

Analyzing the Same Data in Two Ways: A Demonstration Model to Illustrate the Reporting and Misreporting of Clinical Trials

By Joseph Baar and Ian Tannock

The methods used to analyze and interpret clinical trials of chemotherapy may have a major impact on the conclusions that are drawn in papers reporting them. To illustrate this problem, we constructed a hypothetical clinical trial in which patients with metastatic cancer were treated with chemotherapy. The following two articles provide reports of this trial, analyzed by methods that we would interpret as being of low and high quality, respectively. In the present report, we describe briefly the methodological differences that led to the opposite conclusions based

on this single set of data. The errors of reporting and omissions of the first article (A) are similar to those that have been extracted from recent issues of the *Journal of Clinical Oncology* and other leading cancer journals, although they have not all appeared within a single report. This demonstration model illustrates problems in the reporting of clinical trials and suggests guidelines for improved reporting.

J Clin Oncol 7:969-978. © 1989 by American Society of Clinical Oncology.

THERE are large variations in the reported rates of tumor response when patients with a given type of malignancy are treated in different clinical trials with the same drug or combination of drugs. Examples include response rates ranging from 8% to 85% for metastatic colorectal cancer treated with fluorouracil,¹ and from 13% to 81% for metastatic bladder cancer treated with cyclophosphamide, doxorubicin and cisplatin.² Much of this variation may be due to factors that have a real influence on the outcome of therapy: selection and performance status of patients, dose and dose intensity of the drugs, and quality of supportive care. In addition, major differences in reported outcome may arise because of the way in which the data are analyzed and reported. Although minimal guidelines for reporting of trials have now been adopted by the *Journal of Clinical Oncology* and other leading journals,^{3,4} lack of adherence to them may sometimes lead to unwarranted conclusions.

To document and illustrate these problems, we constructed a clinical trial in which 53 fictional patients were treated with combination chemotherapy. We then reported the results of this trial (1) by using methods similar to those that have appeared in selected reports within this and other leading cancer journals, but which we believe to be flawed (report A by Apples and Oranges); and (2) by using methodology that we believe to be appropriate (report B by Prose and Conns). The following report compares these two articles.

COMPARISON OF THE REPORTS

Entry Criteria and Selection of Patients

Report A provides no information as to how patients were selected for the trial, and does not allow any judgment as to the applicability of the results to other patients with the same disease. In contrast, report B states entry criteria precisely, and summarizes patient characteristics in a table. It has an explicit statement about the aims of the trial, which are to examine the role of chemotherapy in palliation; since this is a pragmatic end point, factors such as quality of life and cost benefit are important. Manuscript B sets a target sample size. The paper provides information about the number of eligible and ineligible patients seen within the study period, and allows readers to estimate the degree of selection used to obtain the study population. It describes registration of patients for the study and indicates that one patient withdrew after registration, prior to receiving therapy.

Report A does not discuss violations of the entry criteria. Report B indicates that there were three patients who did not fit the entry criteria

From the Department of Medicine, Princess Margaret Hospital and University of Toronto.

Submitted September 12, 1988; accepted January 3, 1989.

Address reprint requests to Ian Tannock, MD, Department of Medicine, Princess Margaret Hospital and University of Toronto, 500 Sherbourne St, Toronto, Ontario, Canada M4X 1K9.

© 1989 by American Society of Clinical Oncology.

0732-183X/89/0707-0001\$3.00/0

precisely: it includes them in the analysis but provides sufficient information to allow the reader to determine the effect of excluding them.

Description of Chemotherapy

Although both papers provide schedules for chemotherapy, only report B indicates the anti-emetics used, and the criteria that were used for modifying dosage of drugs. This report describes the delivery of chemotherapy in some detail, and estimates the dose intensity⁵ for each drug as a percentage of the intended dose.

Assessment of Tumor Response

Report A gives an incomplete description of response criteria, and includes minor response (MR) and stable disease (SD) as criteria of response, thus allowing for large errors of misclassification.⁶⁻⁸ There is no definition of response duration, or frequency of assessment, and in the absence of a contrary statement one assessment may be assumed sufficient to label a patient as responding. These omissions are addressed in report B, which has more stringent criteria: there are only two categories of response (complete [CR] and partial response [PR]), and to reduce errors of misclassification, criteria must be satisfied on two assessments at least 1 month apart. The start and end of response are defined precisely. All patients who do not satisfy criteria of CR or PR are classified as nonresponders (NR).

Report B requires initial separation of patients with and without measurable disease, and limits assessment of tumor response to the former. All patients with measurable disease are assessed for response, regardless of treatment received. Report A attempts to assess response on patients with nonmeasurable disease and excludes patients who do not complete two cycles of chemotherapy.

Application of the above criteria to estimate rate of response in each of the two reports is summarized in Table 1. The response rate quoted in report B is much lower because the stringent criteria do not allow exclusion of patients with measurable disease from the denominator. Responses of short duration based on one assessment are eliminated since these are of little clinical value or due entirely to measurement error.⁶⁻⁸ In consequence, the median duration of response is longer in report B. The analysis is also subject to peer review, which leads to downgrading of response in three patients. The report includes 95% confidence limits on the rate of response.

The description of six MRs of short duration in report A is similar to (or less than) the artifactual rate that would be predicted by applying estimates of measurement error^{6,7} in patients with slowly progressive disease, but fortunately Apples and Oranges do not regard these as major responses. The designation of SD, unless of long duration, is meaningless: any tumor with exponen-

Table 1. Derivation of Response Rates in Two Reports

Changes in Status Reported After Chemotherapy	Response Category	
	Report A	Report B
Patients with non-measurable disease (N = 9)		
Improved bone scan (1) or recalcification (1)	2 PR	
Reduction in ascites (1) or pleural effusion (1)	2 PR	Excluded
Progression (5)	5 NR	
Patients with measurable disease (N = 43)		
Complete disappearance for 13 + months (1) on one assessment (1) or for 3 months, except residual x-ray abnormality on peer review (1)	3 CR	1 CR 2 PR
Shrinkage > 50% in sum of products of lesions without progression for > 3 months (4), on only one assessment (4), or for 3 months with progression in bone detected on peer review (2)	10 PR	4 PR 6 NR
Shrinkage > 25% on one assessment (6)	6 MR	6 NR
< 25% increase in any lesion on one assessment (7)	7 SD	7 NR
Measured progression at first assessment	7 NR	7 NR
Early death (2), only one course (6), lost to follow-up (3)	Excluded	11 NR
Reported major response rate (%)	3 CR + 14 PR/42 (40)	1 CR + 6 PR/44 (16)

tial growth and a volume doubling time of 2 months (an average value for human solid tumors⁹) will require at least 1 month to increase its cross-sectional area by 25%.

Report B gives a verbal description of response in patients with nonmeasurable disease: the authors recognize that reduction in effusions may occur with diuretics, as well as after chemotherapy. Estimation of response in bone is also unreliable, especially as apparent recalcification can occur in lytic areas after compression. It seems appropriate therefore to register separately patients with disease confined to bone or effusions, and to exclude them from analysis of tumor response, although not from analysis of quality of life, toxicity, or survival.

Analysis of Survival

Report B provides a survival curve for all treated patients, but does not compare survival by response. The inclusion of such analysis is misleading in report A because responders are already selected as having to live long enough for response to be manifest (note the initial "shoulder" on the survival curve), and because the response category may simply indicate patients who have a better prognosis, even in the absence of chemotherapy.¹⁰

Both papers compare survival with that of a group of untreated historical controls. The comparison in report A of responding patients with untreated historical controls is fallacious, since it omits two sources of bias: (1) that patients with higher performance status may have been selected to receive chemotherapy in the study period, and (2) that responding patients may have had a better prognosis in the absence of chemotherapy.¹¹ These biases are minimized in report B by comparing survival of all patients seen in the study period, regardless of whether they were treated, with survival of the entire group of historical controls. Although this does not ensure comparability of the groups, it reduces bias due to selection of patients and tests the policy of giving chemotherapy for effects on survival.

Toxicity

Report B gives a comprehensive analysis of toxicity. It recognizes that unexpected events (eg, death from myocardial infarction) can be

related to chemotherapy, and uses objective criteria to evaluate other side effects. It documents the rate of hospital admission, and the incidence of toxic complications as a fraction of both the number of patients and of the total number of courses of chemotherapy that were given. Report A claims that "toxicity is moderate," but this qualitative description has quite different meanings for different oncologists, and for their patients.

Quality of Life and Economics

Only report B attempts to evaluate quality of life or costs of treatment. Financial costs were based on current costs to non-insured visiting patients at Princess Margaret Hospital. (Costs to Canadian patients are met by government grants and Provincial Health Insurance Plans.) The methodology used to describe both of these factors remains imperfect, and it is probable that future developments will lead the current methods to be judged inadequate. In incurable cancer, however, the aim is to produce palliation, and survival and its quality are direct measures of palliation whereas tumor response is not. Moreover, where therapy causes at most minor changes in outcome it is important to try to evaluate cost effectiveness. The inclusion of such measures should therefore become standard in all trials of chemotherapy where the aim is to provide palliation to patients.

DISCUSSION

Standards for the reporting of clinical trials in cancer chemotherapy have improved considerably during the last few years, and leading journals have tried to adopt standards that encourage authors to review their data carefully. However, some papers are still published, in which methods are used that are subject to considerable error and bias, and where the data do not support the conclusions that are stated in the abstract. Many more reports of this type are rejected during the review process. Since it is frequently only the abstract that is read by busy clinicians, unsound papers can lead to dissemination of misleading information, and to inappropriate treatment of patients.

Although guidelines for reporting of trials have been set by others,^{3,4} they have not been uniformly adopted. The alternative of providing

a demonstration model, spiced with a little humor, may provide another method to encourage improved reporting. We recognize that our model paper for high-quality reporting will be examined intensively for flawed methodology. In recognition of the value of constructive criticism we

encourage this process: may it lead to further improvements in the reporting of clinical trials.

ACKNOWLEDGMENT

We thank Drs P. Goodwin and M. Moore for their constructive comments during preparation of these manuscripts.

REFERENCES

1. Moertel CG: Large bowel, in Holland JF Frei E (eds): *Cancer Medicine*. Philadelphia, Lea and Febiger, 1973, pp 1597-1626
2. Tonkin K, Tannock I: Evaluation of response and morbidity following treatment of bladder cancer, in Raghavan D (ed): *The Management of Bladder Cancer*. London, Arnold, 1988, pp 228-244
3. Zelen M: Guidelines for publishing papers on cancer clinical trials: Responsibilities of editors and authors. *J Clin Oncol* 1:164-169, 1983
4. Simon R, Wittes RE: Methodologic guidelines for reports of clinical trials. *Cancer Treat Rep* 69:1-3, 1985
5. Hryniuk W, Bush H: The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 2:1281-1288, 1984
6. Moertel CG, Hanley JA: The effect of measuring error on the results of therapeutic trials in advanced cancer. *Cancer* 38:388-394, 1976
7. Warr D, McKinney S, Tannock I: Influence of measurement error on assessment of response to anticancer chemotherapy: Proposal for new criteria of tumor response. *J Clin Oncol* 2:1040-1046, 1984
8. Tonkin K, Tritchler D, Tannock I: Criteria for tumor response used in clinical trials of chemotherapy. *J Clin Oncol* 3:870-875, 1985
9. Steel GG: *Growth Kinetics of Tumours. Cell Population Kinetics in Relation to the Growth and Treatment of Cancer*. Oxford, Clarendon, 1977
10. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response. *J Clin Oncol* 1:710-719, 1983
11. Tannock I, Murphy K: Reflections on medical oncology: An appeal for better clinical trials and improved reporting of their results. *J Clin Oncol* 1:66-70, 1983

A. Effective Combination Chemotherapy for Metastatic Carcinoma of the Great Toe

By Colin Apples and Brigitte Oranges

Fifty-three patients with metastatic carcinoma of the great toe (MCGT) were treated with a drug regimen that included cyclophosphamide, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), bleomycin, vincristine (Oncovin; Eli Lilly and Company, Indianapolis), and oral methotrexate (CABOOM). Major responses were observed in 17 of 42 evaluable patients (three complete responses [CRs], 14 partial responses [PRs]; response rate, 40%), with six patients having

a minor response (MR) (14%) and seven with stable disease (SD) (17%). Toxicity was acceptable, although one patient died as a result of drug-related toxicity. Survival of responding patients was improved significantly as compared with nonresponding patients and with untreated historical controls. We conclude that CABOOM is an effective regimen for treatment of metastatic carcinoma of the great toe.

CARCINOMA of the great toe is an uncommon malignancy, and metastases are frequently present at diagnosis. The most common sites of metastatic involvement are lung, liver, and bone. Distant spread is usually associated with short survival, and the role of chemotherapy in this disease is controversial. Blacque and Whyte¹ have reported an increase in median survival (as compared with historical controls) for patients with metastatic disease who were treated with combination chemotherapy. In contrast, Uppe and Downe² have questioned the role of chemotherapy, stating that the marginal benefit in survival does not warrant the toxicity associated with therapy.

Reports of phase II trials using single agents to treat metastatic carcinoma of the great toe (MCGT) have suggested response rates of about 20% for cyclophosphamide,

Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH), or methotrexate.^{3,4} We now report the results of a trial of combination chemotherapy, which includes these agents, for treatment of MCGT.

MATERIALS AND METHODS

Patients were eligible for this trial if they had biopsy-proven MCGT, and had received no prior chemotherapy. They were assessed initially with a complete history and physical examination, complete blood cell count (CBC), serum chemistry, chest x-ray, bone scan, and computed tomographic (CT) scan of the abdomen and pelvis. Entry criteria included a normal CBC and serum creatinine.

Patients were treated with cyclophosphamide (1 g/m² intravenously [IV]), Adriamycin (40 mg/m² IV), and vincris-

tine (1 mg/m² IV) on day 1; oral methotrexate (15 mg/m²/d) on days 1 to 5, and bleomycin (10 U/m²) on days 15 and 22. This cycle was repeated every 4 weeks for a total of six cycles, or until progression of disease. Dose adjustments were used to compensate for toxicity. A 25% reduction in dose of cyclophosphamide, doxorubicin, and methotrexate was employed if severe myelosuppression had occurred on the previous cycle, and subsequent courses were delayed until blood counts had returned to the normal range. Bleomycin was withheld if mucositis was present.

Patients were considered evaluable for response if they completed two cycles of chemotherapy. Response criteria were as follows: Complete response (CR): disappearance of all evidence of tumor; partial response (PR): > 50% reduction in the sum of the cross sections of lesions; minor response (MR): > 25% (and < 50%) reduction in the sum of the cross-sections of lesions; stable disease (SD): < 25% increase in the sum of the cross-sections of the lesions; progressive disease (PD): new lesions or > 25% increase in the sum of cross-sections of the lesions. Patients with evaluable but nonmeasurable disease in bone or malignant effusions were scored as PR if there was evidence of recalcification or improvement in bone scan, or definite reduction in pleural or ascitic fluid.

RESULTS

Fifty-three patients were entered into this study. There were 32 men and 21 women, and their median age was 62 years. Metastases were observed in many sites but were most prevalent in lung, bone, inguinal nodes, and liver.

Two patients died in the early stages of therapy, one from a myocardial infarction, the other from neutropenic septicemia. Three patients were lost to follow-up and six patients did not complete two courses of therapy. Thus, 42 patients were evaluable for response. Of these patients there were three CRs and 14 PRs for a major response rate of 40%. In addition, six patients had a MR and seven had SD. One patient continues in unmaintained CR more than 1 year after starting treatment.

The median duration of response was 16 weeks. Survival curves for responding and nonresponding patients are shown in Fig 1, as well as a survival curve for an untreated group of historical controls. Median survival of responders (29 weeks) was significantly longer than that of nonresponders (18 weeks) or of untreated historical controls (23 weeks).

Toxicity associated with this regimen was moderate. The main toxic side effects included neutropenia, mucositis, and nausea and vomiting. Thirteen patients required hospital admission for treatment of neutropenic fever. Twelve were eventually discharged home, but there was one death from sepsis. Another patient died from unrelated causes (myocardial infarction) during the first course of treatment. The major reason for discontinuation of therapy was evidence of PD.

DISCUSSION

In the present phase II trial, a novel chemotherapeutic regimen was developed to test the effectiveness of a combination of drugs that individually had shown some responses in previous trials. The results of the trial demonstrate a high

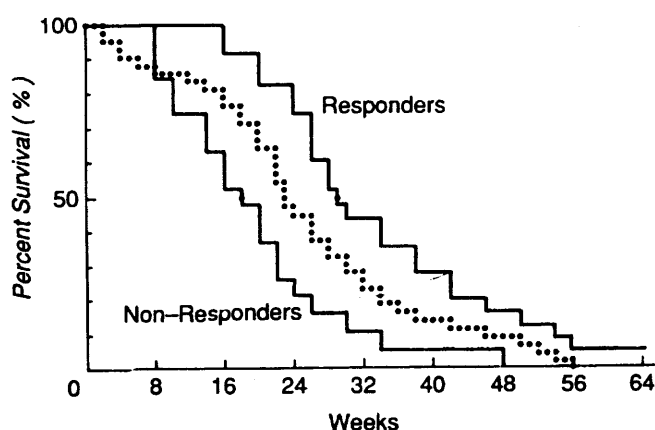


Fig 1. Actuarial survival curves for 23 responding patients (CR + PR + MR) and 19 nonresponding (NR + SD) patients. Shown for comparison is a survival curve for 84 untreated historical controls (dashed line). Survival of responding patients is significantly longer than that of nonresponding patients and historical controls ($P < .05$, both comparisons).

response rate (40% CR + PR, plus an additional 31% with MRs or SD) for the treatment of MCGT. This represents a marked improvement when compared with the results of previous trials. Moreover, the median survival of patients responding to chemotherapy was improved significantly as compared with historical controls. Toxicity was moderate, and most patients tolerated chemotherapy quite well.

In view of the above results we suggest that combination chemotherapy should now be considered for all patients with MCGT. Our results have demonstrated that chemotherapy can provide worthwhile palliation of this disease, and more intensive combinations should be tested in attempts to increase the probability of complete remission. One patient is well and has no evidence of disease at more than 1 year after starting chemotherapy. If the rate of CR can be increased, then a few patients might be expected to achieve long-term disease-free survival.

Our results also suggest that chemotherapy may have a role to play in the adjuvant treatment of carcinoma of the great toe. There is a high rate of systemic relapse following amputation of the great toe, and the incidence of occult micrometastases increases directly with the extent of the primary tumor. We suggest that adjuvant combination chemotherapy is appropriate in patients with primary tumors > 2 cm in extent or in those that extend beyond the great toe and require wider excision. The CABOOM regimen represents a reasonable choice for use as adjuvant chemotherapy, in view of its demonstrated efficacy, although other regimens which lead to a higher rate of CR in metastatic disease may ultimately prove superior.

In summary, the trial reported here has demonstrated significant benefit from use of the CABOOM regimen of chemotherapy for treatment of patients with MCGT.

*From the Solid Tumor Section
Department of Oncology
University of Transylvania Medical Center*

REFERENCES

1. Blacque CD, Whyte RT: A phase II trial of combination chemotherapy for metastatic carcinoma of the great toe. *Podiatr Oncol* 7:256-259, 1985
2. Uppe T, Downe AS: Is there a role of chemotherapy in carcinoma of the great toe? *N Scot J Med* 245:1027-1031, 1986
3. Dangerfield JL: Phase II trial of cyclophosphamide in carcinoma of the great toe. *Podiatrics* 6:18-19, 1979
4. Baggins B, Gollum G, Gandalf A, et al: Randomized phase II trial of methotrexate and doxorubicin for carcinoma of the great toe. A Northwestern Oncology Group trial. *Cancer Ther Rep* 16:275-278, 1981

B. Lack of Benefit of Combination Chemotherapy for Metastatic Carcinoma of the Great Toe

By Richard Prose and Bruce Conns

Fifty-three patients with metastatic carcinoma of the great toe (MCGT) were treated with a drug regimen that included cyclophosphamide, doxorubicin, bleomycin, vincristine, and oral methotrexate (CABOOM). Forty-four patients had at least one bidimensionally measurable metastatic lesion, and there were one complete (CR) and six partial responses (PRs) among these patients (response rate, 16%; 95% confidence limits, 7% to 30%). Median duration of response was 5 months (range, 3 to 13+ months). All 53 patients were assessed for toxicity, which was considerable. There were two treatment-related deaths, and a 38% incidence of hospitaliza-

tion for mucositis or other toxic complications. Assessment of quality of life by linear analog self-assessment scales showed deterioration in most of the patients who were evaluated. The median survival of all patients was 6 months, and the distribution of survival times for patients seen during the period when it was our policy to give chemotherapy is similar to that observed in a population of untreated historical controls. Economic costs of treatment were high. We conclude that the CABOOM regimen is of minimal benefit in the treatment of MCGT.

CARCINOMA of the great toe is an uncommon malignancy, and metastases are frequently present at diagnosis. The most common sites of metastatic involvement are lung, liver, and bone. Distant spread is usually associated with short survival, and the role of chemotherapy in this disease is controversial. Blacque and Whyte¹ have reported an increase in median survival (as compared with historical controls) for patients with metastatic disease who were treated with combination chemotherapy. In contrast, Uppe and Downe² have questioned the role of chemotherapy, stating that the marginal benefit in survival does not warrant the toxicity associated with therapy.

Reports of phase II trials using single agents to treat metastatic carcinoma of the great toe (MCGT) have suggested response rates of about 20% for cyclophosphamide, doxorubicin, or methotrexate.^{3,4} We now report the results of a trial of combination chemotherapy that included these agents for treatment of MCGT. Our aim was to determine whether this type of chemotherapy has a role in palliating patients with MCGT.

MATERIALS AND METHODS

Eligibility

A target sample size of 50 patients was set for this study. Patients were eligible for the trial if they had biopsy-proven MCGT, if they were < 75 years of age, and had received no prior chemotherapy. Patients were required to have a performance status of Eastern Cooperative Oncology Group (ECOG) 2 or better (ie, capable of self-care and out of bed more than 50% of waking hours), and they could have

received at most two treatments with radiation to metastatic lesions.

Patients who participated in the study were assessed initially with a complete history and physical examination, complete blood cell count (CBC), serum chemistry, chest x-ray, bone scan, and computed tomographic (CT) scan of the abdomen and pelvis. Patients were eligible for the study if they had a granulocyte count > 1,500/ μ L, platelet count > 150,000/ μ L, and serum creatinine < 150 μ m/L. Informed consent was obtained after the completion of these studies, and consenting patients were then registered on study. Treatment was to be initiated within 1 week of registration. At registration patients were assigned to one of two groups based on whether or not they had bidimensionally measurable metastatic disease.

A register was also kept of all patients with MCGT who were seen at the institution during the study period. This register included demographic data, sites of disease, and an estimate of performance status (using the ECOG scale), as well as details of previous treatment. This register allowed us to estimate the proportion of patients with MCGT who fitted the criteria of eligibility, and the proportion of eligible patients who were entered in the study.

Treatment

Patients were treated in the outpatient department with cyclophosphamide (1 g/m² intravenously [IV]), doxorubicin (40 mg/m² IV), and vincristine (1 mg/m² IV) on day 1, oral methotrexate (15 mg/m²/d) on days 1 to 5, and bleomycin (10 U/m²) on days 15 and 22. The cycle was to be repeated every 4 weeks for a total of six cycles, or until progression of disease. All patients were prescribed dexamethasone,

lorazepam, and prochlorperazine as antiemetic therapy prior to receiving chemotherapy on the first day of each cycle. Patients were asked specifically about compliance with their schedule of oral methotrexate, and were asked to return the container for this medication on their next clinic visit.

Patients had a weekly CBC, and were asked about the presence of mucositis, constipation, or neurological abnormalities prior to each treatment. Bleomycin was withheld on days 15 and/or 22 if mucositis was present, and doses of methotrexate and doxorubicin were reduced by 25% on the subsequent course. If the nadir of the granulocyte count was $< 500/\mu\text{L}$, and/or the nadir of the platelet count was $< 50,000/\mu\text{L}$, the dosage of cyclophosphamide, doxorubicin, and methotrexate in subsequent courses was reduced by 25%. If the granulocyte count was $< 1,500/\mu\text{L}$ and/or the platelet count was $< 150,000/\mu\text{L}$, on day 28, the next course was delayed by weekly intervals until these values were exceeded. Vincristine was omitted on subsequent courses if neurological symptoms or signs developed. Doses were not escalated in patients who did not experience toxicity. Patients who were responding to chemotherapy after six cycles (cumulative dose of doxorubicin, $240 \text{ mg}/\text{m}^2$) underwent baseline cardiac assessment with a gated nucleotide angiogram. Continuation of chemotherapy was at the discretion of the attending physician.

End Points of Study

All patients were evaluated for toxicity and survival. Survival was measured from the first day of treatment.

Patients were evaluated for tumor response if they had at least one bidimensionally measurable lesion defined by physical or radiological examination. Evaluation required a complete physical examination with serum chemistry and x-rays defining lesions at monthly intervals. Bone scans and CT scans that were abnormal initially were repeated at 2-month intervals.

Response criteria were as follows. Complete response (CR): disappearance of all evidence of tumor, including normalization of laboratory parameters. If lytic lesions in bone were present in addition to measurable disease these were required to show complete recalcification; partial response (PR): $> 50\%$ reduction in the sum of products of the largest diameter and its perpendicular for measurable lesions (up to 5 index lesions if multiple), with no evidence of progression in any site; progression: new lesions or $> 25\%$ increase in the sum of products of the largest diameter and its perpendicular (up to 5 index lesions if multiple), as compared to the lowest value recorded.

The criteria for CR and PR had to be satisfied on at least two consecutive evaluations at least 1 month apart. Duration of response was measured from initiation of chemotherapy to the last occasion on which the above criteria were satisfied. Patients whose disease did not satisfy criteria of response or progression were to continue on therapy. All patients with measurable disease who failed to achieve CR or PR were designated as nonresponders, including those who had early deaths, were lost to follow-up, or had minimal therapy because of toxicity or refusal to continue.

The protocol specified closure of the trial if no responses were observed among the first 15 patients entered with measurable disease, or if there were no more than two responses among the first 30 such patients.

Toxicity of chemotherapy was evaluated for all patients according to the ECOG classification.⁵ The oral mucosa was examined on each visit, and the duration and frequency of nausea and/or vomiting were assessed in a monthly interview with a study nurse. Patients were questioned about any interference with oral intake or bowel problems, and about any unexpected side effects of treatment.

Patients were asked to complete a simple quality-of-life instrument monthly, prior to the start of each course, including the first. The instrument included 6 linear analog self-assessment (LASA) scales relating to pain, physical well-being, nausea and vomiting, appetite, mood, and overall quality of life. Patients were asked to record by a mark on each line their average status during the preceding month. This questionnaire has been shown to be a reliable and valid indicator of quality of life in patients with metastatic cancer.⁶

Prior to publication, all charts, x-rays, and data sheets were made available to an independent external reviewer, Dr Per Roosal of the Danish Cancer Institute. He evaluated all of the patients with respect to criteria of eligibility, adherence to protocol, and documentation of outcome.

Economics of Treatment

We have estimated the costs of treatment using this regimen as the difference between the costs of health care with chemotherapy, as compared with the probable costs without such treatment. It was assumed that all patients would have been seen monthly in the absence of treatment. Thus incremental costs include those of the drugs (including antiemetics and antibiotics), pharmacy and staff costs for additional visits, additional imaging procedures to evaluate response and to make a decision as to whether or not to continue therapy, and costs of hospitalization for management of toxicity.

RESULTS

Characteristics of Patients

Fifty-three patients received chemotherapy in this study, and their characteristics are summarized in Table 1. Seventy-eight patients with MCGT were seen during the study period (1982 to 1987) and 64 of them were judged eligible for the study. Fifty-four patients gave informed consent and were registered, but one withdrew his consent prior to receiving

Table 1. Patient Characteristics (N = 53)

Male/female	32/21
Median age (range)	62 (37-74)
Performance status (ECOG)	
0	12
1	18
2	23
Sites of metastases	
Soft tissue only (nodes, skin, pleura, etc)	9
Bone $\pm$ soft tissue	22
Visceral involvement	22
Prior treatment	
Amputation of great toe	42
Radiation to primary	29
Radiation to metastases	23

any chemotherapy; this patient is excluded from analysis. Thus, 83% of eligible patients, and 68% of all patients with this disease, were entered in the study and received chemotherapy. Subsequent review revealed three protocol violations: two patients had received three courses of radiation therapy, and one had metastatic carcinoma of the little toe. These patients are included in the analysis; all had measurable disease and one had a partial response.

Delivery of Chemotherapy

The median number of courses received by our patients was three (range, one to nine). Two patients died at ten days and 3 weeks after starting therapy, and six additional patients received only one course, four because of progression and two because of toxicity. Three patients were lost to follow-up after completing two (two patients) or three courses. Only one patient completed more than six courses. Thirty-nine patients (74%) required omission or dose reduction of at least one drug, and 58% of 179 courses were prescribed at full dosage. Sixteen patients (30%) admitted incomplete compliance with their prescribed dose of methotrexate. Delay in starting second and subsequent courses was necessary in 12 of 45 patients (27%) who received more than one course. The mean dose intensities calculated for each patient as a percentage of intended dose over the duration of treatment⁷ were cyclophosphamide (88%), doxorubicin (86%), vincristine (62%), methotrexate (68%), and bleomycin (74%).

Tumor Response and Survival

Forty-four patients had at least one bidimensionally measurable lesion and could be assessed for response. There were one CR and six PRs for a response rate of 16% (95% confidence limits, 7% to 30%). Time to achieve response status was one month in five patients and 2 months in two patients. The median duration of response was 5 months (range, 3 to 13+ months). The complete responder continues in unmaintained remission having completed nine cycles of chemotherapy, but all other patients have relapsed.

Of the nine patients who did not have bidimensional measurable disease, one with bone metastases had improvement of pain and decreased requirement for analgesics with an improvement in bone scan at 2 and 4 months. Two patients had transient reduction in pleural effusion or ascites, but both were also treated with diuretics. The remaining patients had evidence of progression within 3 months of starting therapy.

At a median follow-up of 38 months (range, 10 to 65 months), only two patients remain alive. A survival curve for all 53 patients is shown in Fig 1A. Median survival was 6 months.

We have compared the survival curve for all 78 patients with MCGT seen within the study period (including the 53 patients who received chemotherapy) to that for 84 patients with MCGT referred to this institution in the time interval 1975 to 1981 when it was not our policy to administer chemotherapy (Fig 1B). For this comparison survival was measured from the date of referral. The two groups of patients were well matched for distribution of age and sites of disease, although unrecognized differences between the two populations may exist. There was no difference between the survival curves for these two time periods ($P = .77$, log-rank test).

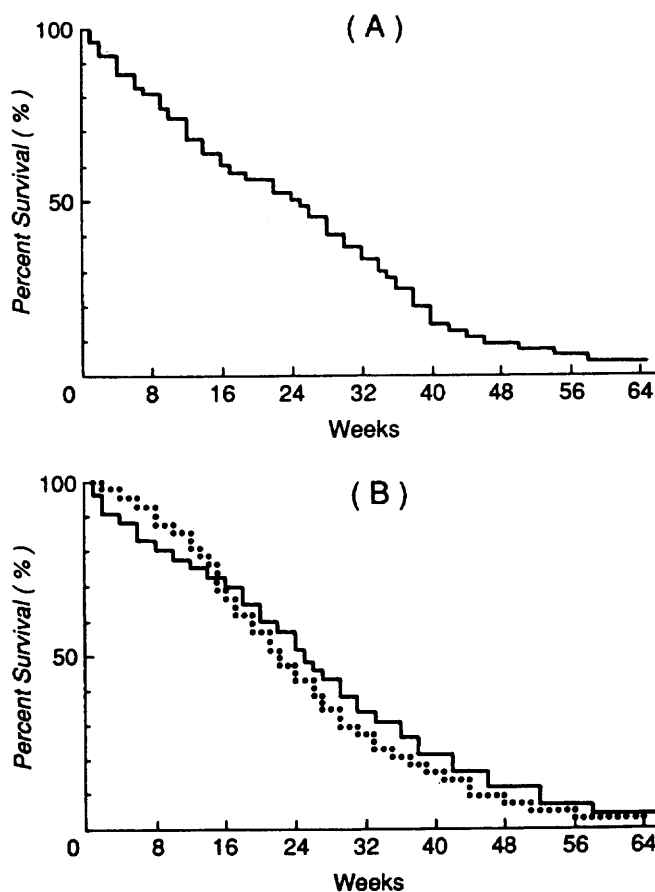


Fig 1. (A) Survival curve for the group of 53 patients receiving chemotherapy in the present study. (B) Survival curves for 78 patients with MCGT referred to this institution during the period when it was our policy to give chemotherapy (solid line) and for 84 patients referred in a previous time interval when chemotherapy was not used (dashed line). The curves are not significantly different ($P = .77$, log-rank test).

Toxicity

Toxicity experienced by the 53 patients is summarized in Table 2. There was one drug-related death from neutropenic sepsis during the first cycle of chemotherapy. A second

Table 2. Toxicity Associated With Chemotherapy in 53 Patients

Toxic Complication	Incidence (%)
Death related to treatment	2 (4)
Neutropenia < 500/ μ L	38 (72)
With sepsis	13 (25)
Thrombocytopenia < 50,000/ μ L	6 (11)
Mucositis	
ECOG grade 2	12 (23)
ECOG grade 3	6 (11)
Neuropathy	
Constipation/loss of reflexes	15 (28)
Weakness (foot drop)	1 (2)
Skin (rash)	3 (6)
Nausea	
Incidence	42 (79)
Median duration	6 h
Vomiting	
Incidence	24 (45)
Median no. of episodes	4

patient died of acute myocardial infarction 3 weeks after starting treatment; this patient had a history of hypertension, but his myocardial infarction occurred six hours after the second dose of bleomycin, and following a period of dehydration after nausea and vomiting associated with initial chemotherapy. Also, chemotherapy has been reported to increase the incidence of thromboembolism,⁸ so it is probable that chemotherapy contributed to this death. Two additional patients experienced deep vein thrombosis that resolved on anticoagulant therapy.

The dose-limiting toxicity was myelosuppression, with ECOG grade 3 or 4 toxicity (neutrophils $< 1,000/\mu\text{L}$, and/or platelets $< 50,000/\mu\text{L}$) occurring in 72% of patients or 58% of courses. Thirteen patients (25%) required hospital admission for neutropenic sepsis. Eighteen patients (34%) experienced grade 2 or 3 mucositis (ie, ulceration), and six required admission to hospital for intravenous therapy. Several patients had constipation and/or loss of deep tendon reflexes, and one patient developed a foot drop. Three patients had skin rashes, probably related to bleomycin. Most patients experienced nausea and/or vomiting after the chemotherapy given at the start of each course. Overall, 20 patients (38%) required 22 admissions to hospital for management of toxic complications.

Treatment was terminated because of disease progression in 36 patients, because of early death in two patients, and because of nonlethal toxicity (including patient refusal or failure to return to clinic) in 15.

Assessment of Quality of Life

The numbers of patients who completed the quality-of-life instrument at 0, 1, 2, and 3 months were 48, 43, 38, and 34, respectively. This attrition was mainly due to loss of patients because of death, or failure to return to clinic after stopping chemotherapy. Median scores for the 34 patients who were assessed serially decreased for all LASA dimensions, indicating a progressive decrease in quality of life (Table 3). This evaluation is subject to bias since it is for a group of patients who continued on therapy, but since most of the remaining patients who survived for 3 months had discontinued treatment because of disease progression or toxicity, it seems unlikely that the excluded patients had improvement in their

Table 4. Estimate of the Additional Costs of Chemotherapy as Compared With Following Patients at Monthly Intervals and Providing Symptomatic Care

Item	Estimated Cost Per Patient Entered on Study (US \$)
Anti-cancer drugs*	\$1,160
Costs of drug administration:	
Physician fees	\$460
Pharmacy costs	\$240
Additional laboratory tests	\$60
Additional imaging procedures†	\$1,670
Hospitalization for toxic complications‡	\$2,960
Total cost	\$6,550

*Based on a median of three courses at the dose intensity stated in the text, and a mean body surface area of 1.5 m^2 .

†Based on a mean of two CT scans (\$660 per procedure), two bone scans, and four plain radiographs to assess and reassess disease. Although these might be regarded as "costs of research," they would appear necessary to make decisions about continuation of treatment if patients were given chemotherapy outside the setting of a clinical trial.

‡Based on a daily rate of \$1,160 including procedures and treatment, plus fees for physician visits. The total cost for 22 admissions for a median duration of six days is averaged over the 53 patients starting therapy.

quality of life. A subset of patients that included the seven responders and two patients with nonmeasurable disease showed improvement in most scales for at least 3 months (Table 3).

Economics of Treatment

The incremental costs of treatment are summarized in Table 4. The estimated cost per patient (approximately \$6,500) is subject to considerable uncertainty and must be balanced against any gains to the patients (for example, possible reduction in the rate of hospital admission for complications of disease) that might be associated with use of chemotherapy.

Table 3. Median Values of LASA Scales* for 34 Patients Who Were Assessed Prior to Initiating Chemotherapy and at 3 Months

Dimension	Median Values (range)		No. of Patients With		
	Initially	3 Months	Improvement†	No Change	Deterioration†
Pain	6.5 (2.0-10.0)	5.5 (1.0-10.0)	8	4	22
Physical well-being	7.0 (3.0-9.5)	5.5 (1.0-10.0)	6	8	20
Nausea and vomiting	8.0 (5.5-10.0)	4.0 (1.5-9.0)	6	3	25
Appetite	6.5 (3.0-9.0)	4.0 (2.0-9.0)	8	7	19
Mood	7.5 (4.5-10.0)	5.5 (3.0-10.0)	10	6	18
Overall quality of life	8.0 (4.5-10.0)	6.0 (2.5-10.0)	9	3	22

*A score of zero indicates the worst possible scenario, and a score of 10 indicates a normal state.

†Indicated by a change of > 0.5 cm compared with baseline. Six patients had improvement in all scores, and three others had improvement or no change in all scores.

DISCUSSION

The response of MCGT to a variety of single anticancer drugs has not been encouraging. Phase II trials evaluating cyclophosphamide, doxorubicin, or methotrexate have reported response rates in the range of 15% to 25%.^{3,4} Responses were generally short-lived (median, 3 months) and patients with higher performance status may have been selected for inclusion in these trials. One previous trial of combination chemotherapy¹ reported an increase in median survival as compared with historical controls, but it is unclear as to whether this is due to chemotherapy, or to other factors such as earlier diagnosis of metastases, improved supportive care, or selection of patients.

The current trial using the CABOOM regimen led to a response rate of only 16%, with major toxicity. To minimize

bias due to selection of patients, we compared the survival of all patients seen when it was our policy to give chemotherapy with that of historical controls, but found no suggestion of improved survival. A few patients showed improvement in symptoms, but indices of quality of life deteriorated in most patients. The data do not allow a conclusion as to whether symptom control might have been better than in the absence of chemotherapy, but any effects to improve symptoms would appear to be small and transient. The treatment is expensive. In conclusion, combination chemotherapy with the CABOOM regimen cannot be recommended for the treatment of patients with MCGT.

From the Division of Clinical Trials

Department of Oncology

University of Transylvania Medical Center

REFERENCES

1. Blacque CD, Whyte RT: A phase II trial of combination chemotherapy for metastatic carcinoma of the great toe. *Podiatr Oncol* 7:256-259, 1985
2. Uppe T, Downe AS: Is there a role for chemotherapy in carcinoma of the great toe? *N Scot J Med* 245:1027-1031, 1986
3. Dangerfield JL: Phase II trial of cyclophosphamide in carcinoma of the great toe. *Podiatrics* 6:18-19, 1979
4. Baggins B, Gollum G, Gandalf A, et al: Randomized phase II trial of methotrexate and doxorubicin for carcinoma of the great toe. A Northwestern Oncology Group trial. *Cancer Ther Rep* 16:275-278, 1981
5. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol (CCT)* 5:649-655, 1982
6. Coates A, Fisher Dillenbeck C, McNeil DR, et al: On the receiving end—II Linear analogue self-assessment (LASA) in evaluation of aspects of the quality of life of cancer patients receiving therapy. *Eur J Cancer Clin Oncol* 19:1633-1637, 1983
7. Hryniuk W, Bush H: The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 2:1281-1288, 1984
8. Levine MN, Gent M, Hirsh J, et al: The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *N Engl J Med* 318:404-407, 1988