 modified in May 1999, first part—generated cutaneous or mucosal toxicity (apart from mucositis). This seems to confirm the fact that etoposide—or its pharmaceutical formulation—alone is not the only factor responsible for the two particular toxicities noted in our study.

These bibliographic and retrospective studies highlight two particular chemotherapeutic associations: etoposide–ifosfamide and etoposide–ifosfamide–Adriamycin–vincristine. Concerning our retrospective study, it is important to note that the number of courses of VP16 and EP were very different (25 and 88, respectively). Moreover, despite this relatively high number of courses, they involved a small number of patients. For these reasons, no statistical tests were performed. Then, although the observed cutaneous side effect may be more specific of VP16 because of its PEG-containing formulation and the incidence of cutaneous and/or anal side effects seems higher with VP16, these toxicities were observed with both formulations of etoposide (VP16 and EP). These results do not justify any particular choice (based on a hypothetical greater toxicity of one or the other formulation) between VP16 and EP for prescription.

In conclusion, despite the small number of patients and the difference in the numbers of VP16 and EP courses, this retrospective study confirmed the occurrence of particular cutaneous and anal side effects when etoposide is used. These reactions concerned more especially two types of chemotherapeutic associations, etoposide–ifosfamide (OS 94 and Ewing 97) and etoposide–ifosfamide–Adriamycin–vincristine (Euro-Ewing 99), which seems to indicate that those lesions result more from the toxicity of certain associations of antineoplastic agents than from the etoposide formulation, but no striking difference in side effects was observed between the two drug formulations. The data available in the literature seem to confirm these findings, as associations of etoposide with nitrogenous mustards and/or anthracyclines are frequently cited when cutaneous toxicity (particularly acral erythema) is observed. But it is very surprising that anal lesions following a chemotherapeutic treatment are mentioned in only one article found in the literature (with etoposide–ifosfamide–carboplatin association [19]). The origin of this latter toxicity is still unclear but may be related to combined epithelial and mucosal toxicity complicated by an infectious mechanism.

As no difference of occurrence in anal and cutaneous side effects was noted between VP16 and EP, the Pharmacy and the Paediatric Oncohaematology Department decided that, based on its chemical and physical properties allowing high concentrations, the use of EP would be limited to patients of <20 kg in weight and to particular treatment indications (graft pretreatment).

References

1. Amantea M, Newman M, Sullivan T, et al (1999) Relationship of dose intensity to the induction of palmar–plantar erythrodysesthia by pegylated liposomal doxorubicin in dogs. Hum Exp Toxicol 18:17–26
2. Baack B, Burgdorf W (1991) Chemotherapy-induced acral erythema. J Am Acad Dermatol 24:457–461
3. Beijnen J, Beijnen-Bandhoe A, Dubbelman A, et al (1991) Chemical and physical stability of etoposide and teniposide in commonly used infusion fluids. J Parenter Sci Technol 45:108–112
4. Beyer J, Grabbe J, Lenz K, et al (1992) Cutaneous toxicity of high-dose carboplatin, etoposide and ifosfamide followed by autologous stem cell reinfusion. Bone Marrow Transplant 10:491–494
5. Breathnach S, Hintner H (1993) Antitumoraux. In: Arnette SA (ed) Réaction cutanées medicamenteuses. Paris, pp 281–304
6. Burova K, Bansal D (1999) Skin eruption to generic prednisolone. Br J Dermatol 141:597–598
7. Collectif (1995) Médicaments anti-cancéreux. De la préparation à l'administration, optimisation. APHIF, Paris
8. Collectif (1999) Liste des excipients à effet notoire. Fréquence CNHIM 3:1–4
9. Dechauffour F, Dompmartin A, Troussard X, et al (1993) Erythème acral après greffe de moëlle osseuse allogénique. Ann Dermatol Venereol 120:219–222
10. DeSouza P, Friedlander M, Wilde C, et al (1994) Hypersensitivity reactions to etoposide. Am J Clin Oncol 17:387–389
11. Hardman J, Limbird L, Molinoff P, et al (1996) Les bases pharmacologiques de l'utilisation des médicaments (édition française 1998). McGraw-Hill, New York
12. Lockard J, Levy R, Congdon W, DuCharme L (1979) Efficacy and toxicity of the solvent polyethylene glycol 400 in monkey model. Epilepsia 20:77–84
13. Lotem M, Hubert A, Lyass O, et al (2000) Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. Arch Dermatol 136:1475–1480
14. Masini E, Planchenault J, Pezziardi F, Gautier P (1985) Histamine-releasing properties of polysorbate 80 in vitro and in vivo: correlation with its hypotensive action in the dog. Agents Actions 16:470–477
15. Montaguti P, Melloni E, Cavalletti E (1994) Acute intravenous toxicity of dimethyl sulfoxide, polyethylene glycol 400, dimethylformamide, absolute ethanol and benzyl alcohol in inbred mouse strains. Arzneimittelforschung 44:566–570
16. O'Dwyer P, Weiss R (1984) Hypersensitivity reactions induced by etoposide. Cancer Treat Rep 68:959–961

17. Pönnighaus J, Fine P, Moreno C (1991) Hypersensitivity to dextran in BCG vaccine. Lancet 337:1039
18. Portal I, Cardenal F, Garcia-del-Muro X (1994) Etoposide-related acral erythema. Cancer Chemother Pharmacol 34:181
19. Prussick R, Horn T, Wilson W, Turner M (1996) A characteristic eruption associated with ifosfamide, carboplatin and etoposide chemotherapy after pretreatment with recombinant interleukin-1 alpha. J Am Acad Dermatol 35:705–709
20. Salmon J, Mythen M (1993) Pharmacology and physiology of colloids. Blood Rev 7:114–120
21. Schacter L, Igwemezie L, Seyedsadr M, et al (1994) Clinical and pharmacokinetic overview of parenteral etoposide phosphate. Cancer Chemother Pharmacol [Suppl] 34:S58–S63
22. Schorderet M (1998) Pharmacologie, des concepts fondamentaux aux applications thérapeutiques. Frison-Roche, Paris
23. Stähelin H, VonWarburg A (1991) The chemical and biological route from podophyllotoxin glucoside to etoposide: Ninth Cain Memorial Award Lecture. Cancer Res 51:5–15
24. Varma R, Kaushal R, Junnarkar A, et al (1985) Polysorbate 80: a pharmacological study. Arzneimittelforschung 35:804–808
25. Witterland A, Koks C, Beijnen J (1996) Etoposide phosphate, the water soluble prodrug of etoposide. Pharm World Sci 18:163–170
26. Yokel B, Friedman K, Farmer E, Hood A (1987) Cutaneous pathology following etoposide therapy. J Cutan Pathol 14:326–330