Targeting acute myeloid leukemia stem cells: a review and principles for the development of clinical trials

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ABSTRACT

Despite an increasingly rich understanding of its pathogenesis, acute myeloid leukemia remains a disease with poor outcomes, overwhelmingly due to disease relapse. In recent years, work to characterize the leukemia stem cell population, the disease compartment most difficult to eliminate with conventional therapy and most responsible for relapse, has been undertaken. This, in conjunction with advances in drug development that have allowed for increasingly targeted therapies to be engineered, raises the hope that we are entering an era in which the leukemia stem cell population can be eliminated, resulting in therapeutic cures for acute myeloid leukemia patients. For these therapies to become available, they must be tested in the setting of clinical trials. A long-established clinical trials infrastructure has been employed to shepherd new therapies from proof-of-concept to approval. However, due to the unique features of leukemia stem cells, drugs that are designed to specifically eliminate this population may not be adequately tested when applied to this model. Therefore, in this review article, we seek to identify the relevant features of acute myeloid leukemia stem cells for clinical trialists, discuss potential strategies to target leukemia stem cells, and propose a set of guidelines outlining the necessary elements of clinical trials to allow for the successful testing of stem cell-directed therapies.

Introduction

Outcomes for adults with acute myeloid leukemia (AML) are poor, with a long-term overall survival (OS) of only 40-50% for younger patients and a median OS of less than one year for older patients.[1] The addition of therapies to the standard remission induction regimen of infusional cytarabine with intermittent dosing of an anthracycline (7+3) has not resulted in added benefit.[2] It has recently been recognized that leukemia stem cells (LSCs), which are capable of giving rise to identical daughter cells as well as differentiated cells,[3] perpetuate and maintain AML.[4,5] LSCs have different properties than the bulk AML population, making them difficult to eliminate with standard chemotherapy, and therefore a source of disease resistance and relapse.

Due to a more sophisticated understanding of the nature of LSCs, we are entering an era in which it will be possible to specifically target this population with novel therapies. Because of the unique properties of LSCs, including their established lack of responsiveness to conventional therapies, the structure of these clinical trials warrants special consideration. The optimal design will achieve the appropriate balance between allowing for an investigation into the degree to which a novel therapy targets the LSC population while also allowing for the best possible clinical outcome for participating patients.[6] This design is not intuitive, and we believe current clinical trial templates used to pilot novel therapies are insufficient to test drugs that purport to target LSCs.

Review of leukemia stem cells

The idea that a small population of stem cells, sharing the properties of differentiation, self-renewal and homeostatic control, allows for the maintenance and propagation of cancer was first introduced decades ago[7-9] and has been more fully characterized in recent years.[10] AML was one of the first diseases in which the existence of cancer stem cells, using xenogeneic transplantation models, was proven,[11,12] and consequently, human AML LSCs represent the most well characterized cancer stem cell population.[13]

Starting in the mid-1990s, it became possible to identify the LSC population by immunophenotype.[11] This technology, enhanced by NOD/SCID mouse xenotransplant models and lentivirus-mediated clonal tracking, further characterized LSC properties and led to the observation that they have many features in common with hematopoietic stem cells (HSCs),[14-17] including self-renewal capabilities and engraftment potential.[18,19] Initial *in vitro* and *in vivo* studies suggested that both normal and malignant stem cells are negative for expression of lineage markers (Lin^-), and are $CD34^+$, $CD38^-$.[3,12,14,20,21] Subsequent studies have shown that the LSC phenotype is more complex, with aberrant expression of various markers occurring sporadically among individual patients and/or as a consequence of disease pathogenesis.[22,23] Importantly, LSCs and HSCs have some critical differences in functional properties,[10,21,24-30] allowing for a therapeutic index that would permit the targeting of LSCs without resulting in toxicity from the elimination of HSCs, which maintain normal hematopoiesis.

LSCs perpetuate the leukemia population, have proliferative capacity, and are functionally defined by their ability to transplant the disease into immunodeficient mouse models.12,28 Despite the heterogeneity of AML, LSCs generally give rise to AML in secondary recipients with a similar phenotype as observed in the original patient.[31]

Although there is notable inter-patient variation, the fre-

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quency of LSCs, as defined by their ability to initiate leukemia in a xenograft model, is typically quite low.[12,32] Therefore, it is thought that AML, like the hematopoietic system as a whole, is in most cases organized as a hierarchy, relying on self-renewing LSCs at the apex to initiate and maintain the overall AML population. The majority of AML cells are comprised of poorly differentiated blasts, which are replenished by the LSC population but are biologically dissimilar, making them difficult to target with the same approach that allows for the effective elimination of the bulk population.

LSCs, like HSCs, are heterogeneous,[17,22,33] which may partially explain the controversy regarding whether AML arises directly from HSCs or from more mature precursors downstream of HSCs.[34,35] The development of more effective immunodeficient xenograft models, which allow for a higher resolution to detect smaller populations of LSCs, has made it clear that, in some cases, LSCs are present in several different phenotypic compartments.[23] Therefore, it is now widely understood that LSCs can vary with respect to CD34 and/or CD38 expression.[22,36,37] This heterogeneity applies in both inter- and intra-patient comparisons.[38] Therefore, in the development of targeted approaches, it is critical to recognize inherent LSC heterogeneity and to strive for therapies that will be effective towards all LSCs irrespective of such differences.

Targeting leukemia stem cells

The importance of minimal residual disease (MRD) as a prognostic factor for relapse and adverse outcomes in AML is clear.[39-45] Because the MRD population highly resembles the diagnostic disease population, and due to the propensity for MRD positivity to correlate with disease relapse, it is likely that the MRD population contains LSCs.[39,46] Therefore, it stands to reason that treatments that focus on elimination of LSCs will reduce MRD and improve outcomes for patients with AML.

LSCs are mostly quiescent in the G0 phase of the cell cycle[29,47] and may also home to bone marrow microenvironments in which they are protected from apoptosis;[48] they are, therefore, only minimally impacted by conventional chemotherapy that targets dividing cells.[3,29,48-51] Therefore, strategies designed to target this stem cell microenvironment may be effective.[52,53] In contrast, the highly proliferative bulk AML population can be targeted by conventional chemotherapy.[17,29,54] allowing for complete remission rates of 50-75%.[55] However, relapse is common, and the majority of AML patients die of their disease, providing clinical evidence that LSCs are rarely effectively targeted with conventional chemotherapy.[28,55] An understanding of the vulnerabilities of LSCs, as well as how they differ from HSCs and the bulk population, is required for the development of targeted and curative therapies.

The observation that treatments that eliminate bulk disease do not target LSCs is important, and lessons related to this can be extrapolated from experiences understanding and treating chronic myelogenous leukemia (CML). CML, like AML, arises from rare stem cells, which differentiate and constitute the bulk population.[56] Unlike their differentiated progeny, CML stem cells are not sensitive to the anti-BCR-Abl tyrosine kinase inhibitor imatinib (Gleevec®, Novartis).[57] While this may be due to overexpression of ABC transporters that block uptake of imatinib into stem cells,[58-61] decreased BCR-Abl expression in the stem cell compartment[62] or a lack of dependence on BCR-Abl for stem cell survival,[63] this differential treatment effect must be considered when designing curative therapies, which, based on this observation, would not be a predicted outcome from imatinib or other related tyrosine kinase inhibitors. However, it should be noted that recent studies reporting on the ability of imatinib to be successfully discontinued in selected patients[64] suggests that LSC eradication may not be an absolute necessity for the long-term control of this disease.

Interferon-alpha (IFN) is less active against CML colony-forming units than imatinib but more toxic to CML progenitors, and clinically, IFN results in a slower, but perhaps more durable, response,[63] suggesting there is superior curative potential for drugs that target LSCs.

Experiences with treatments for multiple myeloma also provide a useful paradigm for considering strategies to target AML LSCs. It has been established that several clinically effective but non-curative treatments (bortezomib lenalidomide) do not target the myeloma stem cell compartment,[65,66] while the anti-CD20 monoclonal antibody rituximab, which is active in targeting myeloma stem cells but not mature plasma cells,[65] was ineffective in clinical studies when used as a single agent.[67,68] Therefore, a challenge for the field is that therapies that fail to target LSCs may result in transient responses, while those that are only effective against the stem cell compartment may be difficult to evaluate due to the presence of large numbers of bulk tumor cells.

It is for this reason that the use of agents to treat stem cell-derived diseases that do not eliminate stem cells is comparable to mowing a lawn full of dandelions; this act can eradicate the weeds to visual inspection, but without impacting the roots, it is expected to be a temporary solution.[56,69] The corollary to this, however, is that an initial treatment focusing only on the dandelion roots would be significantly more time consuming and labor intensive, and in the face of a rapid proliferation of dandelions, may not be effective in a time frame that would prevent the entire yard from being overrun.

A further challenge to designing and testing LSC-directed therapies is that LSCs are more similar to HSCs than they are to their own differentiated progeny,[11] and, therefore, the potential toxicity to HSCs from agents intended to be LSC-directed therapies must be considered. Pre-clinical assessments of HSC-related toxicity should ideally be performed in animal models,[6] in which the ability of an agent to inhibit leukemia repopulation and spare normal engrafting cells can be examined.[51] In human studies, precautions related to monitoring hematologic toxicity as a surrogate for HSC-related off-target effects should be built into clinical trial designs when testing these agents.

It has been shown that AML patients with a greater number of LSCs or a more prevalent stem cell phenotype at diagnosis have inferior clinical outcomes compared to those who had fewer LSCs or a less prevalent stem cell phenotype.[23,70-75] Therefore, there are many reasons why it is logical to attempt to develop therapies that specifically target this population.

LSC-targeting strategies are appealing because targeting the initiating mutation or pathway in the LSC population can result in disease regression even after clonal evolution has occurred.[76] However, due to the heterogeneity of the LSC compartment, the best potential target would be one

that is a conserved feature of this population. The self-renewal properties of LSCs, which depend on the activation of pathways such as WNT/β-catenin, NOTCH and Hedgehog,[18,24] may represent such targets. Strategies that inhibit NFκB signaling and induce oxidative stress can also target LSCs,[51,77] Developing therapies that inhibit antigens, such as CD123, CLL-1, CD44, CD96 and CD47,[26,75,78-81] or kinases, such as c-Kit or SRC family kinases,[33,82-84] that are more highly expressed on LSCs than HSCs, may be effective. Finally, BCL-2 is over-expressed in LSCs and represents an attractive target.[30] A summary of potential LSC targets, inhibitors and related clinical trials is provided in Table 1.

Therapies that target both LSCs and the bulk population would be ideal but may not be practical because of the critical differences between these populations. At the same time, off-target effects that result in toxicity to HSCs may not be acceptable. Therefore, the equation that determines the therapeutic window for treatments that target LSCs must consider the degree to which an LSC-directed therapy targets the bulk population as well as the degree to which an LSC-directed therapy targets normal HSCs.

Table 1. Leukemia stem cell targets, potential interventions that correspond to each target, and related active and recruiting clinical trials (*accessed from clinicaltrials.gov*).

Putative LSC target	Potential intervention(s)	Active and recruiting trials
Hedgehog signaling pathway	Small molecule inhibitors of pathway regulators (e.g. Smoothened)[85]	NCT01841333, NCT01546038, NCT01842646
NFκB Signaling/induction of oxidative stress	Parthenolide, bortezomib[29,51,77,86]	NCT01174888, NCT01861314, NCT01127009, NCT01534260, NCT01371981, NCT01736943, NCT01075425, NCT00410423
MLL	EPZ-5676 (inhibitor of DOT1-L)[87]	NCT01684150
CLL-1	Monoclonal antibody[80]	
CD44	Monoclonal antibody[78]	
CD47	Monoclonal antibody[75]	
CD33	Antibody-based (gemtuzumab ozogamicin, SGNCD33A, actinium-225 labeled HuM195), chimeric antigen receptor (CART33), others in development[26,79,91]	NCT01902329, NCT01864902, NCT00672165, NCT01869803
CD96	Monoclonal antibody[81]	
IL3 Receptor-α (CD123)	Diptheria toxin-IL3 fusion protein; CSL362 (monoclonal antibody)[26,79,91]	NCT00397579 NCT01632852
c-KIT; SRC Family Kinases	Dasatinib[82], RK-20449 (HCK inhibitor)[84]	NCT00892190, NCT01876953,
BCL-2	ABT-199, oblimersen sodium (inhibitors of BCL-2)[30,92,93]	NCT01994837

Principles of targeting LSCs in the context of clinical trials

Improvements in outcomes for adult AML patients over the past several decades are most likely attributable to advances in supportive care, intensification of therapies in subsets of patients, and the ability to extend allogeneic stem cell transplantation to an increasingly older population while managing complications more efficiently. Outside of these advances, there has been little progress in therapeutic strategies, and standard AML regimens likely only provide effective targeting of LSCs for a minority of patients. Buoyed by an improved understanding of the biology of LSCs, and a drug development pipeline that allows for more specific targeting of molecules and pathways, we are entering an era in which it is possible to consider the specific elimination of the LSC population with curative intent. We believe that there are a multitude of nuances that must be considered when testing these strategies in the context of clinical trials. We are also concerned that due to the differential sensitivities of LSCs and blast cells, attempts to simply extend the current clinical trial templates to test LSC-directed therapies will result in studies that arrive at inaccurate, and very likely, falsely negative, conclusions. Therefore, we believe, in these early days of attempting to clinically test LSC-directed therapies, that it is important to consider new principles that must be incorporated into these clinical trials so as to maximize our ability to accurately test these new and important therapies.

Principle 1: quantification of LSC-targeting ability in patient samples

Any clinical trial purporting to target or eliminate LSCs must be designed to allow for LSC frequency to be evaluated in patient samples. As previously stated, due to the differential sensitivities between the bulk and LSC populations, the response of the bulk disease cannot be used as a surrogate for the response of the LSC population. This typically will require scientific correlative studies, as reliance on clinical-grade sampling can result in reports of complete molecular responses even in the presence of viable LSCs.[62]

Primarily, pre-clinical modeling of LSCs after *in vivo* exposure to the investigational agent, using immunodeficient mice, should be considered. During the clinical trial, pre-

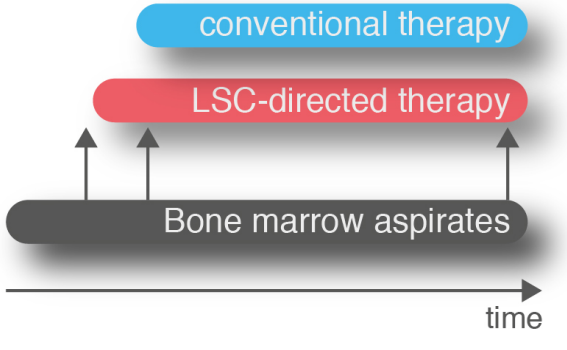

Figure 1. Recommended timing of bone marrow aspirates during the first cycle of an early-phase study combining conventional therapy with an LSC-directed therapy that maximizes correlative end points to determine the ability of an experimental therapy to target LSCs.

and post-treatment tumor samples should be collected. To quantify LSCs, limiting dilution experiments, in which tumor cells are transplanted at decreasing dilutions into xenograft models, should be performed. While not practical to perform for all clinical trial participants or in a prospective manner, and although not definitive proof of efficacy against LSCs, these experiments are highly instructive and should be prioritized.

Other methods to quantify LSCs after treatment are in active development. For example, although it has long been clear that assessing post-treatment stem cell eradication was important, it was recognized that "...in the future, the ability to detect residual (cancer stem cells) in patients following therapy will require substantial advances in...purification strategies."[76] As predicted, immunophenotypic techniques to identify and quantify the LSC population before and after treatment have evolved significantly,[46] and can now be employed to quantify the LSC-targeting ability of candidate drugs. These techniques are less technically difficult than xenograft experiments, and may provide a more versatile means of estimating LSC frequency in those instances in which resources for xenograft studies are limited. Furthermore, the types of mutations that occur in leukemia, as well as improved molecular detection methods, will undoubtedly lead to significant improvements in MRD detection.

For these correlative experiments, the timing of the post-treatment bone marrow aspirate is critical. Although it is theoretically possible to purify the tumor and assay for a particular marker that uniquely identifies the disease, waiting several weeks after an effective treatment may result in a comparison between diseased and normal bone marrow. In the first cycle of therapy, we recommend a bone marrow aspirate prior to treatment, another after roughly seven days of treatment with the LSC-directed agent, and again after completion of a cycle of treatment (usually approx. 28 days) (Figure 1). At each of these time points, the relative tumor burden must also be measured so that LSC frequency can be normalized to total leukemia levels. This level of quantification is essential as a means to determine whether LSCs are targeted, and if so, whether a given therapy is more or less effective towards LSCs in comparison to bulk tumor. At the conclusion of the clinical trial, an assessment regarding whether outcomes correlate with the elimination of the LSC population must be reported.

Principle 2: assessing relevant end points

Recent experiences in which standard clinical trial response assessments were extended to drugs that target the LSC population demonstrate how conventional end points are not necessarily useful in early phase clinical trials. For example, development of the anti-CD33 immunoconjugate gemtuzumab ozogamicin (GO) is instructive. CD33 is expressed by LSCs,[94] although this is now understood to be an inconsistent feature of this population.[94-96] The results of single-agent studies with this agent were varied, at best revealing response rates approaching 30%,[97] but sufficient to lead to an FDA label for this drug.[98] Notably, GO was voluntarily withdrawn from the US market in 2010 based on interim data from a randomized combination study suggesting no improvements in outcome and increased fatal toxicity, perhaps due to the dose of GO.[99] However, other large randomized studies of GO in combination with conventional chemotherapy have shown improvement in clinically meaningful end points such as event-free survival/disease-free survival and OS,[100-103] prompting calls for reconsideration of its approval status.[104] It is an interesting observation that these beneficial end points were observed despite no differences in disease response rates, because in other studies the number of LSCs was prognostic for survival, but response rates did not correlate with LSC burden.[71]

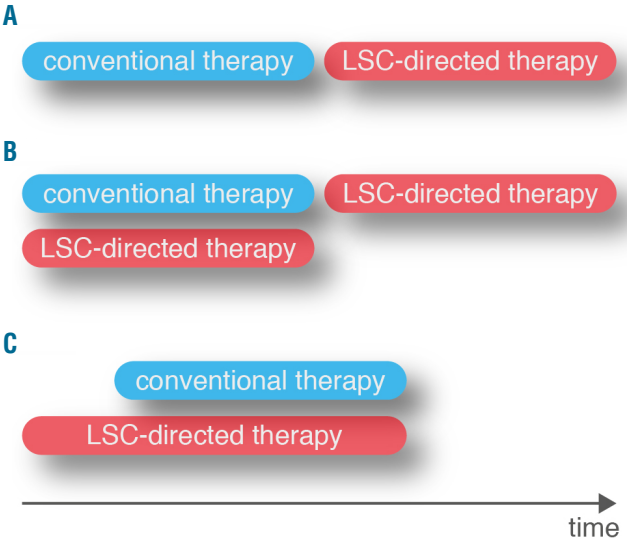

Figure 2. Sequencing of conventional therapies with LSC-directed therapies in the context of combination clinical trials. (A) Sequential treatment with conventional therapy and LSC-directed therapy. (B) Concomitant treatment with conventional therapy and LSC-directed therapy. (C) Modified concomitant treatment for the first cycle of a phase I clinical trial, in which the LSC-directed therapy precedes the conventional therapy for a period of several days.

Therefore, clinical trials that study novel therapies purported to target LSCs must give less weight to disease response rates as an end point,[6,69] and investigators must be cautious when making decisions regarding the continuation of studies based on this end point. Instead, as much as possible, these trials should be powered to study the most clinically relevant end points, such as event-free/disease-free/progression-free survival and OS.

Principle 3: combination therapies

The dandelion hypothesis[56] predicts that LSC-directed therapies administered as single agents require a longer treatment period to derive clinical responses compared with therapies that target the bulk population. Therefore, LSC-directed therapies, even if active, may be insufficiently recognized to be effective when standard definitions used to assess clinical responses are applied. There are two options to design studies that do not inadvertently underestimate or lead to incorrect conclusions regarding the efficacy of these treatments. The first option is to prolong the time to which an assessment of a clinical response would be expected. This is typically not feasible or clinically desirable with hyperproliferative diseases such as AML. A second option would be to design biologically rational combinations of LSC-directed agents with therapies that target the bulk population. This allows the urgent matter of proliferative disease and its related morbidity to be addressed, while simultaneously targeting the root cause of the disease; this can buy the necessary time to allow for a curative therapy to be effective. Invoking the example of the GO experience once

again, AML patients had improved outcomes, including OS, mainly when GO was used in combination with conventional chemotherapy.[96]

Principle 4: sequencing of conventional therapies with LSC-directed therapy

The timing of the conventional and experimental treatments is likely to be important. The two main options would be to de-bulk the disease with conventional treatments (intensive for younger or fitter patients, non-intensive for older or unfit patients) and follow this with administration of the LSC-targeting agent, or to give the LSC-targeting agent concurrently with the de-bulking regimen. During early phase clinical trials, the concomitant option could be further adapted for the first cycle of therapy to allow a run-in period of several days in which the investigational LSC-targeted agent is given alone; subsequent cycles (in the case of a re-induction or when combined with low-intensity therapy) would involve concomitant therapy (Figure 2). We favor the latter design for several reasons. Primarily, this would allow for the study of the pharmacokinetic and pharmacodynamic properties of the experimental therapy independent of other treatments, which may be the only opportunity to study whether the LSC-directed therapy truly targets LSCs, and would serve as a critical end point of a Phase I study. Secondly, this sequence would allow for additive or synergistic properties between agents to be realized, or the sensitization that an LSC-directed therapy may allow. Should it be suggested with experience from an early-phase trial that there is no clinical benefit to co-administration of the therapies, later phase studies may be designed to reserve LSC-directed therapies until completion of induction, or even after achieving a remission. However, based on experience in which relapsed disease is more difficult to treat, likely due to a treatment-induced selective pressure that engenders more resistant disease,[105] and data that suggest intensive therapies fragment and induce clonal evolution in the LSC compartment,[31] we hypothesize there would be added clinical benefit to co-administration of LSC-directed therapies in the up-front setting. Toxicity may result from any overlap of therapies, and trials must be designed to allow for close investigation of adverse events. If toxicities are limiting, alternative sequencing should be considered prior to the abandonment of promising combination studies.

The reality of drug development is that most first-in-human or first-in-disease studies are designed using the single agent. Patients with proliferative disease are unlikely to be responders, and therefore, excluding these patients until later-stage studies combining the novel LSC-directed agent with chemotherapy should be considered.

Principle 5: post-remission therapy

Despite prior attempts, no post-consolidation intervention has led to improved OS for patients with AML.[106-108] However, none of the interventions tested have been LSC-targeted therapies, and therefore, consideration for well-tolerated therapies that target the LSC compartment should be taken in the setting of rationally designed clinical trials, with the intention of eliminating residual LSCs and improving relapse-free survival. One method may be to use the presence of MRD as the main eligibility criteria for such a trial, and explore whether MRD could be used to monitor responses to the LSC-directed therapy. Ultimately a randomized study comparing LSC-targeted maintenance to no maintenance could be designed. Incorporating these treatments into consolidation and maintenance represents hopeful strategies and should be encouraged, ideally to be performed after correlative studies from previous clinical trials suggest the investigational agent truly targets LSCs. Finally, the use of LSC-directed therapies in the post-allogeneic stem cell transplant setting for patients at high risk of relapse are underway (*clinicaltrials.gov identifier:01841333*) and should be further explored.

Conclusions

Given the general lack of continued successes in impacting AML with conventional therapies over several decades, new approaches to treating this disease are warranted. The confluence of a robust characterization of the LSC population with advances in drug development make it likely that the coming years will be an active period for clinical trialists seeking to test therapies that target LSCs. It is exciting to imagine a future trial design in which there are enough promising LSC-directed therapies to support several arms of a "pick-a-winner" study.

However, because of the unique properties of LSCs, it is possible that the infrastructure of current clinical trials will inaccurately assess the efficacy of LSC-directed therapies; indeed, in some circumstances this may have already occurred. Adaptations to extant clinical trial designs, such as considering end points other than disease response, considering drug combinations and their sequencing in first-in-human Phase I studies, quantifying LSC targeting abilities with correlative end points, and prioritizing post-remission trials are all relevant considerations.

The heterogeneity of AML and LSCs presents a formidable challenge to the clinician and clinical trialist, but we believe these principles are valuable considerations in the burgeoning attempt to target LSCs with novel therapies.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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