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Pharmacodynamics and long-term toxicity of etoposide

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Abstract. Etoposide has been used in the treatment of a wide variety of neoplasms, including small-cell lung cancer, Kaposi's sarcoma, testicular cancer, acute leukemia, and lymphoma. Its current therapeutic use is limited by myelosuppression, particularly neutropenia. Pharmacodynamic studies of etoposide show that this toxicity can be modeled using a modified Hill equation and that the dose intensity of etoposide can be successfully increased by adaptive control using this model. Significant influences on the degree of myelosuppression include the pretreatment leukocyte count, the performance status, the extent of prior erythrocyte transfusions, and the serum albumin level. In the past 7 years, interest has developed in a distinct subset of acute nonlymphocytic leukemia that is associated with prior exposure to etoposide. This syndrome has been described in several studies and is characterized by the lack of a preleukemic phase, M4 or M5 morphology, and distinct translocations involving the chromosome 11q23 region. In addition, secondary acute lymphocytic leukemias (involving 11q23) have also been associated with prior epipodophyllotoxin exposure.

Key words: Etoposide – Acute nonlymphocytic leukemia – Myelosuppression

Introduction

Etoposide is a semisynthetic epipodophyllotoxin derived from the mandrake root (May apple), which has found wide use as a front-line agent for a variety of neoplasms, including small-cell lung cancer, Kaposi's sarcoma, testicular cancer, acute leukemias, and lymphomas (both Hodgkin's and non-Hodgkin's) [1]. Etoposide is highly myelosuppressive and has recently been implicated in the pathogenesis of acute leukemias arising after treatment of a variety of solid and hematologic malignancies. The pharmacodynamics of etoposide's hematologic toxicity and the issue of etoposide-associated acute leukemias are reviewed herein.

Pharmacodynamics of etoposide-induced myelosuppression

Formally, pharmacodynamics "... relates drug concentration at a receptor site to biological response" [2]. Pharmacodynamic analyses commonly relate drug concentrations to the magnitude of a specific drug effect, such as neutropenia. In most instances, drug concentrations measured in the central compartment (e.g., blood or plasma) are used, although concentrations in the peripheral compartment of a multicompartmental pharmacokinetic model can also be used. Since many drugs have substantial interpatient variability in both pharmacokinetic and pharmacodynamic parameters, it is hoped that pharmacodynamic studies relating either toxic or therapeutic effects to drug concentrations will lead to improved delivery of chemotherapy by helping to optimize the risk-benefit balance of treatment and by advancing our ability to deliver more dose-intense chemotherapy [3].

Etoposide's major side effect is myelosuppression, including both neutropenia (generally the dose-limiting effect) and thrombocytopenia [1,4]. Although the extent of leukopenia is correlated with the dose, substantial variability at each dose level remains a clinical problem. At the University of Chicago, the University of Tennessee, and

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other centers [4–12], much interest has centered on developing predictive models for etoposide-induced myelotoxicity, and the best relationship is a nonlinear sigmoid function that is formally identical to the oxyhemoglobin dissociation curve first noted by A.V. Hill, also called the sigmoid maximal-effect (E_{max}) model. In the current context, it represents the effects of a reversible interaction between etoposide and a postulated receptor on hematopoietic cells when this interaction takes place in a single pharmacokinetic compartment [13]. The strength of this interaction is measured by a *pharmacodynamic constant*, K_{PD}, which is the plasma concentration of drug that produces a half-maximal response and is thus analogous to the Michaelis-Menten constant. This term can be interpreted as quantitating the influence of dynamic (as opposed to kinetic) factors such as performance status and the effect of prior treatment (expressed as the number of previous erythrocyte transfusions) [5–7]. The exponential Hill constant, H, determines the shape of the dose-response curve.

The important features of this model are: (1) the response is *saturable*, and (2) the concentration-response relationship behaves differently at low, middle, and high concentrations. At the highest range of concentrations (i.e., above 80% of the maximal attainable response), large changes in concentration result in little change in response. In the middle range (between 20% and 80% of the maximal attainable response) the relationship is log-linear, and in the lowest range (less than 20% of the maximal response) the response is linearly related to drug concentration [14]. These differences affect the clinical use of this drug, as is shown below.

The systemic bioavailability of drugs is frequently affected by their degree of protein binding. This phenomenon assumes particular importance in patients with abnormal organ function or other illnesses (such as cancer), in whom the unbound fraction of a particular drug often shows significant interpatient variability. In the case of etoposide, such binding appears to be mediated both by the displacement of etoposide from binding sites by bilirubin and by the degree of hypoalbuminemia [9–11]. The modified Hill model adjusts for differences in the amount of protein binding by using either etoposide concentrations that have been corrected for the serum albumin level or by using directly measured levels of free etoposide. Further emphasizing the importance of the serum albumin level is the appearance of an "albumin-white blood cell interaction term" in Eq. 1 [7].

Models correlating systemic exposure and other pharmacokinetic variables have been successfully incorporated into adaptive control strategies [15–17], and therapeutic drug monitoring is widely used to control the dosing of drugs such as aminoglycosides, digoxin, antiarrhythmic agents, and theophylline. In a series of studies, Ratain and colleagues [6, 7] have extended the concept of such strategies to individualize the dosing of etoposide. Therapy for their patients started with continuous-infusion etoposide at a predetermined dose rate, levels were measured at 24 h, and the infusion was adjusted in accordance with the above-mentioned Hill model to achieve a target leukocyte nadir of 1.7×10^9/l. This group was compared with a control arm in which the patients received a fixed dose rate of etoposide by continuous infusion. Outcome was measured as the total delivered dose, with a secondary outcome measuring the extent of grade 4 leukopenia. The patients in the experimental (dose-adjusted) arm achieved the target leukocyte nadir more consistently and with less variation than did those in the fixed-dose arm. Furthermore, no difference in nonhematologic toxicity was noted between the two groups, and the total delivered dose was increased by 22% in the experimental arm.

Thus, it appears that unbound etoposide exerts an effect on the hematopoietic tissues that is best described by a modified Hill model and that drug dosing can be adaptively controlled using measurements of plasma drug levels and routinely obtained clinical data as variables in the Hill equation. Some efforts have been made to exend the concept of adaptively controlling the etoposide concentration in the single-agent setting to the combination chemotherapy setting, although the published data remain incomplete [18, 19].

Epipodophyllotoxin-induced leukemia

Most known side effects of etoposide occur during the period immediately following administration of the agent. However, a disturbing development has been the late emergence of acute leukemia in some patients who have been successfully treated with either etoposide or teniposide for their primary malignancy. Since etoposide is a major component of treatment regimens for a number of chemotherapy-responsive diseases such as germ-cell tumors and childhood acute lymphocytic leukemia (ALL), this iatrogenic complication has stimulated substantial concern and controversy regarding the role of etoposide in the treatment of these diseases [20, 21].

Therapy-related leukemias have been well described following treatment with alkylating agents and radiotherapy [22]. In general, this type of leukemia is characterized by the initial development of myelodysplasia at 4–5 years after treatment, which progresses to overt acute nonlymphocytic leukemia (ANLL), which is usually refractory to therapy. Characteristic cytogenetic and morphologic abnormalities have been identified that can help differentiate classic therapy-related ANLL (t-ANLL) from de novo ANLL.

In 1987, Ratain et al. [23] reported on a group of four patients who developed ANLL following treatment for non-small-cell lung cancer with etoposide and cisplatin either alone or in combination with vindesine. Two patients had the morphologic appearance of acute monocytic leukemia and one patient had the appearance of classic t-ANLL. Clinically, these patients differed from those with classic t-ANLL in the brief duration of the latency period, the lack of a preleukemic phase, and the absence of characteristic cytogenetic abnormalities involving chromosomes 5 and 7. Although other patients with ANLL secondary to treatment with etoposide had been reported previously [24–26], this group differed in that these patients had received etoposide without the concomitant presence of other known leukemogenic agents (i.e., alkylating agents).

On the basis of their findings, the authors proposed the existence of a distinct subset of t-ANLL caused by epipodophyllotoxins and marked by characteristic cytogenetic abnormalities involving chromosomes 9 and 11.

Substantial indirect evidence links the development of a characteristic subset of t-ANLL to prior treatment with these agents. Patients at the University of Chicago [23], St. Jude Children's Hospital [27–29] the Rigshospitalet in Copenhagen [30], and the University of Texas Southwestern Medical Center [31] have developed ANLL following treatment with either etoposide or teniposide in the absence of other known leukemogenic agents. Most patients have characteristic translocations involving the 11q23 region and have acute myelomonocytic or monocytic morphology (Fab M4 or M5). The latency period varies from 10 to 81 months [32] and no preleukemic phase is evident.

Other confirmatory reports have since linked the development of a characteristic subset of t-ANLL to prior treatment with epipodophyllotoxins for germ-cell tumors [33, 34], non-Hodgkin's lymphoma [35], epithelial ovarian cancer [36], and Langerhans' cell histiocytosis of bone [37]. The spectrum of secondary hematologic malignancies following treatment with etoposide is much more complex than it appears, since several instances of variants of ALL have also been described in this setting [36, 38–41].

Although Pui et al. [29] reported remissions in 13 of 21 patients with aggressive induction therapy, the median duration of remission was 9 months, with 11 of 13 patients relapsing at between 2 and 51 months after the time of ANLL diagnosis. The Danish experience has been similar [30], with patients remaining in complete remission for only 1–3 months and surviving only 2–10 months from the time of ANLL diagnosis.

Treatment with etoposide quantitatively increases the likelihood of developing ANLL. However, the exact magnitude of this effect remains unclear, and current efforts are directed toward establishing the level of risk associated with etoposide treatment. Pedersen-Bjergaard et al. [30] derived a relative risk estimate of 336 for their group of patients with germ-cell tumors treated with cisplatin/etoposide/bleomycin (PEB) as compared with the general Danish population, along with a 4.7% cumulative risk of developing leukemia at 5.7 years after treatment. Follow-up studies of patients treated with etoposide-containing protocols for germ-cell tumors at Indiana University [33] and at Memorial Sloan-Kettering Cancer Center [34], however, suggest a substantially lower level of risk, with incidence rates of less than 1% and relative risk estimates of 66 being reported in these studies. These four studies were retrospective, and the doses of epipodophyllotoxin employed varied widely, with the cumulative doses of etoposide given in the Indiana University and Memorial Sloan-Kettering studies being approximately 2000 mg/m^2, whereas those given in the studies by Ratain et al. [23] and Pedersen-Bjergaard et al. [30] ranged up to 8400 mg/m^2.

The dose-response relationship of secondary acute leukemia to the amount of etoposide received is a question of major importance, given the interest in developing high-dose chemotherapy protocols including etoposide for diseases such as testicular cancer. In the patients with non-small-cell lung cancer treated with epipodophyllotoxin-containng regimens originally reported on by Ratain et al. [23], the median dose of etoposide in patients with subsequent second leukemia was 6795 mg/m^2 as compared with 3025 mg/m^2 in those who did not develop leukemia, although there was substantial overlap between the two groups. In 212 testicular cancer patients treated with PEB, all cases of secondary leukemia occurred in patients receiving cumulative doses of more than 2000 mg/m^2. Pui et al. [28] have offered a contrasting interpretation and have suggested that in children treated for ALL it is the frequency of treatment (either once or twice weekly) rather than the total received dose that affects the subsequent development of leukemia. A prospective study recently initiated by the National Cancer Institute (NCI) to assess the risk of etoposide-associated ANLL in 12 NCI-sponsored etoposide-containing solid tumor treatment protocols spanning a range of etoposide doses from 900 to more than 4000 mg/m^2 [42] should provide information on the dose-response and schedule dependency relationships. An interim report from this study suggests a 6-year cumulative rate of 3.2% for developing leukemia in the low-cumulative-dose group of protocols, consistent with what was reported above.

One of the most striking features of this syndrome is the frequent occurrence of translocations involving the long arm of chromosome 11 and the short arm of chromosome 9 in these patients. For unknown reasons, the R-band-rich regions of chromosomes 1, 11, and 17 appear to be particularly vulnerable to breakage when exposed to etoposide in vitro [43], and it may be that when such events also occur in vivo, pathophysiologic events are initiated that lead to the development of acute leukemia. The gene that contains these breakpoints has been named the *MLL* gene, and a disruption of this gene has been reported in patients with epipodophyllotoxin-associated ANLL [44]. In 1989, DeVore et al. [45] reported on a patient who developed ANLL following therapy for testicular cancer with the PEB regimen. This patient's karyotype also showed an 11q23 abnormality; after reviewing six previously reported patients with etoposide-related ANLL, these investigators concluded that rearrangements involving the long arm of chromosome 11 are both pathogenetically and diagnostically important in this syndrome. Further emphasizing the importance of this chromosomal abnormality to the development of this syndrome is the recent report that balanced translocations of 11q23 and 21q22 occurring in the context of myelodysplastic syndrome/ANLL developing after chemotherapy were found only in patients who had received prior treatment with topoisomerase-II-inhibiting agents (anthracyclines and epipodophyllotoxins) alone or in combination with alkylating agents [46]. Thus, a plausible biologic relationship linking the administration of etoposide, the appearance of this chromosomal abnormality, and the subsequent development of ANLL seems established.

Chemotherapy, particularly with etoposide, can produce significant degrees of damage to the chromosomal material. This damage is related to the cumulative doses received by the patient, and such damage is perpetuated in hematopoietic cells. Sister chromatid exchanges are cytogenetic aberrations thought to be produced by interference with

topoisomerases [47], which are frequently used as sensitive markers of chromosomal damage. When exposed to etoposide (either in vitro or in vivo), human peripheral lymphocytes show such damage in a dose-related fashion. Furthermore, these changes can persist for up to 9 years following the completion of chemotherapy [48–51], and the frequency of sister chromatid exchange was correlated directly to the leukocyte nadir and pretreatment leukocyte counts of the patient. In other diseases, most notably chronic myeloid leukemia and ANLL, balanced translocations act by altering the regulation of certain genes (*bcr-abl* and *bcl-2*, respectively) that play a key role in leukemogenesis. It may be that translocations involving the 11q23 region in etoposide-associated ANLL act in a similar fashion or, alternatively, the translocation may act to alter the expression of tumor-suppressor genes, as in the case of the *Rb* gene in retinoblastoma and osteosarcoma.

Although the weight of the clinical evidence and the cytogenetic data establishing a link between etoposide and abnormalities involving chromosome 11q23 point to an etiologic role for epipodophyllotoxins in the pathogenesis of secondary hematologic malignancy, these diseases may in fact reflect not a defect that is not specific to epipodophyllotoxins but rather one that is attributable to the effects of topoisomerase II inhibitors as a class of agents, whether given alone or in combination with other agents [52, 53]. It is also unclear whether this defect is reversible once incurred. Other instances of diseases with impaired DNA-repair mechanisms, such as xeroderma pigmentosa, in which higher rates of malignancy are due to defective chromosomal repair are well documented, and a recent report from the Pediatric Oncology Group surveying the long-term outcomes of children with T-cell ALL and lymphoblastic lymphomas treated with combination chemotherapy regimens including L-asparaginase showed a 7.8% incidence of second hematologic malignancies at 5 years. Subset analysis showed a substantial (4.6% versus 10.0%) difference in the point estimates between patients treated and not treated with L-asparaginase, although the confidence intervals were overlapping. Although preliminary, this finding is intriguing and suggests the possibility that interference with cellular damage repair may contribute to the development of these disease [54]. A possible role for pharmacogenetic factors is suggested by the finding that among the children in the Pediatric Oncology Group study [31] who were treated for ALL and then subsequently developed secondary etoposide-associated ANLL, 46.7% were Hispanic, whereas white and black children accounted for only 4.5% and 4%, respectively, although only 21.2% of the population of children at risk were Hispanic [55]. It is clear that treatment with etoposide, teniposide, and other topoisomerase II inhibitors will increasingly require long-term follow-up studies to establish the risk of late complications and that their current place in therapy deserves critical reexamination.

In summary, treatment with epipodophyllotoxins (and probably other topoisomerase II inhibitors) can predispose patients to the eventual development of a distinct leukemic entity characterized by a short latency period, the lack of a preleukemic phase, and characteristic cytogenetic abnormalities. To follow the rules of evidence outlined by Sackett et al. [56], the evidence supporting the existence of this syndrome includes a strong association in at least one study, a consistent relationship that has been demonstrated repeatedly, a plausible temporal and biologic relationship, and a dose-response gradient. This suggests that the entity called therapy-related ANLL may in fact be a heterogeneous disorder and that increasing success in treating certain types of cancer may mean that long-term survivors will need careful surveillance to detect and treat secondary leukemias. Future studies, particularly those targeting survivors of testicular cancer and Hodgkin's disease, may provide better estimates of the magnitude of risk and further insight into the natural history, treatment, and biology of this disease.

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