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The Prognostic Value of YKL-40 Concentrations in Nonmyeloablative Conditioning Allogeneic Hematopoietic Cell Transplantation

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Increased plasma concentrations of YKL-40, also called chitinase-3-like-1 protein (CHI3L1), have been correlated with disease severity in a variety of malignant and inflammatory diseases. The objective of the current study was to assess pretransplant recipient and donor *CHI3L1* polymorphisms and plasma YKL-40 concentrations as prognostic biomarkers in a cohort of 149 patients treated with hematopoietic cell transplantation (HCT) after nonmyeloablative conditioning for hematologic malignancies. Recipients with pretransplant YKL-40 concentrations above the age-adjusted 95th percentile (high) had higher relapse-related mortality (33% versus 18%, $P = .04$; hazard ratio (HR) = 4.41, $P = .01$), lower progression-free survival (38% versus 64%, $P < .01$; HR = 2.84, $P = .01$), and overall survival (42% versus 69%, $P = .01$; HR = 3.09, $P = .01$). Recipients transplanted with donors with high YKL-40 concentrations had an increased probability and risk of grade 2-4 acute graft-versus-host disease (aGVHD) (93% versus 62%, $P < .01$; HR = 2.25, $P = .02$). *CHI3L1* polymorphisms were associated with plasma YKL-40 concentrations, but not with clinical outcomes. In conclusion, our study suggests that plasma YKL-40 could function as a biomarker for relapse risk and treatment-related toxicity, and possibly as a tool complementing clinical risk scores such as the HCT comorbidity index.

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INTRODUCTION

With the introduction of reduced-intensity conditioning (RIC), allogeneic hematopoietic cell transplantation (HCT) has become a curative treatment option for a variety of malignant hematologic diseases in older and medically infirm patients. However, complications such as graft-versus-host disease (GVHD), infections, and relapse are still major causes of morbidity and mortality. In the older and medically infirm patient population that is only eligible for RIC, prognostic factors such as the Kahl score [1] or the HCT comorbidity index [2,3] have proven useful in predicting the risk of relapse and treatment-related mortality (TRM). However, to appropriately balance the likelihood of disease control against the risk of debilitating complications, still more accurate pretransplant tools are needed to predict outcome. Inflammatory biomarkers serve as prognostic tools in a variety of disease settings, and in allogeneic HCT it has been shown that rising or increased concentrations of markers such as C reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α in the posttransplantation period are predictive of treatment-related toxicity [4-8]. The predictive value of inflammatory biomarkers in the pretransplant period is less well investigated. However, increased pretransplant concentrations of CRP have been shown to associate with increased incidence of infectious complications, acute GVHD (aGVHD), and TRM [9,10].

YKL-40, also called chitinase-3-like-1 protein (CHI3L1), is a phylogenetically conserved heparin-, chitin-, and collagen-binding member of the family of mammalian chitinase-like proteins. It is regarded

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as an acute-phase reactant, and increased concentrations of YKL-40 have been observed in a variety of inflammatory diseases of infectious and noninfectious etiology (reviewed by Johansen et al. [11]). In cancer, elevated YKL-40 concentrations have been associated with advanced disease [12], and in a large prospective study of a general Danish population cohort, high YKL-40 concentrations were predictive of the development of gastrointestinal cancer in subjects without known cancer [13]. YKL-40 is secreted by cancer cells [14], vascular smooth muscle cells [15], connective tissue cells [16,17], neutrophile granulocytes, and macrophages [18-20], and although its exact biological function is unknown, it is involved in of cell proliferation and differentiation [21], angiogenesis [22], matrix remodeling, and inflammation [14]. Secretion of YKL-40 is induced by interferon (INF)-γ [23] and IL-6 (J.S.J., unpublished results), and it has been suggested that it is involved, as an opsonin, in activating innate immune responses [14,24]. In a murine knockout model, the YKL-40 analog Brp-39 has been shown to be of importance in establishing Th2 polarized immune responses and augmenting the accumulation of macrophages, dendritic cells, and T cells by inhibiting apoptosis [25]. Compared to another acute-phase reactant such as CRP, YKL-40 has a different temporospatial secretion profile and therefore only a weak correlation to CRP [26-29]. Furthermore, YKL-40 may reflect disease activity more accurately, as it originates from cancer cells and inflammatory cells directly involved in the pathological process, whereas CRP is secreted by hepatocytes as a response to IL-6 [14].

Because of the ability of YKL-40 to predict survival and disease severity across a large variety of cancers and inflammatory disorders, and because of its involvement in processes central to oncogenesis and inflammation, we hypothesized that pretransplant YKL-40 concentration or *CHI3L1* genotype could be a valuable prognostic marker in the setting of nonmyeloablative conditioned allogeneic HCT, and that both could capture the inherent risk of relapse associated with cancer and comorbid conditions.

METHODS

Study Cohorts

The study cohort consisted of 149 consecutive recipients treated with allogeneic HCT following nonmyeloablative conditioning for hematologic malignancies (acute myeloid leukemia/myelodysplastic syndrome [AML/MDS], n = 54 [36%]; chronic myeloid leukemia [CML], n = 3 [2%]; chronic lymphocytic leukemia (CLL), n = 21 [14%]; non-Hodgkin lymphoma [NHL], n = 16 [11%]; and multiple myeloma [MM], n = 16 [11%]) between March 2000 and July 2007, at the bone marrow transplantation unit at Rigshospitalet, Copenhagen, Denmark. Sixty-seven (45%) of the recipients were in complete remission (CR), and 82 (55%) were not in complete remission. When stratified according to risk of relapse after allogeneic HCT [1], 32 (21%) had low risk and 72 (48%) and 45 (30%) had standard and high risk, respectively. For related donors (n = 86 [58%]), donor selection was based on serologic typing for HLA-A and -B and on molecular typing for HLA-C, -DRB1, and DQB1. For unrelated donors (n = 63 [42%]), donor selection was based on molecular typing for HLA-A, -B, -C, -DRB1, and -DQB1. When available, HLA-identical siblings were preferred to matched unrelated donors (in 11 unrelated donors, a single allele mismatch was present), and cytomegalovirus serostatus (cytomegalovirus [CMV]-negative recipient and donor, n = 31 [21%]; other combinations, n = 118 [79%]) and gender mismatch (male recipient/female donor, n = 34 [23%]); other combinations n = 115 (77%) were taken into account when possible. All recipients received transplants of peripheral blood stem cells (PBSC) after conditioning with fludarabine 30 mg/m^2 for 3 days and 2 Gy of total-body irradiation (TBI), except for 2 recipients who were conditioned with 2-Gy TBI only. Donor treatment, conditioning regimen, and supportive care have been described previously [30]. Acute GVHD and chronic GVHD (cGVHD) were diagnosed according to standard criteria [31].

Blood samples for plasma measurement and DNA extraction were obtained from recipients during pretransplantation workup, which was scheduled approximately 2 to 3 weeks prior to conditioning. Recipients were not treated with chemotherapy in the time period between pretransplant workup and conditioning. However, some recipients could be recovering from chemotherapy-induced nadirs. From related donors and domestic unrelated donors, samples were obtained during preleukapheresis workup. Plasma samples were obtained before treatment with granulocyte colony-stimulating factor (G-CSF) was begun. For international donors, plasma samples were not available. DNA was available from all recipients and donors, and plasma was available from 112 (75%) recipients and 92 (62%) donors.

For the purpose of comparing the distribution of genotypes in the recipient and donor cohorts to the general population, a cohort of 100 Danish Caucasian healthy blood donors served as controls. DNA and plasma samples were available from all control subjects.

Informed consent was obtained from all recipients, donors, and controls, and the local ethics committee approved the study.

Genotyping

DNA from samples was extracted using the Promega Maxwell 16 blood DNA kit (Promega Corporation, Madison, WI). The control cohort was genotyped