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Teniposide: overview of its therapeutic potential in adult cancers

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Abstract. Teniposide was introduced into clinical trials prior to etoposide, but its role was not defined because interest shifted early on to etoposide. However, long-term encouraging results obtained in acute leukemia treated with teniposide have rekindled interest in this compound. In addition to pharmacokinetic differences, teniposide has greater CNS penetrance and is more lipophilic. Its greater potency is related to enhanced intracellular uptake. Although its antitumor spectrum of activity appears to be very similar to that of etoposide, a search for some differences might prove instructive.

Key words: Teniposide – Solid tumors – Epipodophyllotoxin

Introduction

Extracts from *Podophyllum peltatum* roots attracted the attention of researchers from the National Cancer Institute and from industry in the 1950s because of their long history of medicinal uses and antimitotic effects [25]. Podophyllotoxin or related derivatives such as the peltatins, however, failed to proceed beyond phase I trials in cancer patients in the face of severe acute toxicities related in part to difficulties in formulation [17, 34]. Sandoz chemists focused on the more soluble glucosides which led to the semisynthetic "second generation" compounds SP-I and SP-G and to clinical trials in patients with cancer during the early 1960s [7, 52, 60]. An antileukemic factor characterized as demethylepipodophyllotoxin-benzylidene-glucoside was also identified within SP-G extracts [55]. Teniposide (VM-26) was one of the two derivatives of this factor developed for clinical use: phase I studies began in 1967, preceding the study of etoposide (VP-16-213) by about 3 years. The preclinical spectrum of activity of teniposide and etoposide was quite similar; the most obvious differences between the two agents were found in their solubility and formulation.

Phase I studies of teniposide in the United States and Europe created some enthusiasm because of its tolerability as compared with earlier derivatives and the indications of antitumor effects (Table 1). A weekly dose schedule was readily adopted for phase II studies; in our own study, the recommended dose of 67 mg/m^2 per week [36] was far too low as judged by current standards. Although this dose was often exceeded by subsequent investigators, it may have diminished the chance of identifying antitumor activity comparable with that of etoposide. In fact, in leukemias and lymphomas, where enthusiasm for teniposide was generated early, teniposide soon faced competition from its recently introduced analog. Not only did etoposide have fewer hypersensivity and local reactions, but it also became available for oral administration [43] and had more extensive exploration in various doses and schedules. This eventually led to other indications for etoposide in germ-cell tumors and small-cell lung cancer [22, 38]. In the face of similar preclinical findings and dose-limiting toxicities, the question to be posed is whether differences in antitumor selectivity in fact exist.

Mechanisms of action and pharmacology

From the outset, teniposide and etoposide puzzled investigators because they showed a lack of inhibition of microtubular assembly while exhibiting cytolytic properties for cells in the G2 and M phases. Loike and Horwitz [29] and Loike and co-workers [30] reported in 1976 the effects

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Table 1. Phase I studies of teniposide

Schedule	Number of patients	MTD/recommended dose	Dose-limiting toxicity	Reference
Daily ×10 Daily ×3	29	1 mg/kg daily = 35 mg/m² 2 mg/kg daily = 60 mg/m²	Leukopenia	Trempe et al. [59]
Weekly	24	67 mg/m²	Leukopenia	Muggia et al. [36]
Twice weekly	27	1–3 mg/kg daily or 35–105 mg/m² daily	Hematologic	Dombernowsky et al. [12]
Daily ×5, 3 weeks	185	30 mg/m²	Leukopenia	EORTC [13]
3 consecutive days	18	200 mg/m² daily	Hematologic	deVries et al. [11]
Continuous	28	250 mg/m² daily	Hematologic	Rodman et al. [40]

of etoposide and a teniposide on DNA. The same investigators described effects on the degradation of DNA [29], subsequently shown by Long [31] and Long and Minocha [32] to be due to interaction with topoisomerase II. The role of topoisomerase II in the cytotoxicity of and resistance to these drugs were further defined by Ross and co-workers [41, 42, 56] and by Kerrigan et al. [26]. Extensive structure-activity studies on topoisomerase II actions have been carried out [31]. The selectivity of these drugs for cancer cells has been related to a high level of the enzyme, to its excessive activation, or to both. Conversely, drug resistance occurs in the absence of elevated levels [1] or with mutations in the enzyme [15]. It is uncertain whether these actions are operative and whether they provide explanations for the observed schedule dependency [9]. Since topoisomerase II inhibition is not strikingly different between the two analogs, the greater in vitro cytotoxic potency of teniposide is likely related to its better cellular uptake relative to etoposide.

Pharmacokinetics and protein binding are other variables contributing to differences in the optimal dose schedules between teniposide and etoposide (Table 2). Studies similar to those conducted by Slevin et al. [51] on the relationship of the dose scheduling, pharmacokinetics, and therapeutic and toxic effects available for etoposide have not, however, been done for teniposide. Nevertheless, the use of pharmacokinetics to calculate the optimal dose of teniposide to be used in patients with acute leukemia has been addressed in studies by Rodman and co-workers at St. Jude Children's Hospital [40]. They initially studied the pharmacokinetics of teniposide in children receiving the drug as a 72-h infusion at a dose varying from 100 to 250 mg/m² per day. The interpatient variability in steady-state concentrations was substantial, even though mean concentrations increased with dose. When toxic versus nontoxic courses were compared, the concentrations were significantly higher ($P < 0.05$) when toxicity was encountered. An even more significant correlation ($P < 0.005$) emerged when the steady-state concentration of 12 responders (16.0 ± 17.5 mg/l) was compared with that of 5 nonresponders (5.3 ± 2.1 mg/l). These findings stimulated efforts to dose children with acute leukemia to a maximum tolerated systemic exposure (MTSE) based on the prediction that a dose of 1656 μ*M* h is the tolerable area under the concentration-time curve (AUC) for teniposide, associated with a satisfactory response. A trial by this group is underway to compare the results obtained when the fixed dose schedule of teniposide and cytarabine is used versus a Bayesian dose-adjusted regimen of teniposide in combination with cytarabine, with the adjustment being based on individual measurements and prediction of dosing to achieve the desired MSTE.

Table 2. Comparison of biologic/molecular actions of teniposide and etoposide in vitro and in vivo

Effect	Relative value/finding
Cytotoxicity	Teniposide 10× > etoposide
Topoisomerase II inhibition	Teniposide 1.4× > etoposide
DNA strand breaks	Teniposide 10× > etoposide
IC_{50} growth, cell lines	Etoposide 10–30× > teniposide
Lipid partition coefficient	Teniposide > etoposide
Albumin binding	Teniposide (99%) > etoposide
Plasma elimination	Etoposide > teniposide
Renal clearance	Etoposide 3× > teniposide

Adapted from data of Issell et al. [22], Long [31], and Clark [9]

Resistance to teniposide is presumably related to topoisomerase II mechanisms. However, enhanced efflux with decreased intracellular accumulation of drug has been documented in some resistant cell lines [1, 28]. Such cell lines exhibit cross-resistance to other natural products and have been shown to overexpress the multidrug-resistance P-glycoprotein [1]. In this instance, cross-resistance patterns include the vinca alkaloids, whereas topoisomerase II-mediated cross-resistance is carried in nuclear fractions and does not include the vincas.

Clinical development

Because of the likelihood of suboptimal dose-scheduling in many studies that have been conducted with teniposide to date, one must consider the clinical development to be somewhat preliminary in many areas, although it has spanned more than two decades. The initial phase II studies were conducted in diseases where responses had been seen during the phase I experience. Accordingly, phase II data first appeared in malignant lymphomas, bladder cancer and brain tumors. Trials in acute leukemias and in other pedi-

atric tumors, such as neuroblastoma, also ensued and led to the eventually recognized clinical role for teniposide.

The recent introduction of higher dosing schemes has been followed by a reassessment of teniposide's role in the treatment of adult solid tumors that are responsive to etoposide. In particular, small-cell lung cancer has been found to be a teniposide-responsive tumor. Further interest has been stimulated by the drug's activity against brain metastases in this disease. The pharmacokinetic properties of teniposide may also be responsible for interest in its locoregional administration for the treatment of ovarian cancer. We review below the most prominent applications of teniposide in adult malignancies.

Adult leukemias. Original reports by Mathe et al. [33] stressed the efficacy of both teniposide and etoposide in monocytic leukemias. Regimens for adult lymphocytic leukemia (ALL) have also included teniposide (30–50 mg/m^2 daily × 5 days) together with ifosfamide (1 g/m^2 daily × 5 days): 8 of 49 patients obtained complete responses (CRs) [44]. Teniposide and cytarabine have also been successfully used against adult ALL [46]. Effects against blast crisis of chronic myeloid leukemia (CML) have been reported, whereas no activity was present against chronic lymphocytic leukemia [53]. In adult acute nonlymphocytic leukemia (ANLL), it is surprising that there has been no experience with teniposide, although etoposide is quite active [23].

Hodgkin's disease and non-Hodgkin's lymphoma. Single-agent trials documented very early in its development the activity of teniposide against the lymphomas [12, 13, 33] However, the integration of both etoposide and teniposide has been inexplicably slow, in part because the focus of investigations has been more on dose-intensity issues, which have tended to discriminate poorly on the actual ingredients of combinations. Therefore, induction regimens that omit either of these drugs remain prevalent and their optimal integration is yet to occur.

Table 3 summarizes single-agent results obtained with teniposide, including data obtained during the course of phase I studies and ranging to cooperative group data with substantial accrual but nonetheless falling short for the analysis of response by type of lymphoma. As an example, there are scanty data on the response of refractory Hodgkin's disease (HD) to teniposide alone. The most remarkable feature of these data is the verification of sustained CRs in intermediate and aggressive non-Hodgkin's lymphoma (NHL) obtained with teniposide alone after failure of initial combination regimens (most patients had been extensively pretreated with cyclophosphamide and, often, also with doxorubicin). As a recurrent theme, there are inadequate comparative data with etoposide; this analog has also received relatively scanty single-agent study in spite of its similarly excellent activity.

Drug combinations for salvage have also been explored in an inconsistent manner. The Eastern Cooperative Oncology Group did follow the preceding single-agent study with a combination of weekly teniposide and every-6-weeks lomustine (CCNU) for patients failing one drug treatment (and repeated reinduction with variants of the same) [8]. The results achieved appeared to be no better than those obtained with teniposide alone: again, long-term CRs were recorded in patients with high-grade NHL who had failed prior regimens. Other studies have included combinations with methyl glyoxal-bisguanylhydrazone (M-GBG) and with a number of other drugs in complex regimens [61]. No conclusion can be reached as to the relative merit of these regimens.

Table 3. Activity of teniposide as a single agent in Hodgkin's disease and non-Hodgkin's lymphoma

Reference	Dose (mg/m^2)[a]	Number of patients (previously treated)	CR + PR (% response)
HD:			
EORTC [13]	30 days, 1–5	22 (NS)	6 (27)
Dombernowsky et al. [12]	1–3 mg/kg, biw	8 (8)	3 (38)
Chiuten et al. [8]	100, qw	9 (9)	2 (22)
Mathe et al. [33]	30, days 4–21	22 (NS)	7 (32)
Sonntag et al. [54]	40, tiw; then 50, biw	16 (13)	7 (44)
Tirelli et al. [57]	100, qw	3 (3)	1 (33)
Totals		80	26 (33)
NHL:			
EORTC [13]	30, days 1–5	44 (NS)	19 (43)
Chiuten et al. [8]	100, qw	27 (27)	6 (22)
Mathe et al. [33]	30, days 4–21	33 (NS)	9 (27)
Sonntag et al. [54]	40, tiw; then 50, biw	7 (6)	2 (29)
Tirelli et al. [57]	100, qw	15 (14)	3 (20)
Totals		126	39 (31)

NS, Not stated; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma

[a] unless specified otherwise

Incorporation into first-line regimens has eventually occurred, but the few comparative studies conducted thus far have not indicated obvious advantages for the inclusion of teniposide. The schedule employed in the Australia-New Zealand (ANZ) trial was weekly, and questions about the optimal dose and schedule arise for teniposide as they have for etoposide [34]. As etoposide becomes increasingly included in first-line treatment of both HD and high-grade and intermediate NHL, a similar reassessment of teniposide becomes attractive.

Small-cell lung cancer. The results obtained with teniposide therapy utilizing daily × 5 schedules in previously untreated patients with small-cell lung cancer (SCLC) are noteworthy as compared with those obtained with other agents, including etoposide (Table 4). These data and preclinical data obtained in SCLC cell lines [3, 39] prompted a comparative trial of teniposide versus etoposide in patients aged over 70 years. Most patients received 80 mg/m^2 teniposide daily × 5, versus 90 mg/m^2 etoposide daily × 5; the responses, time to progression, and survival showed no difference [4]. Recent studies have included teniposide in

Table 4. Activity of teniposide as a single agent in SCLC

Reference	Dose (mg/m²)	Number of patients		CR + PR, number of patients/response rate (%)		Median Duration of response (weeks)
		Previously treated	No prior treatment	Previously treated	Untreated	
Samson et al. [45]	20–50, i.v., days 1–5 q3–4w	11	–	0	–	–
Woods et al. [62]	60–100, i.v., days 1–5, 13 weeks	21	4	5 (30)	2 (50)	9
Pedersen and Hansen [39]	60, i.v., days 1–5 q3w	40	–	6 (15)[a]	–	6
Creech et al. [10]	100, i.v., day 1 qw	17	–	1 (6)	–	17
Holoye et al. [20]	60, i.v., days 1–5 q3w	0	24	–	12 (50)	Not given
Bork et al. [3]	60, i.v., days 1–5 q3w	0	33	–	30 (90)	32[b] (range, 7–68)[b]
Cerny et al. [6]	100, i.v., days 1–5 q3w	0	30	–	10 (33)	21
Giaccone et al. [14]	120–140, i.v., days 1, 3, 5 q3w	33	11	11 (33)	4 (36)	33
Totals		122	102	23 (19)	58 (57)	

CR, Complete response; PR, partial response

[a] The partial response rate in patients with prior etoposide treatment was 1/20 = 5% (95% confidence limits, 0–25%), and that for patients without prior etoposide treatment was 5/20 = 25% (95% confidence limits, 0–49%)

[b] Median age, 73 years (range, 52–79); performance status, ≤2

[c] Median age, 73 years (range 56–82); 23% of the patients had a performance status of 3

Table 5. Activity of teniposide as a single agent in NSCLC

Reference	Dosage/schedule	Number of patients		Response rate, % (CR + PR)	Median duration (weeks)	
		Evaluable	PC		Response	Survival
Samson et al. [45]	20–30 mg/m², i.v., daily ×5 q3–4w	44	21	2	36	
Bhuchar et al. [2]	40 mg/m², i.v., ×5 q4w	12	3			
Creech et al. [10]	67 mg/m², i.v., weekly	38	38	5		14
Giaccone et al. [14]	120–180 mg/m², i.v., days 1, 3, 5 q3w	42	8	17	33	40
Sörensen et al. [52]	80 mg/m², i.v. daily ×5 q3w	26	0	11	18	

PC, Prior chemotherapy

combinations, and a large randomized study has indicated some advantage for teniposide-containing arms.

Non-small-cell lung cancer. Single-agent studies including either single, large doses exceeding 360 mg/m² [14] or 80 mg/m² daily × 5 [54] have indicated major response rates of 17% and 11%, respectively (Table 5). Moreover, in both SCLC and non-small-cell lung cancer (NSCLC), patients with brain metastases have responded. The latter finding may encourage additional trials of teniposide in lung cancer.

Brain tumors. Following leads from our phase I study, Sklansky and co-workers [50] reported 4 subjective responses in 13 patients with brain tumors in trials conducted prior to the introduction of computed tomography (CT) scans. In spite of this activity in patients who had failed therapy with nitrosoureas and the activity noted in combination studies reporting response rates of 50%, the mean survival was only 7.2 months [19]. Other randomized studies have not shown a contribution of teniposide to the activity of other drugs, although the doses of teniposide did not exceed 100 mg/m² per cycle [34].

Table 6. Activity of teniposide as a single agent in previously treated and untreated ovarian cancer patients

Reference	Dosage/schedule	Interval (days)	Number of patients	Responders/ response rate (%)
Samson et al. [45]	20–30 mg/m², days 1–5	21–28	16	0
Jankowski and Vahrson [24]	150 mg/m² 200 mg/m² 250 mg/m²	10–14	19	1 CR (5) 7 PR (37)
Sessa et al. [48]	100–150 mg/m²	14–21	20	0
Muss et al. [37]	100–160 mg/m²	7	26	3 PR (12)
van der Burg et al. [5]	100 mg/m², days 1, 2	21	23	0
Totals			104	11 (11)

Table 7. Response according to metastatic site in 41 patients with bladder cancer treated with cisplatin and teniposide in EORTC trial 30802

Site	Number of patients	CR	PR
Lung	14	2	6
Lymph nodes	17	2	7
Liver	4	–	2
Pelvis	6	–	2
Totals (%)		4 (10)	17 (41)

[a] Adapted from Stoter et al. [56]

Ovarian and other gynecologic cancers. As a single agent, teniposide has shown an overall 11% response rate in five studies including mostly previously treated patients (Table 6). To date, teniposide has not been incorporated into combination chemotherapy for this disease. Recently, interest in locoregional intraperitoneal therapy with teniposide has paralleled that in etoposide [35]. Because of its stronger protein binding, the pharmacologic advantage for the free drug in the peritoneal cavity relative to the plasma is greater for teniposide than for etoposide. Studies by the Gynecologic Oncology Group in cervical cancer and in endometrial cancer have shown modest activity for teniposide of 14% and 9%, respectively [37].

Bladder cancer. The EORTC has demonstrated that teniposide has activity in superficial and advanced invasive bladder cancer [56]. The original study was followed by a study of teniposide (100 mg/m², days 1 and 2) given in combination with cisplatin (70 mg/m²) every 3 weeks. Substantial activity was noted, with two CRs occurring in the lung and two, in lymph nodes. Another 17 patients (41%) had PRs. Table 7 indicates the substantial level of response observed at all metastatic sites.

Miscellaneous cancers. Because of etoposide's activity in acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma [27], a recent study from Brazil investigated teniposide given at a dose of 360 mg/m² over 60 min every 3 weeks. In all, 10 of 25 patients (40%) showed PRs that lasted from 6 to 20 weeks (median, 9 weeks). Half of the cycles resulted in grade 3 or 4 leukopenia; two patients developed complicating *Pneumocystis carinii* infection, and one patient developed peritonitis from perforation of a sarcomatous lesion. All patients eventually died of progressive disease and/or opportunistic infections [47]. These findings do not encourage the use of such a myelosuppressive dose schedule in this disease, even though the activity may be comparable with etoposide's. Teniposide has not proved to be active in gastrointestinal cancer. A recent study, not yet published, from the Southwest Oncology Group does not indicate activity in untreated advanced gastric cancer (J. Berenberg, personal communication).

Conclusions and future prospects

Recent experience utilizing doses of teniposide substantially higher than those used in the 1970s indicates antitumor activity for this drug that parallels that of etoposide. The original arguments for the superiority of etoposide based on lesser local toxicities and a better preclinical spectrum no longer appear valid. On the other hand, strong arguments for the further development of teniposide over etoposide cannot be made at this time. Some aspects that could attract clinical investigation are the drug's central nervous system (CNS) penetrance and locoregional advantage [34]. In addition, if one could demonstrate that teniposide achieves greater intracellular concentrations in the face of modest overexpression of P-glycoprotein, additional attractive possibilities could be raised for teniposide vis-à-vis etoposide. Finally, additional exploration of dose schedules, of new locoregional routes of administration, and of action against novel disease targets such CNS lymphomas should be considered. Any future comparative trials of teniposide versus etoposide could benefit from studies of biochemical correlates of response such that we could begin to exploit any differences that emerge between these two analogs.

Among the areas for comparison are the following:

1. Schedule dependency: the convincing studies on daily oral etoposide and its schedule dependency may be equally applicable to teniposide – most disease areas are in need of studies exploring additional schedules. This need is particularly pressing in malignant lymphomas.
2. Drug combinations: the experience in neuroblastoma supports the use of cisplatin with teniposide, and in ALL, synergy with cytarabine has been deemed likely (see Rivera et al., this supplement). However, a range of drug combinations have not been explored. The pharmacokinetic differences between the two drugs and teniposide's greater lipid solubility may lead to advantageous interactions for this agent relative to etoposide.
3. CNS penetrance: particularly for SCLC, better CNS penetrance may promote better activity against brain metastases. Some interest could also be generated in evaluating the contribution of teniposide in the treatment of primary CNS neoplasms such as lymphomas and medulloblastomas.

Table 8. Teniposide: future directions

Established indications:
Comparison with etoposide
New regimens:
Combinations with platinum-based drugs
Topoisomerase II and topoisomerase I-interacting drugs
New disease targets:
CNS lymphomas
Bladder cancer
Kaposi's sarcoma
New routes:
Intraperitoneal
Oral
Continuous infusion and schedules
Laboratory study:
Comparative activity in MDR-expressing tumors
Pathways to apoptosis; DNA-cleavage patterns, drug combinations and sequences
Modulation: uptake, DNA repair

MDR, Multidrug resistance

4. Toxicity consideration: except for the higher incidence of acute (vehicle-related?) reactions, the pattern of toxicity of the two drugs appears to be identical. Moreover, both drugs have been implicated in the development of acute leukemias (see other articles, this supplement). However, it is possible that upon exploration of higher doses and protracted schedules, quantitative as well as qualitative differences may appear. Specifically, gastrointestinal versus marrow toxicity differences may emerge, as for other analog families.
5. Future studies: establishing differences in tumor selectivity between etoposide and teniposide will require comparative testing. Future study of teniposide would be facilitated by adherence to pharmacologic principles and by incorporation of laboratory correlative studies on aspects such as drug transport [21], nucleoside transport [16], and topoisomerase II-related DNA-cleavage patterns. Toxic effects on normal tissues according to schedule need to be studied more fully, as has been done for etoposide. This is particularly noteworthy in view of the likely inadequate dosing achieved with the commonly used weekly schedule. Table 8 provides examples of issues and the rationale for future hypothesis testing with regard to teniposide.

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