Chemotherapy With Mitoxantrone Plus Prednisone or Prednisone Alone for Symptomatic Hormone-Resistant Prostate Cancer: A Canadian Randomized Trial With Palliative End Points

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Purpose: **To investigate the benefit of chemotherapy in patients with symptomatic hormone-resistant prostate cancer using relevant end points of palliation in a randomized controlled trial.**

Patients and Methods: **We randomized 161 hormone-refractory patients with pain to receive mitoxantrone plus prednisone or prednisone alone (10 mg daily). Nonresponding patients on prednisone could receive mitoxantrone subsequently. The primary end point was a palliative response defined as a 2-point decrease in pain as assessed by a 6-point pain scale completed by patients (or complete loss of pain if initially 1+) without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart. Secondary end points were a decrease of ≥ 50% in use of analgesic medication without an increase in pain, duration of response, and survival. Health-related quality of life was evaluated with a series of linear analog self-assessment scales (LASA and the Prostate Cancer–Specific Quality-of-Life Instrument [PROSQOLI]), the core questionnaire of the European Organization for Research and Treatment of Cancer (EORTC), and a disease-specific module.**

Results: **Palliative response was observed in 23 of 80 patients (29%; 95% confidence interval, 19% to 40%) who received mitoxantrone plus prednisone, and in 10 of 81 patients (12%; 95% confidence interval, 6% to 22%) who received prednisone alone ($P = .01$). An additional seven patients in each group reduced analgesic medication ≥ 50% without an increase in pain. The duration of palliation was longer in patients who received chemotherapy (median, 43 and 18 weeks; $P < .0001$, log-rank). Eleven of 50 patients randomized to prednisone treatment responded after addition of mitoxantrone. There was no difference in overall survival. Treatment was well tolerated, except for five episodes of possible cardiac toxicity in 130 patients who received mitoxantrone. Most responding patients had an improvement in quality-of-life scales and a decrease in serum prostate-specific antigen (PSA) level.**

Conclusion: **Chemotherapy with mitoxantrone and prednisone provides palliation for some patients with symptomatic hormone-resistant prostate cancer.**

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PROSTATE CANCER metastasizes most often to pelvic lymph nodes and to bone, and the dominant symptom is usually pain. Initial treatment of metastatic disease by orchidectomy or by drugs that decrease androgen stimulation relieves symptoms in approximately 75% of patients, but all patients progress eventually to hormone-resistant disease. The role of chemotherapy in providing palliation has been controversial.

Many types of chemotherapy are tolerated poorly by patients with prostate cancer, who are often elderly men with concurrent medical problems and limited bone marrow reserve. Although the goal of treatment is palliation, few studies have assessed outcome with validated scales for pain or quality of life that are completed by patients. Some anticancer drugs have biologic activity as assessed by a decrease in the prostate-specific antigen (PSA) level,[1-6] but these agents are often given with corticosteroids, which provide palliation to some patients when used alone.[7] All anticancer drugs cause toxicity, so they have potential to cause some symptoms while relieving others.

We have undertaken previous single-arm studies of prednisone alone[7] and mitoxantrone plus prednisone[8] for treatment of hormone-resistant prostate cancer. Mitoxantrone has low toxicity, and studies have suggested some palliative benefit for patients with metastatic prostate cancer.[8-10] Our studies were also used to develop and evaluate methods for assessing pain and quality of life.[7,8] In the present randomized trial, we address the hypothesis that chemotherapy with mitoxantrone plus prednisone provides better palliation than prednisone alone.

PATIENTS AND METHODS

Patients

From August 1990 to April 1994, 161 patients in 11 Canadian institutions were randomized to receive mitoxantrone plus prednisone (80 patients) or prednisone alone (81 patients). All patients had metastatic adenocarcinoma of the prostate with symptoms that

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included pain, and had disease progression despite standard hormonal therapy. All patients provided written informed consent to participate in the study.

Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 3 (ie, they were capable of at least limited self-care) and were stratified by ECOG score (0,1 *v* 2,3). They had a life expectancy ≥ 3 months and were capable of completing pain and quality-of-life scales. Exclusion criteria were as follows: (1) prior malignancy, except for nonmelanotic skin cancer; (2) prior chemotherapy or treatment of cancer with glucocorticoids; (3) treatment with radiotherapy in the last month or strontium 89 in the last 2 months; (4) contraindications to the use of prednisone such as active peptic ulcer; and (5) uncontrolled cardiac failure or active infection. Eligible patients had serum concentrations of WBCs greater than 3.0×10^9/L, polymorphonuclear granulocytes greater than 1.5×10^9/L, platelets greater than 150×10^9/L, bilirubin less than 54 μmol/L, and testosterone less than 3.5 nmol/L.

Patients had initial adjustment and stabilization of analgesic medication. They were assessed by the following: (1) physical examination; (2) completion of pain- and health-related quality-of-life questionnaires; (3) standard blood tests of hematologic and biochemical parameters plus serum testosterone, prostatic acid phosphatase, and PSA (not available in all centers at initiation of the study); (4) radionuclide bone scan and radiographs of the chest, pelvis, and painful bone sites; and (5) computed tomographic scan or ultrasound scan of the abdomen and pelvis if there was abnormal liver function or other evidence of soft tissue disease in these sites.

Treatment

Patients continued their primary androgen ablation therapy (orchidectomy, luteinizing hormone–releasing hormone agonist, estrogen, or cyproterone acetate); flutamide alone was not regarded as providing adequate androgen suppression. Most patients had discontinued additional antiandrogen treatment. Midway through this study, withdrawal responses to flutamide were recognized,[11,12] and patients were then evaluated for at least 4 weeks after stopping flutamide before entry onto the study.

Patients continued to take analgesic medication and adjusted the dosage to provide optimal control of pain. Following randomization, all patients took oral prednisone 5 mg twice daily. Those randomized to receive mitoxantrone received initially 12 mg/m^2 body-surface area by intravenous injection. Prochlorperazine was recommended as antiemetic medication; dexamethasone or other steroids were not used. Chemotherapy was repeated at 3-week intervals if serum concentrations of WBCs were greater than 3×10^9/L, granulocytes greater than 1.5×10^9/L, and platelets greater than 100×10^9/L; if not, chemotherapy was delayed until these values were exceeded. Blood cell counts were repeated on days 10 and 14 of the first cycle, and at one point within days 10 to 14 in subsequent cycles. If nadir blood cell counts showed granulocytes less than 0.5×10^9/L or platelets less than 50×10^9/L, the dose of mitoxantrone was reduced by 2 mg/m^2 on subsequent cycles. If nadir blood cell counts showed granulocytes greater than 1.0×10^9/L and platelets greater than 100×10^9/L with minimal nonhematologic toxicity, the dose of mitoxantrone was increased by 2 mg/m^2 on subsequent cycles.

Nonresponding patients or those with progressive symptoms after treatment with prednisone alone for ≥ 6 weeks were to receive mitoxantrone in addition.

To minimize the probability of cardiac toxicity, it was recommended that patients who were still responding after a cumulative dose of 140 mg/m^2 mitoxantrone continue treatment with prednisone alone.

Assessment of Outcome

Patients were examined at intervals of 3 weeks. At these visits, they underwent blood tests and completed questionnaires related to pain and quality of life. Bone scans and radiographs to define disease were performed at 3-month intervals. Toxic side effects of chemotherapy were assessed by World Health Organization (WHO) criteria.[13]

We chose pain relief as the primary indicator of palliation, because pain is the dominant symptom in this population. The primary end point of response was a 2-point reduction in the 6-point present pain intensity scale of the McGill-Melzack Pain Questionnaire[7,14] (or complete loss of pain if initially 1+). This criterion had to be maintained on two consecutive evaluations at least 3 weeks apart without an increase in analgesic score. The pain scale has verbal descriptors (0 = no pain, 1 = mild pain, 2 = discomforting pain, 3 = distressing pain, 4 = horrible pain, and 5 = excruciating pain), and patients were asked to classify the average pain level during the previous 24 hours.

Patients kept a diary in which they recorded all medications, and at each visit the average daily quantities taken during the previous week were calculated. A numeric scale was used to compute a daily analgesic score: 1 unit was used for standard doses of nonnarcotic medication (aspirin 325 mg, acetaminophen 325 mg, indomethacin 25 mg, etc.) and 2 units for standard doses of narcotic medication (morphine 10 mg, hydromorphone 2 mg, codeine 60 mg, etc.). These units may not be equivalent in analgesic potency, but patients usually adjusted the dose of the baseline medication(s) rather than switch to a different medication of similar type. A secondary criterion of response was a 50% decrease in analgesic score without an increase in pain maintained for two consecutive evaluations at least 3 weeks apart. All patients were considered assessable for response.

Other end points of the study were duration of palliative response (as defined by the primary end point) and survival. The start and end of response were defined, respectively, as the date of initial treatment and of the last assessment for which response criteria were satisfied.

Progression was defined as either an increase in the present pain intensity scale of ≥ 1 point compared with the nadir, or an increase in analgesic score of greater than 25% compared with baseline, each maintained on two consecutive visits. Unequivocal evidence of new lesions or of radiologic progression or a requirement for radiation therapy also constituted disease progression.

To assess the effects of disease and treatment on health-related quality of life, we used three different patient-based multidimensional instruments that addressed functions, symptoms, and global perceptions, as follows: (1) the Prostate Cancer–Specific Quality-of-Life Instrument (PROSQOLI), which includes nine linear analog self-assessment (LASA) scales that relate to pain, physical activity, fatigue, appetite, constipation, passing urine, family/marriage relationships, mood, and overall well-being, as well as Present Pain Intensity and analgesic score[7]; (2) the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC/QLQ-C30), with 30 ordinal scale items that included multi-item domains for physical function, emotional function, social function, pain, and global quality of life, and single items that included fatigue, appetite, and constipation[15,16]; and (3) a specific module for prostate cancer developed according to EORTC guidelines that will be reported elsewhere.

Statistical Considerations

The planned sample size of 150 patients was based on detection or exclusion of a doubling of palliative response rate due to prednisone alone, which was then (ie, before availability of antiandrogen drugs) anticipated to be approximately 20% with an α of .05 and 1-β of .80. A few additional patients were entered to allow for incomplete data.

One planned interim analysis was undertaken by an independent statistical consultant after entry of 80 patients. None of the investigators were aware of any results before study completion and the current analysis.

Statistical comparisons of the primary end point of response were made by Fisher's exact test. Distributions of survival time and duration of palliative response were compared by the log-rank test. We used nonparametric descriptive statistics to assess the quality-of-life data. Each patient's profile of scores for each domain of health-related quality of life was summarized by the median and best scores. These were converted to median and best-change scores by subtracting the appropriate baseline score. Differences in these summary scores between the two treatment groups were assessed with the Wilcoxon rank-sum test. The change from baseline in the group of responding patients was tested with the Wilcoxon signed-rank-sum test. All statistical tests were two-sided. Corrections were not applied for multiple significance testing; thus, apart from the end points defined a priori in the protocol, apparent correlations should be regarded as hypothesis-generating rather than definitive.

Associations between baseline characteristics and survival duration were assessed with the log-rank test. Factors that appeared important ($P \leq .05$) in univariable analysis were assessed for independent contributions with censored linear regression after a suitable transformation of survival time.[17] This model was chosen in preference to Cox's model, because key variables violated the proportional hazards assumption. Separate analyses were performed for the two alternative measures of health-related quality of life. For each analysis, the "best" subset of variables was chosen from an exhaustive search using Mallows' Cp as the criterion.[18]

External Review

An independent external consultant (provided by the National Cancer Institute of Canada) reviewed the records of all responding patients and of a randomly selected series of additional patients.

RESULTS

Baseline Characteristics

Characteristics of the patients at entry onto the study are listed in Table 1. The patients are well balanced for prognostic factors, although there is a trend for patients randomized to receive mitoxantrone plus prednisone to have a higher analgesic score and to be treated with flutamide. Two patients had pain scores of zero after optimization of analgesic medication; both showed evidence of symptomatic progression.

Response to Therapy

The primary criterion of palliative response was met in 23 of 80 patients randomized to receive mitoxantrone

Table 1. Characteristics of Patients at Entry Onto the Study According to Randomized Group

Variable	Prednisone (n = 81) No.	%	Mitoxantrone + Prednisone (n = 80) No.	%
Age				
Median	67		69	
Interquartile range	64-74		63-75	
Sites of metastasis				
Bone	77	95	78	98
Lymph nodes	15	19	18	22
Visceral	3	4	3	4
Other	8	10	7	9
Serum concentration*				
PSA (μg/L)				
Median	158		209	
Interquartile range	42-548		66-678	
Prostatic acid phosphatase				
Median	3.7		5.3	
Interquartile range	1.1-18.8		1.2-16.5	
Alkaline phosphatase				
Median	2.4		2.0	
Interquartile range	1.6-5.0		1.0-5.3	
Creatinine				
Median	0.8		0.8	
Interquartile range	0.7-0.9		0.7-0.9	
Time from diagnosis, years				
Median	2.9		3.0	
Interquartile range	1.5-4.6		1.6-5.1	
Hormonal therapy (current)†				
Orchidectomy	47	58	46	57
Estrogen	11	14	7	9
LHRH agonist	8	10	15	19
Cyproterone acetate	17	21	20	25
Flutamide	9	11	24	30
ECOG performance status				
0	3	4	5	6
1	47	59	45	57
2	22	28	21	26
3	8	10	8	10
Unknown	1	1	1	1
Present pain intensity				
0	1	1	1	1
1	23	28	30	38
2	37	46	30	38
3	15	19	15	19
4	5	6	4	5
Analgesic score				
Median	14		18	
Interquartile range	6-24		10-30	
Overall quality of life‡				
By LASA scale				
Median	6.5		5.9	
Interquartile range	4.8-8.0		4.7-8.1	
By EORTC QLQ-C30				
Median	50		46	
Interquartile range	33-58		33-58	

*PSA was available for only 134 patients. Serum concentrations of other parameters are expressed as a fraction of the upper limit of normal values.

†Some patients continued on dual therapy.

‡LASA: 0 = extremely ill; 10 = I feel well. EORTC: 0 = very poor; 100 = excellent.

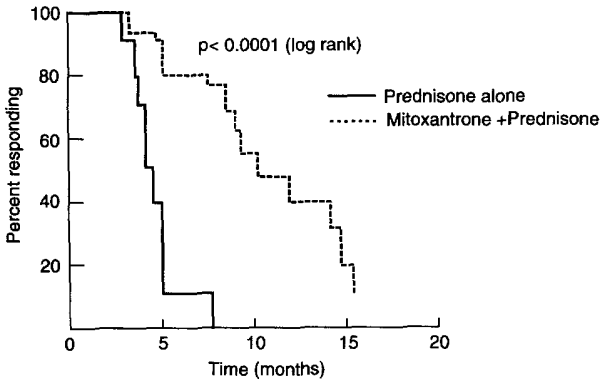

Fig 1. Duration of primary response in patients randomized to receive prednisone (n = 10) or mitoxantrone plus prednisone (n = 23).

plus prednisone and in 10 of 81 patients who received prednisone alone. Response rates were thus 29% (95% confidence interval, 19% to 40%) and 12% (95% confidence interval, 6% to 22%), respectively (P = .01). The duration of palliative response is shown in Fig 1. Response duration was longer for treatment with mitoxantrone plus prednisone than for prednisone alone (median, 43 *v* 18 weeks, $P < .0001$). Most of the patients who satisfied the primary criterion of response reduced their analgesic medication.

An additional seven patients in each arm satisfied the secondary criterion of palliative response, a decrease of ≥ 50% in analgesic score without an increase in pain.

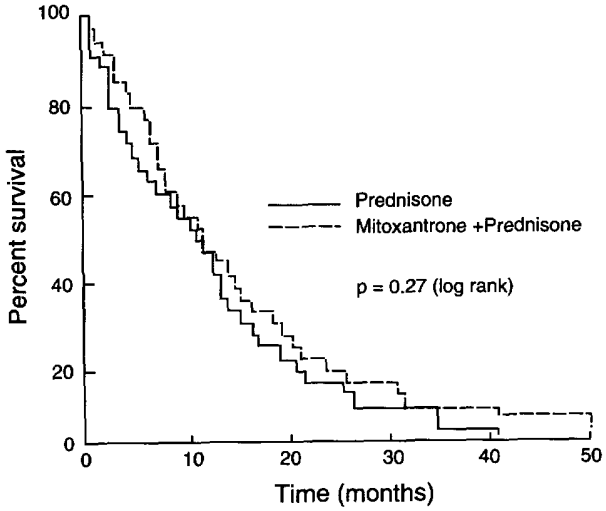

Fig 2. Actuarial survival curves for patients randomized initially to receive prednisone (n = 81) or mitoxantrone plus prednisone (n = 80).

Table 2. Patients With a Reduction in Serum PSA Level According to Treatment

Decrease in Serum PSA	Prednisone (n = 54) No.	Prednisone (n = 54) %	Mitoxantrone + Prednisone (n = 57) No.	Mitoxantrone + Prednisone (n = 57) %
≥ 25%	25	46	28	49
≥ 50%	12	22	19	33
≥ 75%	5	9	13	23

NOTE. Data represent the maximum observed decrease in PSA level compared with baseline while receiving the randomly assigned treatments. The proportion of patients with ≥ 25% decrease in PSA level includes those with ≥ 50% or ≥ 75% decrease; the proportion with ≥ 50% decrease in PSA level includes those with ≥ 75% decrease. The difference between the 2 randomized groups is not significant (P = .11, Wilcoxon rank-sum test).

Twelve of these 14 patients had some reduction in pain. The mean duration of secondary response was 33 weeks (mitoxantrone + prednisone) and 24 weeks (prednisone alone). If both primary and secondary criteria of response are included to indicate palliative benefit from treatment, this was achieved in 30 of 80 (38%) of patients randomized to mitoxantrone plus prednisone and 17 of 81 (21%) of patients randomized to prednisone (P = .025).

Only two responding patients had discontinued flutamide within 4 weeks before study entry; both of these patients received mitoxantrone. There is no influence of prior therapy with flutamide on the primary end point (P = .022, stratified for flutamide).

Fifty patients randomized to receive prednisone were crossed-over subsequently to receive added mitoxantrone. Eleven patients (22%) responded on crossover for a median duration of 18 weeks (range, 9 to 69).

A total of 140 patients died (as of April 1995). The distributions of survival duration for the two groups of

Table 3. Patients With a Reduction in Serum PSA Level According to Criteria of Palliative Response

Decrease in Serum PSA	Primary Response: Yes (n = 27) No.	Primary Response: Yes (n = 27) %	Primary Response: No (n = 84) No.	Primary Response: No (n = 84) %	Primary and/or Secondary Response: Yes (n = 38) No.	Primary and/or Secondary Response: Yes (n = 38) %	Primary and/or Secondary Response: No (n = 73) No.	Primary and/or Secondary Response: No (n = 73) %
≥ 25%	20	74	33	39	26	68	27	37
≥ 50%	13	48	18	21	17	45	14	19
≥ 75%	9	33	9	11	12	32	6	8
		P = .001*				P = .0001*		

NOTE. Data represent the maximum decrease in PSA level compared with baseline while receiving the randomly assigned treatment. Each row includes patients who satisfy more stringent conditions, as in Table 2.

*Wilcoxon rank-sum test for comparison of distributions of the decrease in PSA levels in patients who did and did not meet criteria for palliative response.

patients are shown in Fig 2. There was no significant difference in overall survival ($P = .27$, favoring mitoxantrone plus prednisone).

Assessment of serum PSA at baseline and at least one subsequent visit was obtained on 111 patients. There was a higher probability of reduction in PSA for patients who received chemotherapy, but this was not significant statistically (Table 2). The distribution of change in serum PSA differed among patients who did and did not meet criteria for palliative response (Table 3), but change in serum PSA did not provide useful discrimination between these groups of patients.

Changes in Health-Related Quality of Life During Treatment

Compliance with completion of quality-of-life scales was high. Completed present pain intensity scales were obtained for 92% of clinic visits during initially allocated treatment, with no difference between the arms. LASA scales for pain were completed on 89% of visits, with similar values for other scales.

Median changes in LASA scores and in domains of the EORTC questionnaire during initially assigned treatment and maximum improvements as compared with baseline are shown in Fig 3 for all patients in the randomized

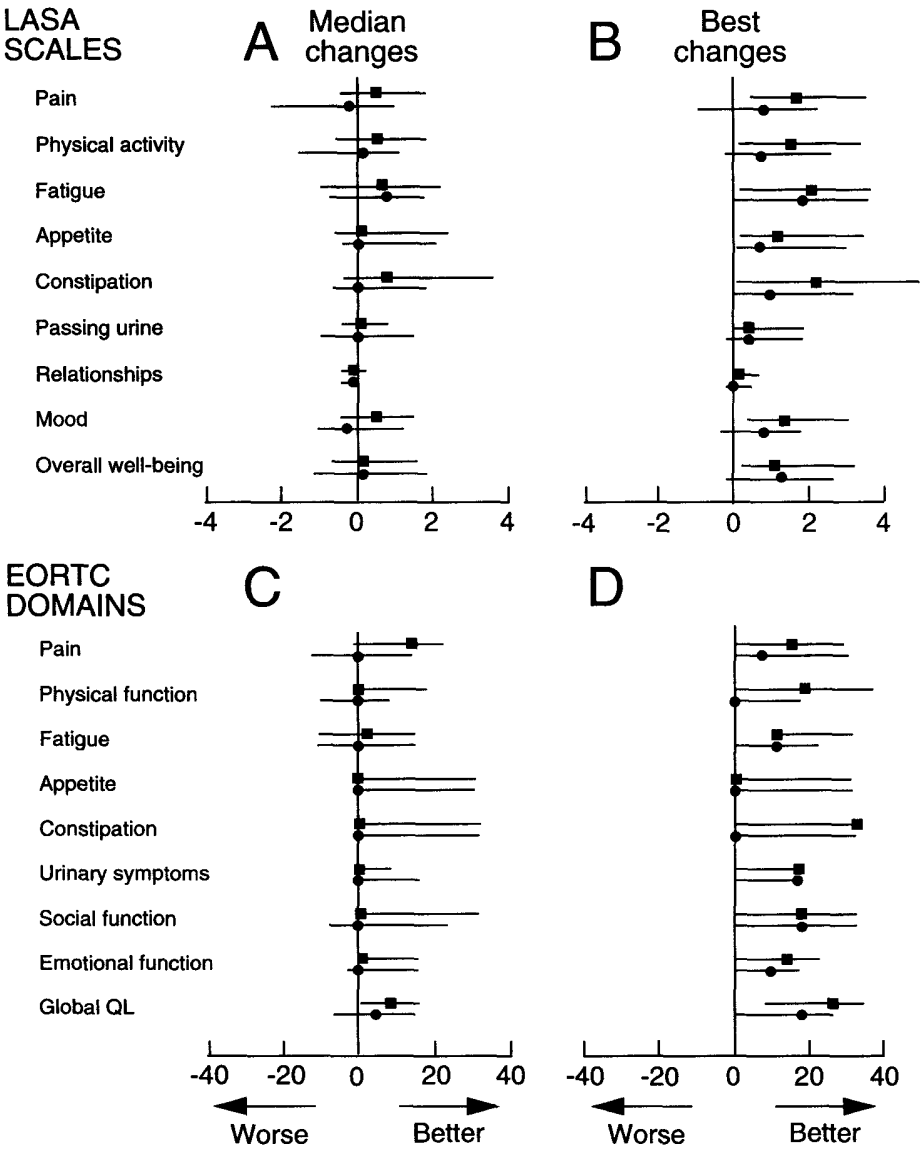

Fig 3. Comparisons during treatment for all patients who had ≥ 2 assessments (n = 154). Median changes (A and C) and best changes (B and D) compared with baseline LASA scales (A and B) and EORTC domains (C and D) that indicate attributes of health-related quality of life. Median and maximum values for each scale were determined for all patients throughout the period that they continued on the therapy to which they were randomized initially. Medians and interquartile ranges are shown for patients randomized to mitoxantrone + prednisone (n = 78, ■) or prednisone alone (n = 76, ●). Differences between groups were significant (by the Wilcoxon rank-sum test) for the dimensions of pain ($P = .01$ for A and B; $P < .05$ for C and D) and constipation ($P < .05$ for A, B, and D), and borderline for mood (A, $P = .06$; B, $P = .02$).

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