

Short-course lenalidomide plus low-dose dexamethasone in the treatment of newly diagnosed multiple myeloma—a single-centre pragmatic study

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ABSTRACT

Purpose We assessed response to treatment, toxicity, time to progression, progression-free survival, and overall survival in patients newly diagnosed with multiple myeloma who were ineligible for or unwilling to undergo transplantation and who were treated with a combination of lenalidomide and low-dose dexamethasone for a fixed 6 cycles in a resource-constrained environment.

Methods This pragmatic study, conducted in a single tertiary cancer centre in South India, enrolled patients from May 2009 till April 2011. Treatment included lenalidomide 25 mg daily for 21 days, with dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle, for 6 cycles. Response was evaluated after the 3rd and 6th cycles of treatment. All patients were followed for 5 years.

Results The study enrolled 51 patients. Median age in the group was 61 years (range: 38–76 years). Immunoglobulin G or A myeloma constituted 70.6% of the diagnoses, and light-chain myeloma constituted 29.4%. Stages I, II, and III (International Staging System) disease constituted 21.4%, 28.6%, and 50% of the diagnoses respectively. All patients were transplantation-eligible, but 34 (66.7%) refused for economic reasons. After treatment, 19.6% of the patients achieved a stringent complete response; 35.3%, a complete response; 5.9%, a very good partial response; and 29.4%, a partial response, for an overall response rate of 90.2%. Stable disease was seen in 3.9% of patients, and progressive disease, in 5.9%. Grade 3 or greater nonhematologic and hematologic toxicity occurred in 35.2% and 11.7% of patients respectively. Pulmonary embolism occurred in 1 patient. No patient experienced deep-vein thrombosis or peripheral neuropathy. The median follow-up duration was 66 months. All patients experienced disease progression. Median progression-free survival was 16 months. In 10 patients, re-challenge with lenalidomide and dexamethasone achieved a second complete response. At the time of writing, 19 patients had died. The overall survival rate at 5 years was 62.74%. Median overall survival is not yet reached.

Conclusions In a resource-constrained setting, lenalidomide with low-dose dexamethasone is an effective treatment with acceptable toxicity in patients newly diagnosed with multiple myeloma and not planned for transplantation. Complete responses were significantly more frequent than reported in the Western literature. Occurrence of clinical deep-vein thrombosis was rare, but hyperglycemia was common. An abbreviated course of treatment is suboptimal in multiple myeloma. Maintenance regimens should be advocated.

Key Words Multiple myeloma, newly diagnosed; lenalidomide; dexamethasone

Curr Oncol. 2017 Oct;24(5):e361-e367

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INTRODUCTION

Multiple myeloma is a clonal plasma-cell disorder that accounts for slightly more than 10% of all hematologic cancers¹. According to hospital-maintained data, the reported incidence of multiple myeloma in India is 0.5–1.2 per 100,000 population².

For many years, melphalan–prednisolone was the standard therapy for this disease³. To maintain patient eligibility for stem-cell transplantation, non-alkylator-based induction therapy with vincristine–doxorubicin–dexamethasone was introduced⁴. Nearly a decade after that, combination thalidomide–dexamethasone emerged as an alternative to vincristine–doxorubicin–dexamethasone in newly diagnosed multiple myeloma⁵. However, grade 3 or greater nonhematologic toxicities were significantly higher with standard-dose thalidomide. Lenalidomide, a derivative of thalidomide and a second-generation immunomodulatory drug, was found to be less toxic and more potent than thalidomide. Responses were observed even in patients for whom thalidomide treatment had previously failed⁶. Lenalidomide has shown significant activity in combination with dexamethasone, with fewer nonhematologic side effects than are seen with thalidomide⁷.

Compared with thalidomide–dexamethasone, lenalidomide–dexamethasone is now accepted as a safer and more effective alternative in newly diagnosed myeloma. The use of lenalidomide for treating newly diagnosed multiple myeloma is not novel, but its use in a resource-constrained Indian scenario is underreported.

The treatment of myeloma is becoming ever more expensive as the years roll on. The per-capita gross domestic product in India was last recorded at 77,524 Indian rupees (US\$1750.60) in 2015⁸. With more than 70% of Indian patients paying out of pocket for medical expenses, expensive myeloma treatment—including stem-cell transplantation—is generally unaffordable⁹. Lenalidomide has become less expensive over the years because of the availability of generic versions.

The present study of lenalidomide and low-dose dexamethasone was a logical extension of our institutional phase II study of thalidomide plus low-dose dexamethasone by Thomas *et al.*¹⁰, which reported 57% complete responses (CRs) and 21% partial responses (PRs), for an overall response rate of 78%—significantly higher than the response rates reported in the literature.

In a developing nation such as India, where sustaining long-term treatment is a challenge, there is a need to assess whether an abbreviated course of treatment for 6 months would be effective. The present study assessed an abbreviated 6-cycle course of treatment with lenalidomide–dexamethasone in patients not planned for transplantation.

METHODS

This single-institution prospective pragmatic study had an enrolment period of May 2009 to April 2011. The study included patients above the age of 18 years who had untreated symptomatic multiple myeloma, measureable disease, and an Eastern Cooperative Oncology Group performance status of 0–2.

Multiple myeloma was diagnosed on the basis of 10% or more clonal bone marrow plasma cells, the presence of serum or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma), and evidence of end-organ damage attributable to underlying plasma-cell proliferative disorder—specifically, hypercalcemia; renal insufficiency; anemia; and lytic bone lesions, severe osteopenia, or pathologic fracture.

All patients were either ineligible for (>65 years of age) or unwilling to undergo autologous stem-cell transplantation, because the aim was to assess response in non-transplanted people, which is generally the norm in most Indian centres.

The investigations were limited to those that were mandatory. For diagnostic purposes, all consenting patients with suspected myeloma underwent serum and urine electrophoresis, bone marrow aspiration and trephine biopsy, skeletal survey, quantitative serum immunoglobulins (G, A, and M) and free light-chain assay (kappa, lambda), and β_2 -microglobulin, in addition to routine investigations such as complete blood count, peripheral blood smear, kidney and liver function tests, serum calcium, and lactate dehydrogenase. Immunofixation was not used in view of lack of local availability and cost concerns. Because of resource constraints, bone marrow conventional karyotyping was performed only in patients who separately consented for the same. Reassessment evaluations were performed after the 3rd and 6th cycles.

A CR was defined as normal serum electrophoresis, normal quantitative serum immunoglobulins and free light-chains, disappearance of any soft-tissue plasmacytomas, and fewer than 5% plasma cells in bone marrow. A stringent CR (sCR) was defined as (in addition to CR criteria) a normal free light-chain ratio and absence of clonal cells in bone marrow by immunohistochemistry. A very good partial response (VGPR) was defined as a 90% or greater reduction in serum quantitative immunoglobulins. A PR was defined as a 50% or greater reduction in the above-mentioned features.

The protocol was reviewed and approved by the institutional review board. All patients provided written informed consent before being enrolled in the trial in accordance with the Declaration of Helsinki.

Patients were treated with oral lenalidomide 25 mg daily for 21 days of a 28-day cycle, and dexamethasone 40 mg orally on days 1, 8, 15, 22 of the cycle. Standard dose modification guidelines were followed for grades 3 and 4 neutropenia and thrombocytopenia. Patients received adjunct treatment with radiation therapy to painful skeletal lesions, acetylsalicylic acid 75 mg for thromboprophylaxis, and bisphosphonates. Antibiotic and antiviral prophylaxes were not administered. Treatment was discontinued after 6 cycles of treatment for all patients other than those with progressive disease. Patients who progressed during or after completion of the proposed 6 cycles were treated according to their physician's discretion. All patients who relapsed after achieving at least a PR were advised to try re-treatment with lenalidomide–dexamethasone; however, patients who could not afford the drug were allowed to proceed with treatment according to the treating physician's discretion.

Endpoints

The primary endpoint was progression-free survival (PFS) with abbreviated lenalidomide–dexamethasone. Secondary endpoints included overall survival (OS), overall response rate, time to response, time to second-line anti-myeloma therapy, and safety.

RESULTS

This study recruited 51 eligible patients over the 2-year study period. All patients were prospectively followed for a period of 5 years. Median follow-up was 66 months (range: 60–74 months), with 4 patients being lost to follow-up.

Median age in the group was 61 years (range: 38–75 years). Of the 51 patients, 17 (33.3%) were more than 65 years of age and therefore transplantation-ineligible. The 34 transplant-eligible patients (66.7%) were counselled for autologous stem-cell transplantation, but all declined for economic reasons.

The overall male-to-female ratio was 1.04:1. Median age at diagnosis was about 6 years less in the women than in the men (58 years vs. 64 years). More than 50% of the women were less than 60 years of age; only 25% of the men were less than 60 years of age. The median duration of symptoms before diagnosis was 6 months (range: 1–28 months). The median delay in diagnosis, defined as the time since the patient presented to a physician for the first time, was 2 months (range: 1–5 months).

Table 1 presents comparative clinical features for patients reported from Indian, Mayo Clinic, and Asian centres.

The most common symptoms in our patients were bone pain (85.7%) and malaise and fatigue secondary to anemia (35.7%). No patient had symptomatic hypercalcemia, cryoglobulinemia, amyloidosis, hyperviscosity symptoms, splenomegaly, or lymphadenopathy. No patient had any polyneuropathy, organomegaly, endocrinopathy, or skin changes (POEMS syndrome). The degree of bone marrow plasmacytosis ranged from 11% to 70%. Immunoglobulin G or A myeloma accounted for 70.6% of the diagnoses, and light-chain myeloma accounted for the remaining 29.4% (21.5% kappa, 7.8% lambda). Immunoglobulin G was the most common myeloma subtype at 55%. Median serum creatinine was 1.16 mg/dL (range: 0.75–2.0 mg/dL). The median glomerular filtration rate was 50 mL/min (range: 22–79 mL/min). Among patients who had serum creatinine values exceeding 1.4 mg/dL, 70% had light-chain myeloma. The distribution of stages I, II, and III disease (International Staging System) was 21.4%, 28.6%, and 50% respectively.

Only 24 patients (47%) agreed to bone marrow conventional karyotyping. Of those patients, 15 (62.5%) had an abnormal karyotype; the remaining 9 patients (37.5%) had a normal karyotype. The most common abnormalities affected chromosome 15 (trisomy and monosomy). Other anomalies noted were aneuploidy, polyploidy, trisomy 22.

Overall, 35.3% of the patients experienced grade 3 or greater nonhematologic toxicities, and 11.7% experienced grade 3 or greater hematologic toxicities. The most common grade 3 and greater nonhematologic toxicities were hyperglycemia (23.5%), fatigue (17.8%), and hypocalcemia (3.9%). A pulmonary embolism (grade 4 toxicity) developed in 1 female patient after 2 cycles of lenalidomide–dexamethasone.

She was morbidly obese. The remaining toxicities were all grades 1–2 and included constipation, anxiety, rash, respiratory infection, agitation, nausea, dyspepsia, anorexia, and stomatitis. No patient experienced transaminasemia, dizziness, or confusion. Among the patients with hyperglycemia secondary to dexamethasone, none developed ketoacidosis.

Table 2 presents a comparison of toxicities in the E4A03 trial and in our study.

Of the 2 patients taken off study (3.9%), the first withdrew consent (cycle 1), and the second experienced pulmonary embolism (cycle 2). No early deaths occurred. The remaining 49 patients (96.1%) completed the intended 6 cycles of treatment. No dose reductions were required.

In our intention-to-treat patient cohort ($n = 51$), 10 achieved a SCR (19.6%), 18 achieved a CR (35.3%), 3 achieved a VGPR (5.9%), 15 achieved a PR (29.4%), 2 had stable disease (3.9%), and the remaining 3 progressed (5.9%). The overall response rate (SCR + CR + VGPR + PR) was 90.2%. Responses were rapid, with 64.8% of patients achieving a significant response at the first planned reassessment at 3 months.

The median PFS was 16 months (range: 2–62 months). During the course of follow-up, all patients experienced biochemical relapse. At that point, re-treatment was offered. Median time to biochemical progression was 8 months. Of the 51 patients, 36 (70.6%) who, because of lack of clinical symptoms, refused re-treatment at the time of biochemical relapse were kept on regular follow-up. Subsequently, in the 6–8 months after biochemical relapse, those patients developed clinical symptoms including bone pain, anemia, and worsening renal parameters. Median time to second-line anti-myeloma therapy was 14 months. In all 10 patients (19.6%) whose relapse occurred more than 12 months after primary therapy, re-challenge with the same schedule of lenalidomide–dexamethasone achieved a second response within 3 months. After achieving a second response, patients were continued on lenalidomide 10 mg as maintenance therapy; at the time of writing, a continued response was observed in 7 of those patients. The remaining patients were treated with other anti-myeloma agents including thalidomide, bortezomib, cyclophosphamide, melphalan, and vincristine–doxorubicin–dexamethasone according to the treating physician's discretion.

The OS rate at 5 years was 62.74%. At the time of writing, the median OS was not yet reached.

At the time of data cut-off, 19 patients (37.3%) had died: 8 because of disease progression; 1 each because of domestic accident, suicide, and colon cancer; and 8 because of age-related comorbidities. No direct relation was observed between either relapse or survival and the initial depth of response to treatment.

DISCUSSION

Our study was intended to assess the utility of fixed-duration treatment with lenalidomide–dexamethasone for newly diagnosed multiple myeloma in patients who were either transplantation-ineligible or -unwilling in a resource-constrained Indian setting. In our cohort, 66.7% of the patients were transplant-eligible, but were unwilling to proceed because of financial constraints. In a large retrospective analysis of Asian data spanning 25 years (1986–2011)

TABLE I Comparative data from Indian, Japanese, pan-Asian, and Western studies

Variable	Present study	Nair <i>et al.</i> , 1993 ²	Kim <i>et al.</i> , 2014 ¹¹	Rajkumar <i>et al.</i> , 2005 ¹²	Lacy <i>et al.</i> , 2007 ¹³	Nair <i>et al.</i> , 2009 ¹⁴	Dutta, 2012 ⁹	Benboubker <i>et al.</i> , 2014 ¹⁵	Palumbo <i>et al.</i> , 2012 ¹⁶
Patients (n)	51	142	534	231	146	26	3405	869	445
Mean age (years)	61.1	61	55.4	51	51	75	62	61.5	65
Age < 40 years (%)	3.9	NR	11.7	13	12	NR	NR	4	NR
Sex (% men)	50.9	63	69	69.7	69	50	55.6	61	56.8
Bone pain (%)	85.7	NR	84	81	79	NR	NR	68	NR
Hepatomegaly (%)	10.7	NR	9.4	0	7	NR	NR	21	NR
Splenomegaly (%)	0	NR	2.4	0	NR	NR	NR	5	NR
Positive lymph nodes (n)	0	NR	1.85	0	3	NR	NR	4	NR
Anemia (%)	75	NR	62.4	59	40	NR	60.7	62	52
Renal failure (%)	28.6	NR	31.3	22	37	7.7	23.4	32	14
Hypercalcemia (%)	10.7	NR	10.3	28	11	NR	16.7	30	NR
Hypoalbuminemia (%)	50	NR	33	23	24	76.9	52	NR	NR
Skeletal abnormalities	92.9	NR	93.7	NR	96	NR	60.2	79	62
Chain type (%)									
IgG	47.1	NR	NR	NR	NR	69.2	55.2	NR	54.5
IgA	21.5					23.1	22.2		22.7
Light chain (%)	32.1	NR	NR	NR	NR	7.7	17.9	NR	NR
Stage by International Staging System (%)									
I	21.4	NR	NR	NR	NR	26.9	19.9	NR	31.1
II	28.6					53.8	36.1		38.9
III	50					19.2	44		24
Missing									16.9
Cytogenetics (%)									
Normal	37.5	NR	NR	NR	NR	NR	67.5	NR	NR
Abnormal	62.5						32.5		

NR = not reported; IgG = immunoglobulin G; IgA = immunoglobulin A.

by the Asian Myeloma Network, only 19.8% of patients underwent autologous transplantation, suggesting that, in community practice, bone-marrow transplantation is still an unaffordable treatment for many in developing nations¹¹.

In our patients, the overall response rate was a little above 90%, which is similar to the 91% reported in the Mayo Clinic experience of lenalidomide–dexamethasone in newly diagnosed myeloma¹²; however, the CR rate was significantly higher in our study. In the Mayo Clinic study, 6% of patients had a CR, and 32% had a VGPR or near-CR. In 2006, at a median follow-up duration of 36 months, the Mayo Clinic experience was updated¹³. The CR rate had improved to 18%, and the VGPR rate was 38%, for a CR + VGPR rate of 56% at 4 months, which further increased to 67% in patients who continued to receive lenalidomide–dexamethasone as

primary therapy beyond the stipulated 4-month period. In our study, reassessment at 6 months showed a 60.7% SCR + CR + VGPR rate and an overall response rate of 90.2%. Because treatment was stopped after 6 months in our study (unlike in the Mayo Clinic study), we are unable to assess any increasing depth of response with prolonged treatment. Our results are similar to those in a study by Nair *et al.*¹⁴ from northern India, who also reported a significantly higher CR rate (30% near-CR + CR) and an overall response rate of 95% in newly diagnosed patients with multiple myeloma treated with lenalidomide–dexamethasone.

At the time of our study, most Western studies had also assessed response to a fixed duration of treatment. In 2014, Benboubker *et al.*¹⁵ of the FIRST trial, which evaluated lenalidomide–dexamethasone for fixed duration of 18

TABLE II Toxicity comparison

Toxicity type	Occurrence (%)		
	ECOG study		Present study
	High-dose arm ¹⁶ (n=223)	Low-dose arm ¹⁸ (n=222)	Low-dose only (n=51)
Anemia	8	7	3.9
Neutropenia	12	20	7.88
Thrombocytopenia	6	5	3.9
Cardiac ischemia (≥3)	3	0.5	0
Hyperglycemia (≥3)	11	6.0	23.5
Infection or pneumonitis (≥3)	16	9.0	3.9
Neuropathy (≥3)	2	2	0
Thromboembolism (≥3)	26	12.0	1.9
Any nonhematologic toxicity (≥3)	65	48.0	35.3
Any toxicity (≥4)	21	14	14.3

ECOG = Eastern Cooperative Oncology Group.

weeks compared with the same treatment until progression, reported durable responses with continuous treatment. Similarly in the Multiple Myeloma 015 trial, patients in the arm with continuous use of lenalidomide experienced a better PFS even though OS was similar¹⁶.

In our study, the median PFS with 6 cycles of treatment was 16 months (range: 2–62 months). That duration is inferior to the 20.7 months reported in the 18-cycle lenalidomide–dexamethasone arm of the FIRST trial. However, the 5-year OS rate in our study population was 62.74%, which is marginally better than the 56% OS rate reported for the 18-cycle lenalidomide–dexamethasone arm in the FIRST trial. In the present study, median OS had not yet been reached at the time of reporting.

The median time to second-line anti-myeloma therapy was 14 months in our study, which is again inferior to the 28.5 months reported for the 18-month lenalidomide–dexamethasone arm and the 39.1 months reported for the continuous lenalidomide arm in the FIRST trial.

It was easy to achieve a second response with lenalidomide–dexamethasone rescue therapy in patients who had previously achieved a CR. That observation echoes results in the FIRST trial, in which patients on the 18-cycle lenalidomide–dexamethasone arm achieved a second remission with more ease.

The 35.3% grade 3 and greater nonhematologic toxicities in our study contrast with the 48% reported in the Mayo Clinic series¹⁷. The most common grade 3 toxicities included hyperglycemia (23.5%), fatigue (17.8%), and hypocalcemia (3.9%).

In 1 female patient who was morbidly obese, a pulmonary thromboembolism (proven by computed tomography angiography) developed and had to be lysed, resulting in improvement. We believe that the morbid obesity would have contributed to the occurrence of thromboembolism in this patient. No other patient experienced deep-vein thrombosis or pulmonary embolism. That finding is in stark contrast to the high (up to 17%) reported incidence

of venous thromboembolism in patients with myeloma on lenalidomide–dexamethasone therapy¹⁴. Pooled data from 6 studies involving 1125 adult patients with newly diagnosed or relapsed multiple myeloma reported that the risk of venous thromboembolism in patients on acetylsalicylic acid was 1.5 per 100 patient–cycles, with a total risk of venous thromboembolism of 10.7%¹⁸. The low risk of thromboembolic phenomena in our Indian patients is corroborated by the study reported by Nair *et al.*¹⁴, in which, of a cohort of 41 patients treated with lenalidomide–dexamethasone and routine acetylsalicylic acid prophylaxis, none developed deep-vein thrombosis.

Grade 3 hyperglycemia (fasting blood glucose ≥ 250 mg/dL) occurred nearly 4 times as often in our study as in results from the Eastern Cooperative Oncology Group (23.5% vs. 6.0%). Many epidemiology studies in urban and rural Indian populations have found a very high prevalence (up to 21.1%) and incidence (20.2 per 1000 person–years) of impaired glucose tolerance and impaired fasting glucose. This glucose intolerance is unmasked very easily by introduction of steroids for therapeutic purposes in various diseases including in multiple myeloma. That unmasking is the most likely cause for a different hyperglycemia profile in our patients.

The rate of grade 3 and greater infection was lower in our patient cohort, although the reason for that finding is not very clear. We assume that it might be attributable to herd immunity against common pathogens in the Indian subcontinent, considering the socioeconomic and living circumstances.

The reasons for a higher response rate and a different toxicity profile in our patient cohort cannot alone be explained on the basis of simple clinical variables such as age, stage, performance status, and so on. It probably is more likely attributable to tumour biology or genetic variations, or both.

Myeloma karyotypes are complex, and cytogenetic abnormalities are known to predict poor response in the

patients carrying them. Areas of common recurrent and nonrandom changes that have been noted with multiple myeloma include the 14q32 region (involving the immunoglobulin H gene) and chromosomes 1q and 13. Detection of partial or complete deletions of chromosome 13 at diagnosis or after high-dose cyclophosphamide therapy for peripheral stem-cell mobilization, followed by two autografts, has been found to portend a poor prognosis¹⁹. In our study, conventional karyotyping, which was available as an in-house facility, was carried out. Because of resource constraints, plasma-cell enrichment and fluorescence *in situ* hybridization (FISH) studies were not done. Lack of the latter tests would be a limitation to our interpretation of the cytogenetic data because, using standard metaphase analysis, abnormal karyotypes are seen in only 18%–30% of samples²⁰. With conventional karyotyping, 62.5% of patients showed an abnormal karyotype, the most common abnormalities being trisomy and monosomy of chromosome 15. Other anomalies included aneuploidy, polyploidy, and trisomy 22. None of our patients had a chromosome 1, 3, 13, or 14 abnormality. That finding contrasts with results from an Asian Myeloma Network study that reported only 32.5% abnormal cytogenetics¹¹. Hyperdiploidy in myeloma is known to be associated with good prognosis and is characterized by trisomies of chromosomes 3, 5–7, 9, 11, 15, 17, 19, and 21 by both metaphase cytogenetics and FISH²¹.

The limitations of our study are twofold. Both relate to economics and logistics. The first limitation is the lack of immunofixation studies, which are the basis for assessing response in both the International Myeloma Working Group and the European Group for Blood and Marrow Transplantation criteria. In our study, response was instead assessed by quantitative serum immunoglobulin levels and serum free light-chain estimations. Those measures are definitely cruder than immunofixation methods and might be responsible for the higher response rates reported in our study. The second limitation is the use of conventional karyotyping and the lack of FISH studies. At the time of the study, immunofixation and FISH analyses were scarcely available and carried an exorbitant cost for the average Indian patient.

Because this trial was designed before the advent of the routine use of maintenance therapy, we cannot comment on the survival benefits of maintenance lenalidomide.

CONCLUSIONS

Lenalidomide–dexamethasone is an effective first-line treatment for patients who, in an economically constrained environment, are newly diagnosed with multiple myeloma and are not candidates for transplantation. However, short-duration treatment is suboptimal, and patients should be advised to take continuous treatment with these agents.

ACKNOWLEDGMENTS

We acknowledge the support of Natco Pharma, India, who provided lenalidomide free of charge to all the patients enrolled in this study. Natco Pharma had no role whatsoever in the planning, execution, or final writing of this study.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none. The

trial was an independent initiative by the principal investigator (WMJ); the drug sponsor had no influence on trial design, data analysis, or manuscript preparation.

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