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Hematopoietic cell transplantation in Fanconi anemia and dyskeratosis congenita: A minireview

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Abstract
Bone marrow failure syndrome is an epithet of bone marrow failure (all or single-cell lineage) that is attributable to an underlying genetic aberration usually with a constellation of somatic abnormalities. Multiple inheritance patterns have been described in these disorders; many are transmitted in an autosomal recessive pattern, which may consequently lead to a higher prevalence of such illnesses in homogeneous societies such as Saudi Arabia, where consanguineous marriages are not uncommon. At King Faisal Specialist Hospital and Research Center, the most common entity referred for allogeneic hematopoietic cell transplantation (HCT) is Fanconi anemia, followed by pure red aplasia, and, less commonly, dyskeratosis congenita, congenital neutropenia, and others. Of all the congenital bone marrow failure syndromes, two of them-Fanconi anemia and dyskeratosis congenita-represent a real challenge in terms of conditioning for HCT and require special attention. This minireview is a snapshot of the recent international and local experience of HCT in these two entities.

Introduction

Beneath the term ''bone marrow failure syndromes" lies a large number of heterogeneous diseases and what was once considered a straightforward diagnosis based on hypoplastic marrow findings in a child with cytopenia, and some somatic abnormalities, has turned out (with our expanded knowledge) to be a much more challenging task. In fact, many patients previously diagnosed with ''acquired aplastic anemia" were later reported to have an underlying genomic instability disorder [1–5].

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Because the underlying pathophysiology in the majority of these disorders appears to be at the stem cell level, allogeneic hematopoietic cell transplantation (HCT) is the logical and only established curative modality for the hematological manifestations (bone marrow failure, development of an abnormal clone, or leukemia) in these illnesses [6–24].

One size does not fit all, however. As the past two decades have witnessed a dramatic paradigm shift in understanding the bone marrow failure syndromes with an explosion in the availability of molecular means to diagnose them, we now understand that special precautions have to be taken in some of these syndromes, and that HCT outcome is best when conditioning is tailored to the disease itself. Understandably, HCT does not reduce the risk of secondary malignancies outside the bone marrow, and many of these patients remain at risk for solid tumor malignancies [25,26].

Fanconi anemia

Fanconi anemia (FA) is the epitome of disorders where the discovery of the core pathophysiological mechanism (FA pathway) has led to major concomitant improvements in understanding a variety of seemingly unrelated cancers such as breast and ovarian cancers. Thus far, more than 16 complementation group genes have been well characterized, such as *FANCD1* (*BRCA2*), *FANCJ* (*BACH1*), *FANCN* (*PALB2*), and *FANCO* (*RED51C*)–several of which are now also known to be familial breast cancer genes. The FA pathway is genetically extremely complex, and the encoded proteins are grouped into three categories; the first is referred to as the FA core complex, including the E3 ligase, FANCL. The second group is the ID2 complex, which is the substrate for the E3 ubiquitin ligase activity of the core complex; and finally there are the downstream proteins that possess a DNA repair or damage tolerance function [1,2]. An abnormality in any of the encoded proteins will disrupt the pathway and result in hypersensitivity to agents that cause interstrand DNA cross-links, which is translated into chromosomal fragility, the hallmark of FA. HCT is considered the only potentially curative modality to restore normal hematopoiesis in FA patients [8–17]. However, the genomic instability of FA cells and the resulting hypersensitivity to alkylating agents was a major obstacle in the early attempts to perform HCT in these patients, until it was shown categorically that FA patients should receive considerably reduced doses of alkylating agents and radiation for conditioning [27–29]. Since then, and for the past 3 decades, low-dose cyclophosphamide (CY) has become the mainstay of the preparatory regimens used. Over the years, the ''low" dose of CY regimens used CY on its own, or together with thoracoabdominal irradiation (TAI)/or total body irradiation (TBI), and with or without antithymocyte globulin (ATG). More recently, the incorporation of fludarabine in the conditioning regimen has had a very positive impact on outcome. The CY dose has subsequently varied from one study to another; doses as low as 20 mg/kg and up to 80 mg/kg have been used with favorable outcomes, particularly in recipients of matched related HCT [9–17].

We, at King Faisal Specialist Hospital and Research Center (KFSHRC), recently reported our experience in 94 pediatric patients with FA [17]. We used different regimens over the years with CY as the backbone; one of two doses of CY was used according to the time when the patient underwent HCT: a higher dose, CY 60 mg/kg, used with ATG with no other agents ($n = 40$), or a lower dose, CY 20 mg/kg, used in combination with ATG and TBI ($n = 11$); or TAI ($n = 22$), or used in combination with ATG and fludarabine ($n = 21$). Graft-versus-host disease (GVHD) prophylaxis was with cyclosporine (CSA). We reported overall survival (OS) probabilities at 1 year, 5 years, and 10 years of 92.5%, 89%, and 86%, respectively. We found on univariate analysis that higher dose CY conditioning was associated with a better 10-year OS than lower dose CY conditioning (91% vs. 82%, respectively; $p = .035$), and that use of radiation-containing regimens was associated with a significantly lower 10-year OS than nonradiation regimens (76% vs. 91%, respectively; $p = .005$). Of the four regimens reported in our study, the fludarabine-based regimen was associated with the highest survival (95.2%; $p = .034$). Other studies now support the use of nonradiation preparatory regimens for FA patients [30].

In our study, all donors were cleared using chromosomal breakage studies. Carrier status, however, was not ruled out. In fact, some of our donors were obligate carriers (parents), and we had no issues with cell dose upon harvesting and no increased delayed graft failure. Currently, there are no data in the literature to suggest that carriers of FA should be avoided as donors.

FA patients who present with pretransplantation cytogenetic abnormalities, myelodysplastic syndrome, or acute leukemia are a special challenge. Recent data, however, support that long-term survival in these patients is achievable, and that younger patients and recipients of Human Leukocyte Antigen (HLA)-matched related donor transplantations who have cytogenetic abnormalities only have the best survival [31].

When there is no matched related donor, many alternative donor options are now available. The first attempts at alternative donor HCT for FA patients were associated with excessive morbidity and mortality [32,33]. Excellent results have been reported lately, however; a study from the University of Minnesota recently described the outcome of 130 FA patients after alternative donor HCT [34]. Patients received CY, single TBI, and ATG with or without fludarabine, and then T cell-depleted bone marrow or unmanipulated umbilical cord blood transplantation. The best results were obtained in patients without a history of opportunistic infection or transfusions and who received conditioning with TBI 300 cGy, CY, fludarabine, and ATG; these patients had a probability of survival of 94% at 5 years. The incidence of grades 2–4 acute and chronic GVHD was 20% and 10%, respectively. Severe toxicity was highest in patients >10 years of age or those with a history of opportunistic infections or transfusions prior to HCT. Alternatively, haploidentical HCT with post-transplant CY has also appeared on the horizon as a valid option. The challenge here is that the use of the traditional dose of CY 50 mg/kg/dose on Days +3 and +5 is bound to result in excessive toxicity, and reducing the dose may not have the desired effect on the healthy non-FA donor lymphocytes with potential ensuing severe GVHD. A study recently published on 30 FA patients used fludarabine 150 mg/m^2 + TBI 200–300 cGy

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