Cancer Chemother Pharmacol (1993) 31: 363–368

Cancer Chemotherapy and Pharmacology

Phase II trial and pharmacokinetic assessment of intravenous melphalan in patients with advanced prostate cancer*

David C. Smith[1], Duncan I. Jodrell[2], Merrill J. Egorin[2], Roy M. Ambinder[3], Eleanor G. Zuhowski[2], Willi Kreis[4], Peter G. Ellis[1], and Donald L. Trump[1, 5]

Division of Hematology/Oncology, Department of Medicine, Duke University Medical Center[1], the Division of Developmental Therapeutics, University of Maryland Cancer Center[2], Florida Hospital[3], Department of Medicine, North Shore University Hospital, Cornell University Medical College[4], and the Duke Comprehensive Cancer Center[5], Durham, NC 27710, USA

Received 16 July 1992/Accepted 4 November 1992

Summary. Alkylating agents have been reported to yield response rates of up to 20% in hormone-refractory prostate cancer. Melphalan was studied in four small trials in which the drug was given orally. In this phase II trial, melphalan (30 mg/m^2) was given intravenously every 28 days to 27 patients with hormone-refractory prostate cancer. Pharmacokinetic sampling was performed so as to describe the clearance of melphalan in this population and in an attempt to carry out pharmacodynamic modeling for toxicity and response. Prostate-specific antigen (PSA) was also assessed prospectively. No objective responses to this regimen were documented. The median survival for patients on this trial was 11.5 months. There was no correlation between drug clearance and measured creatinine clearance and no relationship between systemic exposure and toxicity. A decrease of >50% in serum PSA that was sustained for >6 weeks was documented in two patients, most notably in one patient who has survived for more than 29 months. Intravenous melphalan is not an active agent in hormone-refractory prostate cancer.

Introduction

Prostate cancer is the second most common malignancy affecting men in the United States, with the estimated annual incidence being 122,000 cases [7]. Almost one-third of patients will present with regionally metastatic or disseminated disease requiring systemic therapy [45]. Local palliative therapies and testicular androgen ablation are the primary treatments for disseminated prostate cancer. Approximately 80% of symptomatic patients benefit from hormonal therapy, with the median time to treatment failure after primary endocrine manipulation being 14–18 months [9, 14, 26]. Although a number of secondary hormonal manipulations have been investigated, responses to such maneuvers are infrequent (<20%), and no benefit for survival is evident [21, 49, 50].

Despite decades of study, the role of cytotoxic chemotherapy in the management of advanced prostate cancer is unclear. Little benefit, if any, has been shown in numerous studies [11, 18, 22, 24, 29, 32]. In randomized studies using response criteria that include "stabilization" as a treatment effect, the National Prostate Study Project found cyclophosphamide, 5-fluorouracil, estramustine phosphate, and dacarbazine to be active [35, 36]. In phase II trials, doxorubicin [44] and several combinations, including cyclophosphamide/doxorubicin/5-fluorouracil [13] and doxorubicin/5-fluorouracil/mitomycin C [27], have also been reported to be active. However, the difficulty in defining objective response criteria and the inability to demonstrate a convincing survival advantage or consistent palliative effect have led many investigators to conclude that cytotoxic chemotherapy has no role in the standard therapy of advanced prostate cancer [16, 42, 43, 52].

Alkylating agents may have activity in prostate cancer. Single-agent studies of cyclophosphamide [10], nitrogen mustard [10], estramustine phosphate [46], prednimustine [11], and diazoquinone [29] suggest response rates of 10%–20%. Despite the long history of alkylating agent use in prostate cancer, melphalan has not been adequately studied. Four groups of investigators have reported trials of melphalan given either alone or in combination [18, 22, 24, 32]. All of these trials used oral melphalan and studied small numbers of patients. The absorption of melphalan following oral administration is erratic and incomplete [3, 8, 51]. It has been estimated that intravenous melphalan yields up to a 4-fold higher systemic exposure as compared with the same dose given orally [3]. Intravenous adminis-

* Supported in part by grants 5T32-CA-09307, P30-A-14236-18, and U10-CA-44691 from the NIH, by the Burroughs-Wellcome Corporation, by the Don Monti Memorial Research Foundation, and by the P. B. Cohen Fund for Urologic Cancer Research. One of the authors (D. I. J.) is a recipient of a Cancer Research Campaign (United Kingdom) Travelling Fellowship

Correspondence to: D. C. Smith, Division of Medical Oncology, Pittsburgh Cancer Institute, 3459 5th Ave, Main North, Pittsburgh, PA 15213, USA

tration of melphalan may therefore demonstrate activity for this agent in situations in which none has been seen after oral dosing. In addition, the toxicity of melphalan is limited to myelosuppression, making it an attractive agent for dose-escalation studies in selected patients or in combination with hematopoietic growth factors if activity can be demonstrated. Finally, melphalan is being studied in combination with a number of modulatory agents such as buthionine sulfoximine and the nitroimidazoles [5, 25].

To estimate the single-agent activity of intravenous melphalan in advanced prostate cancer and to provide a basis for subsequent trials in this disease, we undertook a phase II trial of this agent in patients with hormone-refractory disease. The secondary goals of this study were to characterize further the pharmacokinetics of intravenous melphalan in patients with prostate cancer and to attempt to define relationships between drug exposure, as reflected in the area under the curve of plasma melphalan concentrations versus time (AUC), and the observed toxicity and response to this agent. Finally, we attempted to assess the correlation between the recognized parameters of response in this disease and the changes in serum prostate-specific antigen.

Patients and methods

Patients. From April 24, 1989, through October 4, 1990, 27 patients with advanced prostate cancer were enrolled and treated on this study at three institutions: Duke University Medical Center (17 patients), Florida Hospital (8 patients), and North Shore University Hospital (2 patients). Eligible patients had a histologic diagnosis of prostate cancer with evidence of progressive measurable or evaluable disease following initial testicular androgen ablation (orchiectomy, diethylstilbestrol, luteinizing hormone-releasing hormone agonists). Patients were allowed no more than one prior cytotoxic drug regimen, and any prior cytotoxic or radiation therapy must have been completed at least 28 days prior to the initiation of melphalan treatment (8 weeks for mitomycin C or nitrosoureas). Eligible patients had a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, an expected survival of at least 8 weeks, and adequate bone marrow (WBC, >3,999/μl; platelet count, >99,999/μl), renal (serum creatinine, <2.1 mg dl), and hepatic (bilirubin, <2.0 mg/dl) function. Written informed consent was obtained from all patients.

Treatment plan. Prior to treatment, all patients underwent a complete physical examination and a laboratory evaluation consisting of a complete blood count and determinations of serum electrolytes, liver transaminases, bilirubin, alkaline phosphatase, calcium, phosphorus, creatinine, acid phosphatase, and prostate-specific antigen. Creatinine clearance was measured and a chest X-ray, an abdominal/pelvic computerized tomographic (CT) scan, and a bone scan were obtained to document the extent of disease.

Melphalan (30 mg/m^2) was given intravenously in a 5% dextrose/water solution over exactly 30 min. Plasma samples for pharmacokinetic assay (see below) were obtained preinfusion, at 15 minutes into the infusion, at the end of the infusion, and at 5, 10, 15, 30, and 45 min and 1, 2, 3, 4, 6, and 8 h following the end of the 30-min infusion. The plasma was immediately separated and stored at –20° C until analyzed. Thawed samples were stored on ice and processed as quickly as possible to minimize ex vivo decay.

A complete blood count, serum electrolytes, transaminases, bilirubin, alkaline phosphatase, calcium, phosphorus, and creatinine were obtained weekly while the patient was on study. A physical examination, determinations of acid phosphatase and prostate-specific antigen, and a chest X-ray were repeated prior to each cycle of therapy, and a bone scan and an abdominal/pelvic CT scan were obtained every 3 months.

Chemotherapy was repeated every 28 days until evidence of progressive disease or intolerable toxicity developed. Radiation therapy given for pain control or for a severe or life-threatening condition was taken as evidence of progressive disease sufficient to result in removal of the patient from the trial.

Assessment of toxicity and dose modification. The dose of melphalan was modified for subsequent cycles of therapy if severe toxicity developed. If nadir counts showed a WBC of <1,500/μl or a platelet count of <50,000/μl, subsequent doses were reduced to 75% of the initial dose of melphalan. If day-of-therapy counts were not sufficient to meet the entry criteria (WBC, >3,999/μl; platelet count, >99,999/μl), therapy was delayed and weekly counts were obtained. If after a 2-week delay the counts remained suppressed, the following dose modification was employed: doses were reduced by 50% for patients with platelet counts of >74,999/μl and WBCs of 2,000–3,499/μl or if the platelet count was 50,000–74,999/μl and the WBC, >3,499/μl; patients whose counts did not meet these criteria were removed from the study. Doses were also reduced by 50% for any grade 3 (NCI common toxicity criteria) nonhematologic toxicity or renal toxicity as manifested by a doubling of the baseline serum creatinine value or a rise above 2.0 mg/dl. Any grade 4 toxicity other than myelosuppression resulted in the removal of the patient from the study. Patients who received any melphalan were evaluable for toxicity.

Assessment of response. Patients who were followed for 28 days after receiving melphalan were evaluable for response. A complete response was defined as the disappearance of all evidence of disease for a period of >28 days. A partial response was defined as continued evidence of tumor but a reduction of ≥50% in the sum of the perpendicular diameters of all measurable masses. In the case of evaluable nonosseous disease, a partial response was defined as a reduction of >75% in the amount of disease and required the agreement of two independent observers. Progression was defined as an increase of >25% in the sum of the perpendicular diameters of measurable lesions, an increase of 30% in evaluable nonosseous lesions, or the development of new lesions. Evaluable osseous disease on bone scans was scored only as a response (≥50% reduction in the area of bone involvement), stable disease, or progression (>25% increase in the area of bone involvement) based on a comparison of scans obtained at least 3 months apart. Stable disease was defined as lesions meeting none of the criteria for response or progression in each type of disease. Patients were also evaluated for performance status, with improvement being defined as a decrease of one level in their ECOG performance status (from 1 to 0, from 2 to 1). Deterioration was defined as a decline in performance status of two levels or a weight loss of >10% during the first 12 weeks of therapy or as a decline of one level or a weight loss of >5% after 12 weeks of therapy. Any evidence of progression or clinical deterioration was grounds for removal from the study. Prostate-specific antigen (PSA) was not used as a criteria for response but was assessed prospectively for its correlation with any measurable response.

Pharmacokinetics studies

Chromatographic analysis of melphalan in plasma. The high-performance liquid chromatographic (HPLC) analysis used to measure concentrations of melphalan in plasma was a modification of the method previously described by Chang et al. [12]. Briefly, 1 ml plasma was mixed with 10 μl of a 1.5-mg/ml solution of dansylproline (Sigma Chemical Co., St. Louis, Mo.) and then applied to a 1-ml SPEED solid-phase extraction device (Applied Separations, Bethlehem, Pa.) that had been preconditioned with 2 ml methanol and 2 ml distilled water. The columns were then washed twice with 1-ml aliquots of distilled water

before melphalan and internal standard were eluted with two 200-µl washes of absolute methanol. Of this methanol eluate, 200 µl was injected into a Hewlett-Packard (Palo Alto, Calif.) 1090L HPLC fitted with a Brownlee (Applied Biosystems, Inc., San Jose, Calif.) RP 18 guard column and a Brownlee Spheri-5 RP 18 HPLC column. The isocratic mobile phase, consisting of methanol:distilled water:1% acetic acid (75:24:1, by vol.), was pumped at 2 ml/min. Column eluate was monitored at 254 nm, and areas under absorbing peaks were integrated with a Hewlett-Packard 3393A integrator. Melphalan concentrations were calculated by comparing the ratio of the area under the melphalan peak to that under the internal standard peak in each respective sample with a concomitantly prepared and analyzed standard curve.

Population pharmacokinetic modeling

Standard two-stage analysis. A two-compartment, linear, open structural model involving drug elimination from the central compartment was fitted to the melphalan pharmacokinetic data. Four model parameters were defined: (1) V_C, the volume of the central compartment; (2) V_P, the volume of the peripheral compartment; (3) CL_d, a distributional clearance; and (4) CL_{tb}, the total body clearance. Curve fitting was initially performed using the maximal likelihood function of ADAPT II [15] running under UNIX on a Hewlett-Packard HP9000/835 minicomputer. In all analyses, the model was described using a state matrix. The maximal likelihood algorithm estimated both structural and residual variance models. The variance model assumed that the standard deviation of the observation was linearly related to plasma concentration. Therefore, the error variance could be described using two parameters, SDslope and SDintercept.

Iterative two-stage analysis. The results of the standard two-stage analysis were used as initial prior values in a maximal a posteriori (MAP)-Bayesian estimator for the iterative two-stage analysis [39]. Iterative two-stage analysis used MAP-Bayesian regression as implemented in ADAPT II [15] to refine individual estimates and the population model recursively until means and covariances were stable. The updating and reanalysis was an automated process using a computer program, PopIT [17], which allowed multiple iterations to be performed. The recursive process was continued until convergence at the third significant figure was reached, i.e., <1% variation in both the parameter means and the variance estimates. The residual variance model remained fixed at that which was derived from the standard two-stage analysis. Where two pharmacokinetic data sets were obtained from one patient, each was given a weight of 0.5 in the population analysis to avoid bias.

Results

The characteristics of the 27 patients enrolled on this protocol are summarized in Table 1. The age distribution was typical of patients with prostatic malignancy. Most patients had experienced progression of their disease despite multiple hormonal manipulations. In all, 21 had previously been treated with radiation and 3 had received prior chemotherapy. The 27 patients received a total of 85 cycles of melphalan, with the range being 1–6 cycles/patient (median, 3 cycles/patient).

Table 1. Patients' characteristics

Number of patients enrolled	27
Median age (range)	68 (48–81) years
Prior radiation	21
Prior hormonal therapy[a]	
Orchiectomy	21
Flutamide	14
Diethylstilbesterol	7
Leuprolide	7
Aminoglutethamide	5
Megesterol acetate	5
Ketoconazol	1
Prior chemotherapy[b]	3

[a] Most patients had undergone combination or multiple prior hormonal therapies

[b] One patient had been treated with 5-FU/cisplatin; one with cyclophosphamide/5-FU; and one, with chlorambucil/prednisone

As expected, the primary toxicity of this regimen was bone marrow suppression. Seven cycles of treatment were complicated by grade 4 leukopenia (WBC, <1,000/µl) and eight, by grade 4 thrombocytopenia (platelets, <25,000/µl). Three patients were admitted with febrile neutropenia and two additional patients received red cell transfusions (one on two occasions). There were no treatment related deaths. In all, 25 cycles (29%) were given at reduced doses due to toxicity on prior cycles. In all patients the therapy was discontinued due to progression of disease.

According to the criteria defined in the protocol, there were no objective responses to this therapy. With 27 patients enrolled, the 95% confidence interval for the response rate ranges from 0 to 12.8%. It is therefore highly likely that the true rate of response of hormone-refractory prostate cancer to intravenous melphalan is <15%. Several patients did have stable disease and tolerated multiple courses of therapy; seven patients received four or more cycles of treatment. In addition, several patients reported a reduction in bone pain along with an improvement in their activity levels; however, this was typically of brief duration and there was no significant change in performance status. The median survival of patients as determined from the date of enrollment on the study was 11.5 months; one patient is presently alive (>29 months).

PSA was assessed prospectively and, in most cases (67%), increased during therapy. In five patients, there was a decline of ≥50% in PSA with therapy. In two of these patients the decline was sustained for >6 weeks (8 and >52 weeks, respectively). Three of these patients were removed from the study due to evidence of disease progression despite the decline in PSA. In one striking case the PSA value fell from 508 to 76.9 ng/ml over two cycles of therapy. This decline of >50% in PSA lasted for

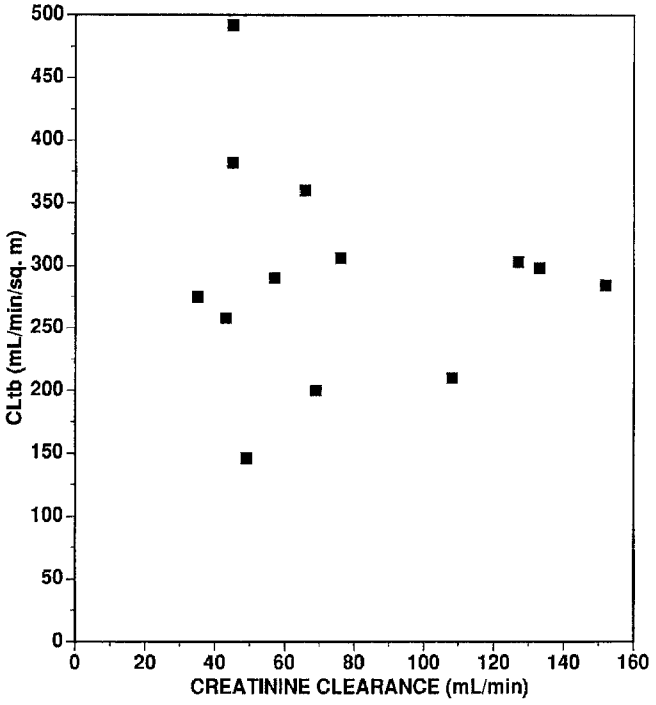

Fig. 1. Relationship between creatine clearance and total body clearance of melphalan

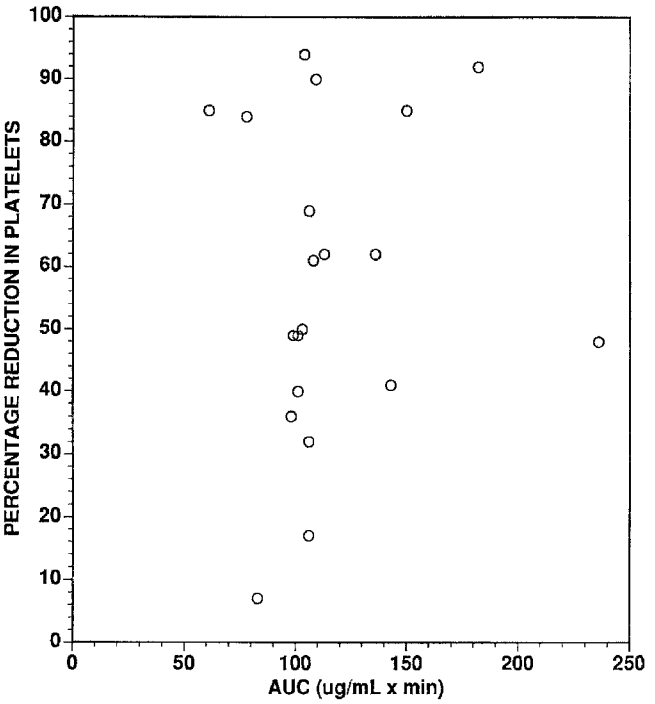

Fig. 3. Relationship between melphalan exposure and the percentage of reduction in platelet count

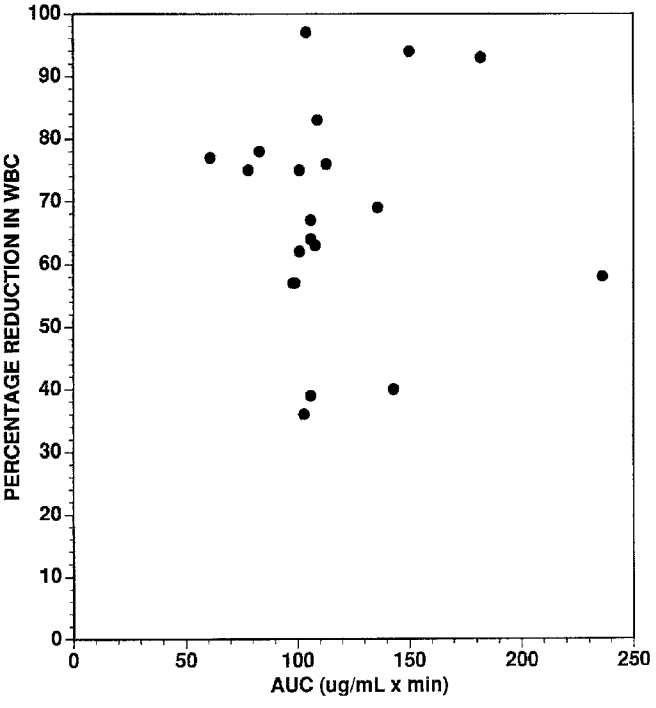

Fig. 2. Relationship between melphalan exposure and the percentage of reduction in WBC

>12 months and was observed in the patient who remains alive today at >29 months after his enrollment on the study.

Pharmacokinetic data were available from 21 courses of therapy in 17 patients. The median SDslope and SDintercept from the standard two-stage analysis were 0.135 and 2.05×10^{-6}, respectively. These values were used in the subsequent iterative two-stage population analysis. The final results of the iterative two-stage analysis gave the following population estimates and coefficients of variation (CV%): V_C, 10.5 l/m^2 (55%); V_p, 17.7 l/m^2 (62%); $V_{dss} = V_C + V_p$, 28.2 l/m^2; CL_d, 385 ml min^{-1} m^{-2} (61%); and CL_{tb}, 293 ml min^{-1} m^{-2} (50%).

Parameter estimates for individual patients were used to calculate α- and β-half-life values for the disappearance of melphalan from the plasma in the population studied (n = 17 patients). The mean ± SD α-half-life was 9.3±5.9 min (range, 2.7–19.6 min), and the mean ± SD β-half-life was 105±78 min (range, 40–368 min). Individual CL_{tb} values did not correlate with creatinine clearance values in the 12 patients for whom this measurement was available (Fig. 1). Neither could pharmacodynamic relationships be demonstrated between the development of leukopenia or thrombocytopenia and the melphalan AUC in the 20 patients for whom these data were available (Figs. 2, 3).

Discussion

This study demonstrates that melphalan is not an active agent in hormone-refractory prostate cancer. The number of patients studied provides substantial confidence that this is a reasonable estimate of the true response rate. The toxicity of melphalan at these doses was significant in these older men, whose disease typically involves the bone marrow.

The pharmacokinetic parameters calculated to describe the disappearance of melphalan from the plasma of patients enrolled in the current study agree well with those determined in a number of earlier studies of the pharmacokinet-

ics of intravenous melphalan [1, 2, 4, 8, 20, 28, 31, 34, 40, 51, 53], despite the single patient with an extreme value for the β-half-life (368 min). Although a number of studies have claimed a relationship between the clearance of melphalan and renal function [1, 31, 53], no such relationship was apparent in the current study population. Other studies of melphalan pharmacology have also failed to define a relationship between renal function and melphalan clearance [4, 30, 40, 41].

An even greater disappointment was the inability to define a relationship between the pharmacokinetics of melphalan and myelosuppression. On the initiation of the current trial, it was anticipated that a relationship between melphalan exposure, as reflected in the area under the curve of plasma melphalan concentrations versus time, and the percentage of reduction in leukocytes or platelets would be seen. This expectation was based on the finding that the in vitro survival of cells exposed to non-cell cycle-specific agents is best correlated with exposure [38] and on the observation that such relationships have been defined for a number of antineoplastic agents [33]. The utility of such a pharmacokinetic/pharmacodynamic relationship in optimizing doses for individual patients is obvious. The reasons for the inability to define such a relationship are unknown, although other investigators have alluded to the importance of plasma concentrations of amino acids, such as leucine and glutamine, that may compete with melphalan for transport into cells and thereby modulate cytotoxicity [6, 19, 31, 34, 47, 48]. Alternatively, the variability of this population in terms of marrow involvement, prior irradiation, and previous therapy may have contributed to the lack of a clear pharmacodynamic effect.

Our analysis of changes in serum PSA values also failed to reveal any indication of an antitumor effect. This correlates with the lack of objective evidence of response according to the standard criteria. The one patient who showed a striking and sustained decline in PSA remains alive and has survived longer than any of the other patients enrolled in this trial. Sustained declines in PSA of $\geq 50\%$ with therapy have been correlated with a statistically significant improvement in survival [23, 37]. Our single patient may be an example of this category of responsive patients.

References

1. Adair CG, Bridges JM, Desai ZR (1986) Renal function in the elimination of oral melphalan in patients with multiple myeloma. Cancer Chemother Pharmacol 17: 185
2. Alberts DS, Chang SY, Chen HSG, Moon TE, Evans TL, Furner RL, Himmelstein K, Gross JF (1979) Kinetics of intravenous melphalan. Clin Pharmacol Ther 26: 73
3. Alberts DS, Chang SY, Chen HSG, Evans TL, Moon TE (1979) Oral melphalan kinetics. Clin Pharmacol Ther 26: 737
4. Ardiet C, Tranchand B, Biron P, Rebattu P, Philip T (1986) Pharmacokinetics of high-dose intravenous melphalan in children and adults with forced diuresis. Report in 26 cases. Cancer Chemother Pharmacol 16: 300
5. Bailey H, Mulcahy RT, Tutsch KD, Arzoomanian RZ, Alberti D, Feierabend C, Tombes MB, Wilding G, Spriggs D (1992) Phase I trial of intravenous melphalan (L-PAM) and L-buthionine sulfoximine (BSO): an attempt at modulation of glutathione (GSH) chemoprotection. Proc Am Soc Clin Oncol 11: 114
6. Begleiter A, Froese EK, Goldenberg GJ (1980) A comparison of melphalan transport in human breast cancer cells and lymphocytes in vitro. Cancer Lett 10: 243
7. Boring CC, Squires TS, Tong T (1991) Cancer statistics, 1991. CA 41: 28
8. Bosanquet AG, Gilby ED (1982) Pharmacokinetics of oral and intravenous melphalan during routine treatment of multiple myeloma. Eur J Cancer Clin Oncol 18: 355
9. Byar DP (1973) Proceedings: the Veteran's Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer 32: 1126
10. Carter SK, Wasserman TH (1975) The chemotherapy of urologic cancer. Cancer 36: 729
11. Catane R, Kaufman JH, Madajewicz S, Mittleman A, Murphy GP (1978) Prednimustine therapy for advanced prostatic cancer. Br J Urol 50: 29
12. Chang SY, Alberts DS, Melnick LR, Walson PD, Salmon SE (1978) High-pressure liquid chromatographic analysis of melphalan in plasma. J Pharm Sci 67: 679
13. Chlebowski RT, Hestorff R, Sardoff L, Weiner J, Bateman JR (1978) Cyclophosphamide (NSC 26271) versus the combination of Adriamycin (NSC 123127), 5-fluorouracil (NSC 19893), and cyclophosphamide in the treatment of metastatic prostate cancer. Cancer 42: 2546
14. Crawford ED (1990) Hormonal therapy of prostatic carcinoma. Defining the challenge. Cancer 66 [Suppl]: 1035
15. D'Argenio DZ, Schumitsky A (1990) ADAPT II User's Guide. Biomedical Simulations Resource, University of Southern California, Los Angeles
16. Eisenberger MA, Simon R, O'Dwyer PJ, Wittes RE, Friedman MA (1985) A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. J Clin Oncol 3: 827
17. Forrest A, Hawtof J, Egorin MJ (1991) Evaluation of a new program for population PK/PD analysis applied to simulated phase I data. Clin Pharmacol Ther 49: 153
18. Franks CR (1979) Melphalan in metastatic cancer of the prostate: a pilot study. Cancer Treat Rep 63: 228
19. Goldenberg GJ, Lam H-YP, Begleiter A (1979) Active carrier-mediated transport of melphalan by two separate amino acid transport systems in LPC-1 plasmacytoma cells in vitro. J Biol Chem 254: 1057
20. Gouyette A, Hartmann O, Pico J-L (1986) Pharmacokinetics of high-dose melphalan in children and adults. Cancer Chemother Pharmacol 16: 184
21. Havlin KA, Trump DL (1988) Aminoglutethimide: theoretical considerations and clinical results in advanced prostate cancer. In: Osborne CK (ed) Endocrine therapies for breast and prostate cancer. Kluwer, Boston, p 83
22. Houghton AL, Robinson MRG, Smith PH (1977) Melphalan in advanced prostate cancer: a pilot study. Cancer Treat Rep 61: 923
23. Kelly WK, Scher H, Mazumdar M, Schwartz M, Vlamis V (1992) Prostate specific antigen (PSA) as a measure of disease outcome in metastatic hormone refractory prostate cancer (PC). Proc Am Soc Clin Oncol 11: 199
24. Kvols LK, Eagan RT, Myers RP (1977) Evaluation of melphalan, ICRF 159, and hydroxyurea in metastatic prostate cancer. Cancer Treat Rep 61: 311
25. Lacreta F, Brennan J, Padavic K, Hamilton T, Tew K, Young R, Comis R, Ozols R, O'Dwyer P (1991) Phase I clinical, biochemical and pharmacokinetic study of buthionine sulfoximine (BSO) in combination with melphalan (L-PAM). Proc Am Soc Clin Oncol 10: 104
26. Leuprolide Study Group (1984) Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 311: 1281
27. Logothetis CJ, Samuels ML, Eschenbach AC von, Trindade A, Ogden S, Grant C, Johnson DE (1983) Doxorubicin, mitomycin-C, and 5-fluorouracil (DFM) in the treatment of metastatic hormonal refractory adenocarcinoma of the prostate, with a note on the staging of metastatic prostate cancer. J Clin Oncol 1: 368
28. Loos U, Musch E, Engel M, Hartlapp JH, Hügl E, Dengler HJ (1988) The pharmacokinetics of melphalan during intermittent therapy of multiple myeloma. Eur J Clin Pharmacol 35: 187

29. Nichols WC, Kvols LK, Richardson RL, Benson RC (1982) A phase II study of azyridinylbenzoquinone (AZQ) in advanced genitourinary cancer. Proc Am Soc Clin Oncol 1: 117
30. Ninane J, Baurain R, Selys A de, Trouet A, Cornu G (1985) High dose melphalan in children with advanced malignant disease. Cancer Chemother Pharmacol 15: 263
31. Österborg A, Ehrsson H, Eksborg S, Wallin I, Mellstedt H (1989) Pharmacokinetics of oral melphalan in relation to renal function in multiple myeloma patients. Eur J Cancer Clin Oncol 25: 899
32. Paulson DF, Berry WR, Cox EB, Walker A, Laszlo J (1979) Treatment of metastatic endocrine unresponsive carcinoma of the prostate gland with multiagent chemotherapy: indicators of response to therapy. J Natl Cancer Inst 63: 615
33. Ratain MJ, Schilsky RL, Conley BA, Egorin MJ (1990) Pharmacodynamics in cancer therapy. J Clin Oncol 8: 1739
34. Sarosy G, Leyland-Jones B, Soochan P, Cheson BD (1988) The systemic administration of intravenous melphalan. J Clin Oncol 6: 1768
35. Schmidt JD, Scott WW, Gibbons R, Johnson DE, Prout GR, Loening S, Soloway M, DeKernion J, Pontes JE, Slack NH, Murphy GP (1980) Chemotherapy programs of the National Prostatic Cancer Project (NPCP). Cancer 45: 1937
36. Scott WW, Gibbons RP, Johnson DE, Prout GR, Schmidt JD, Saroff J, Murphy GP (1976) The continued evaluation of the effects of chemotherapy in patients with advanced carcinoma of the prostate. J Urol 116: 211
37. Seidman AD, Scher HI, Petrylak D, Dershaw DD, Curley T (1992) Estramustine and vinblastine: use of prostate specific antigen as a clinical trial end point for hormone refractory prostatic cancer. J Urol 147: 931
38. Skipper HE, Schabel FM, Mellet LB, Montgomery JA, Wilkoff LJ, Lloyd HH, Brockman RW (1970) Implications of biochemical, cytokinetic, pharmacologic, and toxicologic relationships in the design of optimal therapeutic schedules. Cancer Chemother Rep 54: 431
39. Steimer JL, Mallet A, Golmard JL, Boisvieux JF (1984) Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the non-linear mixed-effect model. Drug Metab Rev 15: 265
40. Taha IAK, Ahmad RA, Gray H, Roberts CI, Rogers HJ (1982) Plasma melphalan and prednisolone concentrations during oral therapy for multiple myeloma. Cancer Chemother Pharmacol 9: 57
41. Taha IAK, Ahmad RA, Rogers DW, Pritchard J, Rogers HJ (1983) Pharmacokinetics of melphalan in children following high-dose intravenous injection. Cancer Chemother Pharmacol 10: 212
42. Tannock I (1985) Is there evidence that chemotherapy is of benefit to patients with carcinoma of the prostate? J Clin Oncol 3: 1013
43. Torti FM, Carter SK (1980) The chemotherapy of prostatic adenocarcinoma. Ann Intern Med 92: 681
44. Torti FM, Aston D, Lum BL, Kohler M, Williams R, Spaulding JT, Shortliffe L, Freiha FS (1983) Weekly doxorubicin in endocrine refractory carcinoma of the prostate. J Clin Oncol 1: 477
45. U. S. Department of Health and Human Services (1988) 1987 Annual cancer statistics review. NIH Publication 88-2789. National Institutes of Health, Bethesda, Maryland, p II. 118
46. Veronesi A, Zattoni F, Frustaci S, Galligioni E, Tirelli U, Trovo G, Tumolo S, Merlo A, Artuso G, Cosciani-Cunico S, Grigoletto E (1982) Estramustine phosphate (Estracyt) treatment of T_3-T_4 prostatic carcinoma. Prostate 3: 159
47. Vistica DT (1979) Cytotoxicity as an indicator for transport mechanism. Evidence that melphalan is transported by two leucine-preferring carrier systems in the L1210 murine leukemia cell. Biochim Biophys Acta 550: 309
48. Vistica DT, Toal JN, Rabinovitz M (1978) Amino acid-conferred protection against melphalan. Biochem Pharmacol 27: 2865
49. Walsh PC, Siiteri PK (1975) Suppression of plasma androgens by spironolactone in castrated men with carcinoma of the prostate. J Urol 114: 254
50. Wein AJ, Murphy JJ (1973) Experience in the treatment of prostatic carcinoma with cyproterone acetate. J Urol 109: 68
51. Woodhouse KW, Hamilton P, Lennard A, Rawlins MD (1983) The pharmacokinetics of melphalan in patients with multiple myeloma: an intravenous/oral study using a conventional dose regimen. Eur J Clin Pharmacol 24: 283
52. Yagoda A, Watson RC, Natale RB, Barzell W, Sogani P, Grabstald H, Whitmore WF (1979) A critical analysis of response criteria in patients with prostatic cancer treated with *cis*-diamminedichloride platinum II. Cancer 44: 1553
53. Zucchetti M, D'Incalci M, Willems Y, Cavalli F, Sessa C (1988) Lack of effect of cisplatin on I. V. L-PAM plasma pharmacokinetics in ovarian cancer patients. Cancer Chemother Pharmacol 22: 87