A Randomized Phase II Trial of Thalidomide, an Angiogenesis Inhibitor, in Patients with Androgen-independent Prostate Cancer

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ABSTRACT

Purpose: Thalidomide is a potent teratogen that causes dysmelia in humans. Recently, in vitro data suggested that it inhibits angiogenesis. Prostate cancer is dependent on the recruitment of new blood vessels to grow and metastasize. Based on those data, we initiated a Phase II trial of thalidomide in patients with metastatic androgen-independent prostate cancer.

Experimental Design: This was an open-label, randomized Phase II study. Thalidomide was administered either at a dose of 200 mg/day (low-dose arm) or at an initial dose of 1200 mg/day (high-dose arm). To escalate to 1200 mg/day (high-dose arm).

Results: A total of 63 patients were enrolled onto the study (50 patients on the low-dose arm and 13 patients on the high-dose arm). Serum prostate-specific antigen (PSA) decline of ≥50% was noted in 18% of patients on the low-dose arm and in none of the patients on the high-dose arm. Four patients were maintained for >150 days. The most prevalent complications were constipation, fatigue, neurocortical, and neurosensory.

Conclusion: Thalidomide, an antiangiogenesis agent, has some activity in patients with metastatic prostate cancer who have failed multiple therapies. A total of 27% of all patients had a decline in PSA of ≥40%, often associated with an improvement of clinical symptoms. Because our preclinical studies had shown that thalidomide increases PSA secretion, we believe that the magnitude of PSA decline seen in our trial justifies further study.

INTRODUCTION

Prostate cancer is the most common malignancy in American men and is the second leading cause of cancer mortality (1). Whereas hormonal ablation is the cornerstone of therapy for metastatic disease, androgen independence develops and is ultimately fatal. AIPC is a therapeutic dilemma for which no treatment prolongs survival.

Angiogenesis is the process of new blood vessel growth and is necessary for growth of solid malignant tumors (2). Vessel growth is controlled by a balance of endogenous inhibitors and stimulators (2). Angiogenesis allows a tumor to increase in size and increases the probability of metastasis (3). Staining for microvessels within a tumor is one means of assessing this recruitment. Weidner et al. (4) reported a correlation between microvessel count within a tumor and the diagnosis of metastatic prostate cancer. The mean microvessel count among patients with metastatic disease was 76.8 vessels/field, as compared with 39.2 vessels/field for those without metastasis (P < 0.0001; Ref. 4). Thus, angiogenesis inhibition is the center of much work as a potential therapeutic modality (2).

Thalidomide is a potent teratogen that causes dysmelia (stunted limb growth) in humans (5, 6). It was marketed in Europe as a sedative but was withdrawn 30 years ago because of its teratogenic effects (5, 6). The compound was later discovered to be effective in lepromatous leprosy (7, 8) and received United States Food and Drug Administration approval in 1998 for the treatment of leprosy. It is presently in clinical development for the treatment of a variety of diseases with an autoimmune character, including recurrent aphthosis of nonviral and nonfungal origin in immunodeficient patients (9). Recently, in vitro data sug-

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Received 11/17/00; revised 3/9/01; accepted 3/22/01.

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1 Supported by the United States Government Intramural Program of the National Cancer Institute and the National Center on Minority Health and Health Disparities.

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3 The abbreviations used are: AIPC, androgen-independent prostate cancer; PSA, prostate-specific antigen; NCI, National Cancer Institute; CT, computed tomography; bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; TGF, transforming growth factor; TTF, time to treatment failure; XRT, X-ray therapy; LHRH, luteinizing hormone-releasing hormone; EMG, electromyography; PFS, progression-free survival.
suggested that thalidomide has antiangiogenic activity (10). Based on those data, a randomized Phase II trial of thalidomide in patients with metastatic AIPC was initiated.

MATERIALS AND METHODS

Study Design. This was an open-label, Phase II, randomized study of thalidomide in patients with AIPC. This study was approved by the Institutional Review Board of the NCI and conducted within the Warren G. Magnuson Clinical Center of the NIH. Thalidomide (NSC#66847) was provided to the Pharmacy Department of the Clinical Center by the Cancer Treatment Evaluation Program of the NCI through an agreement with EntreMed, Inc. (Rockville, MD). Patients were randomly assigned to receive thalidomide at a dose of 200 mg/day (low-dose arm) or at an initial dose of 200 mg/day that escalated in increments of 200 mg/day every 2 weeks to a maximum daily dose of 1200 mg (high-dose arm) administered every evening. Patients were evaluated monthly. If there was no significant toxicity or evidence of disease progression (as defined below), then therapy continued. Patients were assessed every 2 months by radiographic studies (CT scans of the chest, abdomen, and pelvis and technetium-99m bone scintigraphy). PSA was measured by the Hybritech Tandem-R (San Diego, CA) assay. PSA and standard chemistries and hematological tests were obtained monthly.

Dosing modifications were allowed in two situations. For somnolence that persisted during daylight hours, the dose could be reduced by 100 mg/day. Patients who developed grade 2 peripheral neuropathy and who had no other criteria for withdrawal from the study had their drug held until the neuropathy resolved to ≤ grade 1. Patients were allowed to resume thalidomide treatment within 2 months after discontinuing the drug provided that neuropathic symptoms had resolved or decreased in severity to less than grade 1. Patients who developed recurrent peripheral neuropathy ≥ grade 2 after resuming thalidomide and those whose symptoms did not decrease after a 2-month hiatus off treatment were withdrawn from further study participation.

Patient Eligibility. All patients had failed combined androgen blockade, as well as antiandrogen withdrawal. Each patient met the following eligibility criteria: (a) histological diagnosis of adenocarcinoma of the prostate; (b) an increasing PSA despite continued testicular suppression (testosterone < 50 ng/ml) as defined by Ref. 11, and/or new lesions on radionuclide bone scan, and/or enlargement of a soft tissue mass; and (c) Eastern Cooperative Oncology Group performance status ≤ 2. All patients gave informed consent before enrollment. Other forms of antitumor therapy were prohibited (including radiation therapy), except LHRH agonist. Exclusion criteria included: (a) abnormal hematological or biochemical parameters; (b) brain metastases; or (c) prior suramin treatment. Prior cytotoxic chemotherapy was not among the exclusion criteria.

Response Evaluation. Standard objective criteria were used to assess soft tissue lesion changes. Disappearance of >50% of the number of metastatic lesions on bone scan was also considered a partial response. We have reported PSA declines in a manner similar to that put forward by the Prostate-specific Antigen Working Group to assess changes in PSA (11). Because thalidomide has been shown to up-regulate PSA expression in an in vitro model (12), we analyzed any decline in PSA that was confirmed by a second measurement (14 days later and maintained for 28 days). No other evidence of disease progression was allowed during this period.

Progressive disease was defined by any of the following criteria: (a) 25% increase in the size of all soft tissue masses and/or the appearance of new masses; (b) the need for radiation therapy; and (c) two consecutively increasing PSA measurements, one of which was ≥50% of the patient’s baseline PSA. Patients with a baseline or nadir PSA less than 20 ng/ml were not declared to have disease progression until the PSA had increased by an absolute value of 10 ng/ml or more. We also analyzed disease progression using the working group’s criteria for progression and found no difference in time to progression. Disease stabilization was felt to be an important end point in evaluating angiogenesis inhibitors. Therefore, we also report TTF below.

Toxicity Assessment. Toxicity was defined by Cancer Therapy Evaluation Program, NCI, Common Toxicity Criteria (October, 1993; Ref. 13).

Neurological Analysis. Before starting therapy, patients underwent electrodagnostic studies that included nerve conduction of four sensory nerves (median, ulnar, radial, and sural nerves) and two motor nerves [median and peroneal nerves (14)]. Measurements of perceptual vibration thresholds at the index finger and great toe were obtained. These studies were repeated every 3 months.

Concomitant Hormonal Therapy. Those patients who had not undergone bilateral orchiectomy continued to receive medical castration with LHRH agonist [leuprolide (Depot Lupron; TAP Pharmaceuticals, Deerfield, IL) or goserelin acetate (Zoladex; Zenea, Wilmington, DE)].

Pathology Analysis. A baseline prostate biopsy was obtained from each patient with an intact prostate gland. Patients who had previously undergone radical prostatectomy were required to have disease involving soft tissues that was accessible for biopsy. A transrectal quadrants biopsy was performed within 4 weeks prior to starting therapy and then repeated between 2 and 6 months after starting therapy. Micravessels count (using antibodies against CD34), Gleason score, and immunohistochemistry staining for both bFGF and VEGF were evaluated.

Assessment of Changes in Circulating Growth Factors. Serum was obtained at each clinic visit and analyzed by ELISA kits (R&D, Minneapolis, MN) for bFGF, VEGF, TNF-α, and TGF-β.

Statistical Analysis. The objective of this study was to evaluate the response rates (objective tumor measurements and PSA changes) associated with low-dose and high-dose thalidomide in patients with AIPC. Other objectives included evaluation of time to progression and documentation of any toxicity.

All patients who received any drug were evaluable for toxicity and disease response. Initially, 14 patients were scheduled to be entered into each arm of this study. If none of the 14 patients exhibited a complete or partial response or disease stabilization (>6 months), or if the side effect profile was unacceptable, then accrual would cease for that arm. We would then conclude with 95% power and confidence that the true response proportion was <20% for that dosing regimen. If at
RESULTS

Fifty patients were enrolled on the low-dose arm, and 13 patients were enrolled on the high-dose arm. Their demographic data are reported in Table 1. The median time on study was 2.1 months for the low-dose arm and 2.0 months for the high-dose arm (median time on study, 109 days; range 35–247 days). A total of 30% of patients were unable to escalate the dose above 200 mg/day due to complications associated with the drug (sedation and fatigue). The high-dose arm was terminated early after 13 patients were enrolled because none of the patients had a >50% decline in PSA and due to the high number of individuals who could not tolerate a dose above 200 mg. The low-dose arm was expanded to 50 evaluable patients.

Clinical Activity. Nine of the 63 patients enrolled on the study (14%) had PSA declines of ≥50%. Eighteen percent (18%) of patients in the low-dose arm had a ≥50% decline in PSA, and none of the patients in the high-dose arm achieved a decrement of ≥50% in PSA. Although we are unsure of the significance of this observation, 60% of all patients enrolled had some degree of PSA decline that was maintained for >28 days while on study (see Table 2). A total of 28% of all patients had a >40% decline in PSA. Eight individuals (13%) had a PSA decline of between 40% and 50%. Four patients had PSA declines of ≥50% that were maintained for >150 days (153, 191+, 191+, and 384 days).

Thirty-five patients had measurable disease by CT scan. No individual developed a partial response by CT criteria. Five patients had some reduction in measurable disease (although less than a 50% decline). Eight individuals (13%) had a PSA decline of between 40% and 50%. Four patients had PSA declines of ≥50% that were maintained for >150 days (153, 191+, 191+, and 384 days).

The median TTF was 2.2 months for the low-dose arm and 2.1 months for the high-dose arm (see Fig. 1). Fifteen patients were on the drug for more than 4 months, six patients were on the drug for more than 6 months, and four patients were on the drug for more than 8 months. Thirty-four patients are currently alive, and the median survival duration for the all 63 patients enrolled is 15.8 months (see Fig. 2). There was no difference in survival between the two treatment arms.

Molecular Assessment of Angiogenesis End Points.
Fifty-three patients underwent a pretreatment baseline biopsy (52 of the prostate gland and one of the inguinal node). In addition, five patients had a follow-up biopsy. Twelve patients were found not to have disease present in the baseline prostate biopsy cores analyzed. These patients did not receive prior XRT to the prostate. The remaining patients had a median Gleason grade of 8 (range, 6–10). The microvessel counts among these patients ranged between 6 and 25.8 vessels/high-power field. However, there did not appear to be a clear correlation between microvessel count and response (PSA decline or radiographic changes). Likewise, a correlation between VEGF or bFGF expression and response could not be made on the pretreatment biopsy.

Circulating Growth Factor Changes. We analyzed all patients who received the drug for >4 months (n = 15 patients)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-dose arm</td>
</tr>
<tr>
<td>N</td>
<td>50</td>
</tr>
<tr>
<td>Age (median, range) (yrs)</td>
<td>68 (50–83)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
</tr>
<tr>
<td>D1</td>
<td>7</td>
</tr>
<tr>
<td>D2</td>
<td>23</td>
</tr>
<tr>
<td>Days from diagnosis to on study (median, range)</td>
<td>1918 (361–7683)</td>
</tr>
<tr>
<td>Gleason score at diagnosis (median, range)</td>
<td>8 (5–10)</td>
</tr>
<tr>
<td>ECOG performance status</td>
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<tr>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prior pelvic XRT</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Prior radical prostatectomy</td>
<td>9 (18%)</td>
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<tr>
<td>No. of patients receiving a LHRH agonist during study</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>No. of orchiectomy</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Baseline PSA (mean ± SD)</td>
<td>315 ± 450</td>
</tr>
<tr>
<td>No. of patients with soft tissue lesion</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>No. of patients with bone lesions</td>
<td>64 (48%)</td>
</tr>
<tr>
<td>Prior palliative XRT</td>
<td>19 (38%)</td>
</tr>
<tr>
<td>No. of 2nd hormonal therapies</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>3</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>No. of patients that received at least one chemotherapy regimen</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>No. of patients requiring opioid analgesics prior to enrolling</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Prior investigational drugs</td>
<td>7 (14%)</td>
</tr>
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</table>

*ECOG, Eastern Cooperative Oncology Group.
for changes in bFGF, VEGF, TNF-α, and TGF-β (baseline and after approximately 4 months of treatment). For the eight patients who demonstrated a PSA decline at 4 months, the serum bFGF levels decreased from a mean of 4.96 ± 5.63 pg/ml (median, 2.78 pg/ml) to a mean of 1.03 ± 0.8 pg/ml (median, 1.4 pg/ml; Fig. 3). Six of eight patients had a decline in bFGF, the bFGF level in one patient remained the same, and one patient’s bFGF level increased. In contrast, VEGF levels varied from a mean of 135.93 ± 122.8 pg/ml (median, 92.68 pg/ml) at baseline to a mean of 156.79 ± 162.86 pg/ml (median, 83.79 pg/ml) after 4 months of treatment. Three of eight patients had a VEGF decline, one patient’s VEGF level remained the same, and the VEGF level of four patients increased. The TNF-α values went from a mean of 0.57 ± 1.17 pg/ml (median, 0.185 pg/ml) to 1.21 ± 1.53 pg/ml (median, 0.792 pg/ml). One patient had a decline in TNF-α, three had undetectable levels, and four patients had an increase in TNF-α. The TGF-β values went from a mean of 115.2 ± 64.9 pg/ml (median, 86.41 pg/ml) at baseline to a mean of 154.9 ± 182.6 pg/ml (median, 86.41 pg/ml) after 4 months of treatment.

**Toxicity.** There were 560 adverse events reported. The most prevalent complications were constipation, dizziness, edema, fatigue, mood changes, and peripheral neuropathy. Eighteen events were classified as ≥grade 3. The incidence of complications of ≥grade 3 was only slightly higher for the high-dose arm (5 incidents in 13 patients) compared with the low-dose arm (13 incidents in 50 patients). There was one grade 5 event. A patient committed suicide within 30 days of stopping thalidomide for progressive disease. It is possible thalidomide contributed to his depression because there were 16 other mood

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**Fig. 1** A Kaplan-Meier graph showing TTP of high- and low-dose groups for patients treated with thalidomide. The median PFS was 2.2 months for the low-dose arm and 2.1 months for the high-dose arm.

**Fig. 2** A Kaplan-Meier graph of overall survival for all patients treated with thalidomide (both high- and low-dose groups). The median survival was 15.8 months with 8 patients still receiving the drug and 34 patients alive at the time of analysis. Fifteen patients were on the drug for more than 4 months, six patients were on the drug for more than 6 months, and four patients were on the drug for more than 8 months.
toxicities reported. A patient with prolonged prior exposure to cytotoxic chemotherapy agents developed acute myeloid leukemia. Retrospective assessment showed a small number of myeloid blast cells in his pretreatment peripheral smear. After 28 days of treatment, his circulating blast population had increased to 50%, and a bone marrow biopsy was consistent with acute myelogenous leukemia. The possible contribution of thalidomide to this event is unclear. Grade 2 neutropenia was noted in eight patients. One additional patient had grade 3 neutropenia that improved with discontinuation of therapy.

Baseline neurological evaluations were performed on all 63 patients. Baseline neurological examinations were grade 0 for 28 patients, grade 1 for 32 patients, and grade 2 for 3 patients. (None of the patients with baseline neurotoxicity had received prior taxanes.) Baseline nerve conduction studies showed electrophysiological evidence of a preexisting underlying polyneuropathy in 27 patients and other focal nerve abnormalities in 10 patients, including 7 patients with asymptomatic median nerve abnormalities at the carpal tunnel. In most patients, polyneuropathy could be attributed to underlying diseases such as diabetes or prior chemotherapy, and needle EMG showed chronic, inactive denervation. Twenty of the 23 patients who continued to receive study medication for at least 3 months had follow-up evaluations, as did 2 patients who discontinued medication after 2 months. All six patients who received thalidomide for 6 months had follow-up studies, four patients who continued on medication had follow-up studies at 9 months and 12 months.

No patients developed symptoms of polyneuropathy, change in clinical grade, or significant changes in nerve conduction studies at the 3- or 6-month follow-up evaluation. Two patients had mild worsening of previously documented carpal tunnel abnormalities, and one patient complained of worsening tumor. Four patients who received the drug for >9 months experienced symptoms of peripheral neuropathy (all were receiving 200 mg/day). In one patient, paresthesias in feet were not accompanied by changes in neurological exam grade, nerve conduction studies, or perceptual thresholds. Another patient had loss of vibratory sensation in feet and deep tendon reflex consistent with nerve conduction changes (grade 2). For the other two patients, one developed tingling in his feet with a reduction of 40% in conduction sensory amplitude after 11 months and tingling in his hands after 13 months (both of these were slow to resolve after 6 months off drug), and the other nondiabetic patient experienced moderate stocking glove paresthesias of his feet after about 9 months of treatment (grade 2). Both patients had an increase in clinical toxicity grade, a decrease in combined sensory nerve amplitudes of >40%, elevation of perceptual threshold by >2 units, and EMG evidence of active denervation.

DISCUSSION

Thalidomide, a glutamic acid derivative, was first described in 1953 (15). It was later marketed as a sleeping pill and was subsequently blamed for nearly 12,000 birth defects (15). It has been postulated that limb defects seen with thalidomide were secondary to an inhibition of blood vessel growth in the developing fetal limb bud (10). D’Amato et al. demonstrated that thalidomide inhibited angiogenesis in the rabbit cornea assay (10). Bauer et al. (16) evaluated thalidomide in two in vitro models (rat aorta model and human endothelial cell culture) and demonstrated antiangiogenic activity in the presence of human liver microsomes. Based on these data, it was suggested that thalidomide might be useful in the treatment of solid tumors.

Fourteen percent of patients on this study had a ≥50% decline in serum PSA. An additional 13% of patients showed a PSA decline of between 40% and 50%. This group is important because thalidomide promotes the secretion of PSA in vitro (both mRNA and protein; Ref. 12).

We anticipated that antiangiogenic agents would not regress lesions but would simply halt expansion. We were pleased to note that five patients had some reduction in measurable disease (although less than a partial response). One additional patient with a painful penile lesion had symptom improvement (decrease narcotic use; patient reported improvement in urination). Sequential bone scan studies demonstrated improvement in lesions in two patients who received thalidomide for >9 months. Furthermore, scintigraphic improvement coincided with clinical improvement (decreased opioid analgesic use and improved urine flow). However, despite these favorable findings, it is important to recognize that changes on bone scan cannot be definitively ascribed to an objective response to treatment.

In theory, the best opportunity for antiangiogenesis agents to have a therapeutic impact is when there is minimal tumor burden (i.e., concurrent with hormonal ablation or cytoreduction therapy). In this cohort of 63 patients, disease volume was substantial, and all patients were resistant to standard therapy. A decline in PSA of >50% in nine patients strongly suggests the need to study this agent in patients for whom the theoretical considerations are more favorable.

The median survival for our patients was 15.8 months. It is important to remember that 65% of patients enrolled on this study had metastatic disease at the time of diagnosis, the median Gleason score was 8, and the median PSA was 326 ng/ml. The
patients studied were a heavily pretreated population with 40% requiring opioid analgesics, 48% having failed at least one secondary hormonal manipulation, 24% having failed at least one chemotherapy regimen, and 35% requiring palliative radiation treatment before enrollment.

Thalidomide was well tolerated in the vast majority of patients. Constipation, dizziness, edema, and fatigue were the most common complaints noted. Whereas grade 1 (minimal) and grade 2 (mild) toxicities were frequent, they were easily remedied with basic conservative management. Grade 3 (substantial) and grade 4 (severe) toxicities were uncommon; these too responded to conservative management and dose reduction in the vast majority of cases. The one case of grade 5 neuro-mood (suicide) may or may not have been due to thalidomide because it occurred after the discontinuation of drug. One case of sinus bradycardia required placement of a cardiac pacemaker in a patient who also had grade 3 peripheral neuropathy and was on drug for >8 months. Two other patients required pacemaker implantation while on study. The relationship to the drug is unclear in this elderly male population. Finally, about one-third of the patients complained of rebound insomnia after coming off study; this again was manageable with conservative treatment.

It is unlikely that angiogenesis inhibitors will work with the same rapidity as cytotoxic agents, and they may, in some cases, increase the secretion of PSA (12, 17). Thus one needs to be cautious in comparing PSA results when trials use vastly different classes of agents. Based on preclinical information, we expected that we would see increases in serum PSA in virtually different classes of agents. Based on preclinical information, we expected that we would see increases in serum PSA in virtually all patients (12). Thus the fact that approximately 30% of patients had a decline of >40% is encouraging. There was often other evidence of clinical benefit in patients with a falling or stable PSA. Thus, we believe that this is the first evidence that thalidomide may have modest antitumor activity in patients with AIPC. It is likely that this drug may have more activity in patients with lower volume disease, and we are designing clinical trials using thalidomide to answer that question.

ACKNOWLEDGMENTS

We thank Drs. Raymond Bergan, Alice Chen, and Otis Brawley for clinical assistance with the conduct of this trial. We thank Delmar Harner for data management assistance. Valerie Dyer, Patricia Davis, and Toni Jones-Wells are research nurses who contributed to this trial. In addition, the residents/clinical fellows in both the Urology and the Medicine Branches of the NCI have contributed substantially to the patient care within this study. Catherine Nevers of the National Institute of Neurological Disorders and Stroke assisted with the neurodiagnostic studies.

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