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Article *in* Hematology · May 2016

DOI: 10.1080/10245332.2016.1182695

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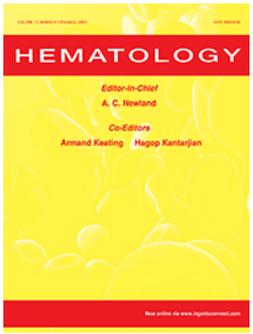

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Hematology

ISSN: 1024-5332 (Print) 1607-8454 (Online) Journal homepage: http://www.tandfonline.com/loi/yhem20

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To cite this article: David Gómez-Almaguer, Olga G. Cantú-Rodríguez, Cesar H. Gutiérrez-Aguirre & Guillermo J. Ruiz-Argüelles (2016): The treatment of CML at an environment with limited resources, Hematology, DOI: 10.1080/10245332.2016.1182695

To link to this article: http://dx.doi.org/10.1080/10245332.2016.1182695

Accepted author version posted online: 27 Apr 2016.
Published online: 24 May 2016.

The treatment of CML at an environment with limited resources

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Objectives: This article reviews clinical experiences in the treatment of chronic myeloid leukemia (CML) in an environment of limited resources.
Methods: We reviewed recent publications on Pub med and abstracts from mayor congresses relevant to the disease.
Results: CML is a hematological neoplasm observed more frequently in adults, regardless of their socioeconomic status. Until recently, available treatments improved patients' quality of life but did not modify survival. It was not until interferon appeared that patients received a drug that reduced and even eliminated Philadelphia chromosome-positive (Ph+) cells.
Discussion: With the start of the new millennium, the International Randomized Study of Interferon-α plus cytarabine versus STI571 (IRIS) trial demonstrated a dramatic improvement in survival by comparing imatinib versus interferon alpha plus cytarabine. The Food and Drug Administration (FDA) approved imatinib as first-line treatment for newly diagnosed CML in 2001 due to its outstanding effectiveness. Years later, three second-generation (dasatinib, nilotinib, bosutinib) and one third-generation (ponatinib) tyrosine-kinase inhibitors (TKIs) were developed and approved. These highly effective treatment options, however, are not affordable for many low-income patients. Additionally, the use of drugs that effectively treat but do not cure the disease has resulted in an important economic impact for patients and health care systems worldwide, especially those in developing countries. Imatinib is the least expensive and a very effective TKI in many low-income countries. Early allogeneic stem cell transplantation must be considered in the management of selected patients before CML transformation.

Keywords: Chronic myeloid leukemia, Imatinib, Low-income, Generic, Allogeneic stem cell transplantation, Complete cytogenetic remission, Nilotinib, FISH

Introduction

Before the year 2000, chronic myeloid leukemia (CML) treatment was based on the use of busulfan, hydroxyurea, and interferon alpha.[1] At that time, the treatment with the highest potential for disease-free survival and cure was allogeneic stem cell transplantation (Allo-SCT); however, this procedure was not free of important morbidity and mortality, and thus was reserved for younger patients with an human leukocyte antigen-identical related donor. Imatinib mesylate changed the panorama for CML.[2] In most cases, a high response rate with prolonged survival can be obtained. Transformation to accelerated or blast phase has been reduced to 1–1.5% per year, compared to over 20% in the pre-imatinib era.[3] However, achieving these results depends on continuous drug intake. The use of an expensive drug, which effectively treats but does not cure the disease, has increased the prevalence of CML with an important economic impact for patients and health care systems worldwide, especially in developing countries.[4] Affording treatment is not the only problem when economic conditions are not ideal; accurate diagnosis and subsequent monitoring of the disease by the detection of the Ph+ or BCR/ABL transcript require specialized and expensive equipment.[4,5]

Unfavorable circumstances are found in most developing countries, which include 80% of the world's population according to the United Nations. Cases where hematologists initiate treatment taking into account only symptoms, signs, complete blood count and blood film findings are commonplace. In some circumstances, the hematologist is forced to use outdated treatments such as busulfan or hydroxyurea until access to tyrosine-kinase inhibitors (TKIs) is obtained.

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DOI 10.1080/10245332.2016.1182695

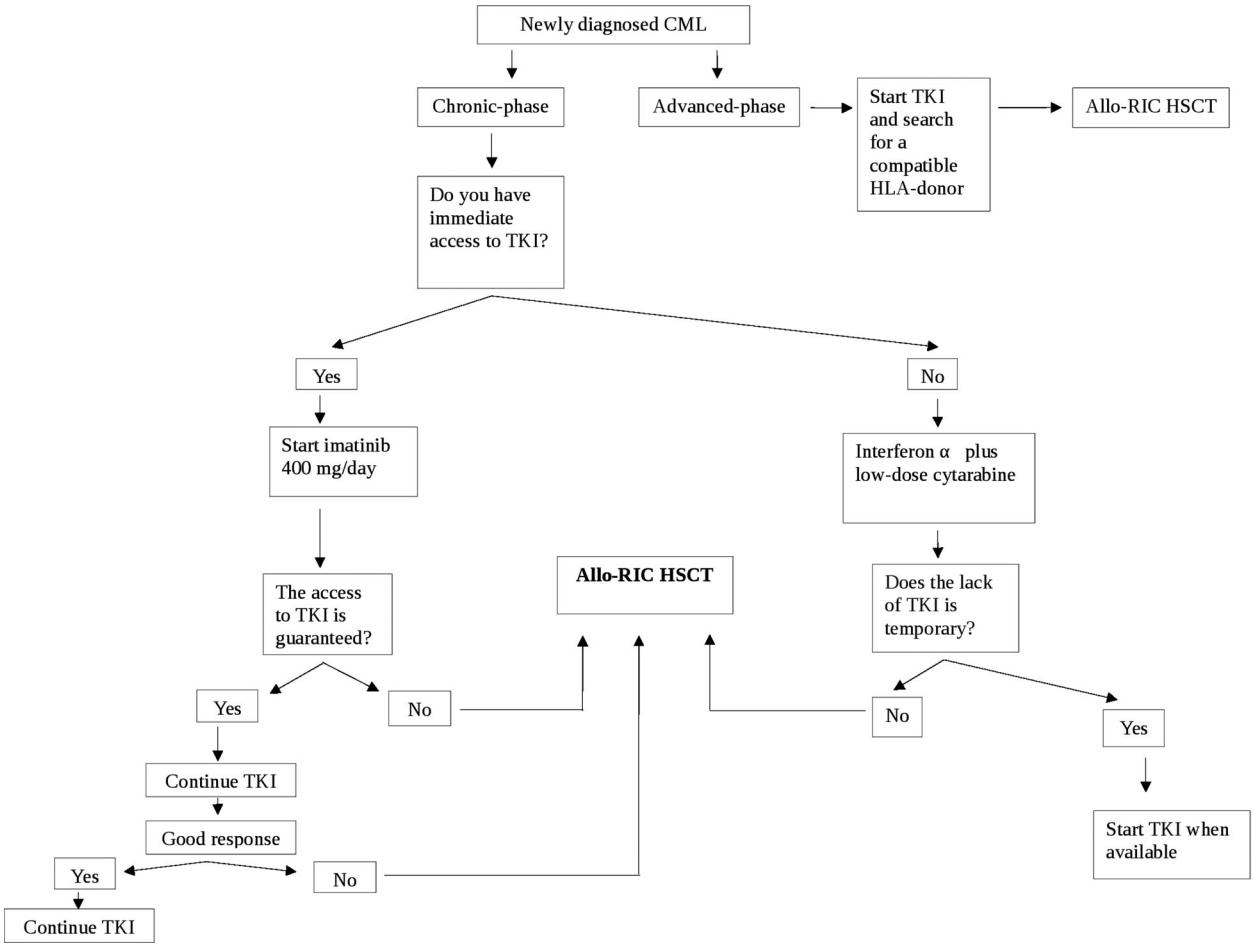

Figure 1 Proposed schema for newly diagnosed CML patients treatment based on drug availability in an environment with limited resources.

This article describes our experience in the diagnosis and treatment of CML in an environment that lacks ideal resources.

Diagnosis

The combination of an elevated white blood cell count and an enlarged spleen is very suggestive of CML. The blood smear usually reveals eosinophilia, basophilia, and a normal or elevated platelet count. The amount of blasts and basophils in blood and marrow must be determined for disease staging. Many patients are initially treated using this simple information, but correct diagnosis requires demonstration of Ph+ through conventional karyotyping or by fluorescent *in situ* hybridization (FISH), or determination of the BCR-ABL hybrid gene by polymerase chain reaction (PCR) techniques.[5] Good quality cytogenetic analysis can be found in most hospitals. On the other hand, FISH is a faster technique, which is why it is preferred in some cases. In a Mexican institution, FISH was found to be more useful technique compared with cytogenetics for initial diagnosis.[6] However, in a survey run by Latin America Leukemia Net, cytogenetics was still the preferred method for initial diagnosis (78%), whereas FISH was preferred by only 26% of 435 hematologists and oncologists.[7] PCR is usually more expensive and not easily available, but it is most helpful for minimal residual disease monitoring and should be considered a priority for optimal treatment follow-up.[5] It is noteworthy that commercial PCR kits allow detection of common translocations but fail to amplify rare variants (b3a3, b2a3). This can generate false negative results and an impression of complete molecular response (CMR) later on.[8] Therefore, assessment of the BCR-ABL transcript by PCR at diagnosis is important to establish the type of fusion present.

Cytogenetics or FISH are good options for monitoring in places where PCR is not available. After diagnosis patients must be staged into chronic (CP), accelerated (AP), or blast phase (BP).[9] In our center, patients who present in AP or BP are usually treated with imatinib and the search for a stem cell donor is initiated. If the patient is in CP, risk evaluation should be performed. Several risk stratification scores have been published including Sokal, Hasford, and EUTOS.[10] We prefer the Sokal score because only age, spleen size, platelet count, and peripheral blast cell count are required.[11] The new EUTOS score is simple, only basophil percentage in peripheral blood and spleen size is

required. It has been designed for patients treated with imatinib, but there are doubts regarding its validity.[12] In a study by Jabbour *et al.*,[13] the EUTOS score was not predictive of outcome or survival. In selected cases, high-risk patients could be initially treated with higher doses of imatinib or, if available, a second-generation TKI Figure. 1.

Monitoring

Around two thirds of CML patients will have a good response to imatinib. In this setting, it is of great importance to provide continuous optimal therapy, achieve good adherence, treat common adverse events and have adequate monitoring. When there are multiple good quality monitoring options available, cytogenetics and PCR are the ideal methods. Bone marrow cytogenetics is considered the 'gold standard', and a complete cytogenetic response is clearly associated with improved survival. Additionally, this method can demonstrate other chromosomal abnormalities, some of which can predict resistance, an advantage over FISH or PCR. Performing PCR from a peripheral blood sample every 3–6 months, at least for the first year, is important as long-term outcomes can be predicted by very early responses (3 months). For patients with BCR-ABL1 > 10% IS increasing the imatinib dose or switching to a second-generation TKI should be considered. In the case of a young patient (<45 years), the search for a stem cell donor should begin when the possibility of gaining access to a second-generation TKI is low.

In our practice, we have frequently been forced to use FISH for monitoring. This study, correlates well with cytogenetics, is faster and can also be performed on a peripheral blood sample. When FISH, and/or PCR become negative for the Ph+, we recommend performing these studies every 6–12 months thereafter. Because of its increased sensitivity PCR is preferable to FISH for monitoring after achieving a complete response. Nevertheless, FISH is an option if PCR is not available or affordable. In a survey of 435 Latin American hematologists/oncologists on monitoring responses, 72% reported routinely using cytogenetics, only 59% used PCR, 30% used mutational analysis, and 19% used FISH. Interestingly, 13% of hematologists reported never using PCR.[7] In a recent study from the United States, Di Bella *et al.* analyzed molecular and cytogenetic response assessment patterns in 300 patients who received first-line imatinib, dasatinib, or nilotinib in a community setting and found that 40% of patients never had any cytogenetic or molecular monitoring at any time.[14]

Initial treatment

Second-generation TKIs such as dasatinib or nilotinib have been suggested as the ideal initial CML treatment. Comparative phase III studies like DASISION[15] and ENESTnd[16] have shown initial superiority for both dasatinib and nilotinib versus imatinib. Nevertheless, the cost of this strategy has an important economic impact. It is essential, when treating patients in low-income countries, to emphasize that imatinib is highly effective as a first-line treatment for CML, and according to the data of the IRIS study, an overall survival (OS) rate of 86% was obtained.[2] Imatinib has a good safety profile, thousands of patients take it daily, and in many cases have been doing so for over 15 years. Many may complain of gastrointestinal discomfort, fluid retention, muscle cramps, and soreness, yet, in our experience only a few will eventually discontinue treatment. In a study that included 832 patients who had been on imatinib treatment for a median of almost six years only 2.3% discontinued the drug, OS was not significantly different from the general population and CML was the cause of death in only six patients.[17] In another study from Italy that included 559 newly diagnosed CP patients treated with front-line imatinib the 6-year OS was 89% and only 5% of the patients were considered as having a leukemia-related death.[18] In the setting of imatinib adherence, in contrast with a British patient group with a reported adherence rate of 97.6%,[19] our experience with a group of 38 patients receiving the drug at no cost, adherence was poor. We found that 95% of patients had an adherence rate below 85%. No association with age or gender was found, however, educational level (median 8 years of school attendance) was lower in contrast to other studies, and this may have had an impact on these findings.[20] In this scenario, Rego *et al.*,[21] from Brazil, also showed that low educational level but not low income has an impact on achieving cytogenetic remission.

In the ENESTnd study, nilotinib achieved a greater cytogenetic and molecular response at a dosage of 300 or 400 mg twice a day, compared to imatinib at 400 mg daily. However, not everything favors nilotinib as it can cause serious vascular events and an increase in glycemia, lipase, and hepatic enzymes.[16,22] Other aspects to consider are convenience and adherence since nilotinib must be administered twice daily and its absorption is affected by food.[16] Moreover, its cost is higher than imatinib,[23] and most importantly, a survival benefit has not been demonstrated so far.

Dasatinib is the most potent of the three most studied TKIs.[15] It can be administered once a day without compromising efficacy, and its absorption is not affected by food. The drug is usually well tolerated; however, the development of pleural effusion and pulmonary hypertension are major concerns.[24] As would be expected, these patients used more

health-related resources and thus costs increased. The DASISION study was designed to compare up-front dasatinib verus imatinib. In this study dasatinib 100 mg was more effective than imatinib 400 mg daily. Earlier molecular remissions were obtained with a lower rate of progression. But as was the case with nilotinib, no survival advantage was demonstrated. Additionally, the cost of dasatinib in Mexico is higher than both imatinib and nilotinib (Table 1). It is noteworthy that low doses of dasatinib have been used without compromising its efficacy.[25] Since dasatinib has 100–300-fold activity compared to imatinib, a reduced dose (50 mg per day) could be sufficient for optimal response at cost similar to full-dose imatinib as front-line treatment, making this an attractive option that warrants further investigation.

We believe that imatinib is the most cost-effective drug for starting treatment in patients with chronic-phase CML who are in unfavorable economic circumstances. Clinicians throughout the world are more familiar with this TKI, and more importantly, generic imatinib is already available in many countries. This will reduce the cost burden of long-term therapy. We usually initiate imatinib at 400 mg per day Figure. 1. However, in selected high-risk patients, unless there is another TKI, high-dose imatinib (600–800 mg/day) is expected to result in higher rates of complete cytogenetic and molecular responses.[26] In a study by Cortés *et al.*, in 115 patients with CP-CML the MMR was 48% at six months and CMR 39%, while only 10 patients discontinued imatinib because of adverse events.[27] It is important to be aware of the economic impact of these higher doses with the associated risk of lower tolerance and adherence.

Generic imatinib

In Mexico the cost of one year of imatinib (Gleevec®) is less than $30 000 USD dollars, whereas in the United States is $92 000 USD per year. In the United Kingdom imatinib costs $33 500 USD. In both the United States and Mexico nilotinib and dasatinib are more expensive than imatinib.[28] Generic imatinib is already available in several countries, and it appears to be as effective and safe as the original molecule. In a recent study from Turkey,[29] two groups of CML patients received the same dose of generic or original imatinib, 400 mg per day. One group switched from Gleevec® to generic and after a median follow up of 63 months this group was not inferior to the original drug group of patients in relation to tolerance and efficacy. Similar information has emerged from India and elsewhere.[30,31] The imminent availability of generic imatinib will make this drug even more attractive to the health authorities worldwide. Imatinib should be considered the drug of choice at least for low risk CML patients.

Table 1 Cost of CML treatment in Mexico using a tyrosine-kinase inhibitor

Drug	Dose	Cost per year (USD)
Imatinib 100 mg	400 mg/day	21 754.00
	600 mg/day	32 631.00
	800 mg/day	43 508.00
Nilotinib 150 mg	600 mg/day	27 972.20
Dasatinib 50 mg	100 mg/day	41 318.00
Ponatinib	45 mg/day	Not available in Mexico

Allo-HSCT in the TKI era

Therapeutic options for CML have changed in the last 12 years. The number of Allo-HSCT performed has decreased markedly in developed countries and imatinib and other TKIs have replaced this procedure as the first-line therapy for CML patients.[32] However, this is not so true for less fortunate patients living in developing countries where imatinib and other TKIs costs can be prohibitive. Thus, it is cheaper to perform Allo-HSCT than to provide imatinib for many years. In China, Mexico, Eastern Europe, and other Latin American countries costs favor Allo-HSCT, since this is a 'once in a lifetime' procedure compared to lifelong therapy with a TKI.[33,34] The annual cost for imatinib in China is $41 000 USD, but economically disadvantaged patients may be eligible to receive partial financial help from the national health system. Nonetheless, patients are still responsible for covering $10 300 USD per year.[34] On the other hand the cost of an Allo-HSCT is between $20 000 USD and $30 000 USD. In a cohort of 46 Chinese patients who underwent myeloablative Allo-HSCT with a low EBMT risk score, the estimated probability of OS and event free survival (EFS) was 91% after a median follow up of 43 months.[34] In Mexico a year's worth of imatinib costs around $21 754.00 USD compared to Allo-HSCT at $12 000–18 000 USD if reduced intensity conditioning (RIC) is employed.[33,35] In our experience, 72 patients were followed during a six-year period, among these 50 were treated with TKIs and the remainder were transplanted, with a projected 90-month OS of 84 and 77%, respectively. It is noteworthy that 21 of 22 allografted patients chose transplantation because they were unable to afford the high cost of long-term TKI treatment.[33] The safety and effectiveness of Allo-SCT are continually improving and thus every health care system must consider it an option in a context of cost-effectiveness when compared with TKI treatment.

Factors to consider in Allo-HSCT

Several factors influence patients' outcomes after undergoing Allo-HSCT including age, disease stage, and treatment response; stem cell donor and source;

and type of conditioning used. In the pre-TKI era, the major factor influencing transplantation outcomes was disease phase at time of transplant, with patients in advanced phase faring poorly (a fact which remains unchanged).[35] Allo-HSCT is still preferred for patients in the more advanced phases of the disease. Imatinib has proven EFS and OS at 6 years of 83 and 88%, respectively,[36] versus OS at 5 years in patients who underwent Allo-HSCT ranging from 75 to 87% depending on the patient's clinical condition and disease stage.[37] Patients transplanted within the first year after diagnosis had better OS and disease-free survival, which meant that earlier transplantation was favored.[38]

An important factor when considering transplantation is age, taking into account that this disease occurs most often in adults with a median age of 62 years. This may represent an obstacle especially if myeloablative conditioning schemes are used. Nevertheless, age at diagnosis from low and middle-income countries appears to be lower than that found in developed countries, with a median age ranging from 37 to 38.5 years; this may allow more patients to be considered for Allo-HSCT.[6,39]

CML has been thought of as a disease with an increased susceptibility to graft-versus-leukemia effects, which suggests that RIC might be at least equal to myeloablative conditioning as it is associated with a lower TRM.[33,40] Other benefits exist when using RIC, including the possibility of outpatient management, fewer hospitalizations and reduced costs, making it an attractive option for developing countries. In a study by Or *et al.*[40] OS was 85% at 5 years using this strategy.

Allografting must be considered not only as salvage treatment in advanced disease stages, but also as a valid early treatment alternative for young selected patients without access to long-term TKI therapy. Our results show an OS equal to that observed in our patients treated with TKI. Despite that the incidence of acute and chronic graft versus host disease is around 50% (Table 2) its most severe form is less frequent. It is worth mentioning that 10% of patients experience grade II–IV aGVHD and 8% have extensive cGVHD.[41–42] Finally, another important issue to consider is quality of life, in a recent Chinese study it was concluded that long-term CML-CP survivors receiving allo-SCT can attain desirable quality of life comparable to or better than that of patients receiving imatinib.[34]

TKI treatment expectations

Imatinib and the new TKIs are capable of long-term leukemic control or molecular remission in the majority of CML patients; however, lifelong treatment is considered to be necessary. International guidelines recommend indefinite continuation of TKI treatment in all responding patients. The cost of many years of imatinib treatment is substantial. In Mexico 20 years worth of imatinib is around $435 000 USD. Therefore, the possibility of stopping therapy without serious risk of transformation/complications in an expensive chronic disease is appealing, especially in an economic environment with limited health resources. In the French Stop Imatinib trial (STIM) in 100 patients, 41% were still in CMR after a 12 month follow-up, moreover, all patients who relapsed responded again to imatinib. It was concluded that imatinib can be safely interrupted in patients with a CMR of at least 2 years.[43] In a recent evidence-based mini review presented at the American Society of Hematology meeting in 2013, seven prospective and two retrospective trials were analyzed; it was concluded that selected patients, perhaps half of them, may remain treatment-free for a long period of time.[44] The information in relation to dasatinib and noilotinib discontinuation in CML-CP is limited,[45] but since these drugs are more potent than imatinib and capable of producing higher CMR rates, it is reasonable to expect similar or better long-term results after discontinuation of these second-generation TKI. We can assume that cure is possible in a subset of CML patients, but further identification of this subgroup is necessary. In our institution we are now halting imatinib in selected patients who have been in CMR for more than 2 years. Therefore, the availability of PCR is crucial for this purpose and it

Table 2 Comparison of two treatment options in patients with CML: Allo-HSCT verus TKI

Trial ID	*n* =	Treatment received (*n* =)		Age (median)	OS%	PFS%
Ruiz-Argüelles *et al.*	72	Allo-HSCT	22	38	77 (6y)	NA
		TKI	50	39	84 (6y)	NA
Qian Jiang *et al.*	132 AP	Allo-HSCT	45	34	83.3 (6y)	92.5 (6y)
		Imatinib	87	44	51.4 (6y)	48.3 (6y)
Xu *et al.*	93 AP	Allo-HSCT	60	NA	86.4 (5 y)	78.1 (5y)
		TKI	33	NA	42.9 (5y)	28.6 (5y)
Hamidieh *et al.*	33	Allo-HSCT	14	12.8	84 (2y)	59 (2y)
		Imatinib	19	9.5	87 (2y)	82 (2y)

Allo-SCT, allogeneic stem cell transplantation; TKI, tyrosine-kinase inhibitor; AP, accelerated phase; OS, overall survival; PFS, progression free survival; aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease.

is also very important for after-therapy monitoring. This practice should become more frequent in countries where the resources for long-term TKI therapy are not available.

Summary

The majority of CML patients in the developing world do not have easy access to long-term TKI treatment. Until last year, thousands of patients living in low and middle-income countries were treated using free-of-charge imatinib provided by the Gleevec International Patient Assistance Program initiative (GIPAP).[46] With the end of this program (March 2015), forced by the worldwide arrival of the generic drug, many patients will require new therapeutic strategies.

Hematologists working in a limited-resource environment must be creative. The use of generic imatinib must be weighed against the option of early Allo-HSCT in patients with a compatible donor if long-term TKI treatment is unavailable.[3] Another strategy that should be considered is TKI discontinuation in patients who meet the selection criteria. All of these considerations should be taken into account not only to decide the treatment of an individual patient, but also to design and implement healthcare policies in the developing world.

Disclaimer statement

Contributors All should be cited as Authors.

Funding None.

Conflict of interest There are no conflicts-of-interest.

Ethics approval None.

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