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Allogeneic Hematopoietic Stem Cell Transplantation Is an Effective Salvage Therapy for Patients with Chronic Myeloid Leukemia Presenting with Advanced Disease or Failing Treatment with Tyrosine Kinase Inhibitors

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Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only known curative therapy for chronic myeloid leukemia (CML); however, it is rarely utilized given the excellent long-term results with tyrosine kinase inhibitor (TKI) treatment. The purpose of this study is to examine HSCT outcomes for patients with CML who failed TKI therapy or presented in advanced phase and to identify predictors of survival, relapse, and nonrelapse mortality (NRM). Fifty-one patients with CML underwent HSCT for advanced disease at diagnosis (n = 15), TKI resistance as defined by the European LeukemiaNet guidelines (n = 30), TKI intolerance (n = 2), or physician preference (n = 4). At a median follow-up of 71.9 months, the 8-year overall survival (OS), event-free survival (EFS), relapse, and NRM were 68%, 46%, 41%, and 23%, respectively. In univariate analysis, predictors of OS included first chronic phase (CP1) disease status at HSCT ($P = .0005$), European Society for Blood and Marrow Transplantation score 1 to 4 ($P = .04$), and complete molecular response (CMR) to HSCT ($P < .0001$). Donor (female) to patient (male) gender combination ($P = .02$) and CMR to HSCT ($P < .0001$) predicted lower relapse. In multivariate analysis, CMR to HSCT remained an independent predictor of OS (odds ratio [OR], 43), EFS (OR, 56) and relapse (OR, 29). This report indicates that the outlook is excellent for those patients who remain in CP1 at the time of HSCT and achieve a CMR after HSCT. However, only approximately 50% of those in advanced phase at HSCT are long-term survivors. This highlights the ongoing need to try to identify patients earlier, before disease progression, who are destined to fail this treatment to optimize transplantation outcomes.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by marrow hyperplasia associated with a specific cytogenetic abnormality, known as the Philadelphia chromosome (Ph), consisting of the reciprocal translocation between chromosomes 9 and 22. This results in the fusion of the Abelson (ABL) oncogene on chromosome 9 to the breakpoint cluster region (BCR) gene on chromosome 22 creating a fusion gene (BCR-ABL). This encodes for a tyrosine kinase and is instrumental in the phosphorylation of other proteins, resulting in a leukemic phenotype.

Historically, treatment for CML included either interferon alpha (IFN) or, alternatively, allogeneic hematopoietic stem cell transplantation (HSCT) for those patients considered appropriate candidates and where a suitable matched donor was available. However, with the introduction of the tyrosine kinase inhibitor (TKI) imatinib mesylate (IM), therapy for CML changed dramatically. The landmark international randomized trial between IFN and IM (IRIS) for patients with newly diagnosed CML in chronic phase (CP) showed a cumulative best complete cytogenetic response (CCR) of 82% with the corresponding overall survival (OS) and freedom from progression at 6 years of 88% and 93%, respectively [1].

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These remarkable results remain durable for the majority of patients; however, approximately 15% to 25% of patients treated with IM will develop resistance or intolerance, necessitating a change in therapy. More recently, the second-generation TKIs dasatinib, nilotinib, and bosutinib have been introduced for the treatment of patients with IM resistance and/or intolerance, with reported response rates that approximate 50% [2-4]. The second-generation TKIs have also been studied for the treatment of newly diagnosed patients with CML, where faster and deeper molecular responses and lower progression rates have been observed in comparison to IM [5-7].

Given the excellent long-term results with TKI treatment for the majority of patients with CML in CP, allogeneic HSCT is now rarely utilized. Indeed, the indications for HSCT are now generally limited to patients with TKI resistance or intolerance or for patients with advanced phases of disease where TKI therapy is not considered durable [8]. Although studies have shown that prior treatment with TKIs does not appear to increase immediate transplantation-related morbidity or mortality [9], fewer reports are available detailing the long-term HSCT outcomes for this patient population. In particular, whether overall survival (OS), progression-free survival (PFS), and relapse for patients with CML undergoing allogeneic HSCT in the TKI era have been altered by an initial therapeutic approach with IM remain less well studied. Therefore, the purpose of this report is to examine the clinical characteristics, HSCT outcomes, and long-term follow-up of patients diagnosed with CML in CP who fail initial TKI treatment and to identify predictors of post-HSCT survival, relapse, and nonrelapse mortality (NRM). In addition, patients presenting with advanced disease at diagnosis (accelerated phase [AP] and blast phase [BP]) and who received initial treatment with TKIs as a bridge to HSCT were also studied to further evaluate HSCT outcomes in this patient population.

PATIENTS AND METHODS

From January 1, 2002 to April 30, 2013, 55 consecutive patients diagnosed with CML underwent allogeneic HSCT at our institution. This represents 7% of all allogeneic HSCTs performed during this time interval. Indications for transplantation included resistance to TKI therapy as defined by the European LeukemiaNet (ELN) guidelines [8] in 30 patients, intolerance to TKI therapy in 2 patients, advanced disease (AP or BP) at diagnosis in 15 patients, and physician or patient preference in 4 patients. An additional 4 patients had not received TKI treatment during this time period and were excluded from further analysis. Therefore, 51 patients were reviewed and are the subject of this report.

Pretransplantation Therapy and Monitoring

All patients underwent a bone marrow (BM) aspirate and biopsy with cytogenetic analysis at diagnosis. Patients with CML CP received IM as initial therapy, except for 5 patients who were treated with IFN before commencing IM when it became commercially available. Second generation TKIs (dasatinib and nilotinib) were only utilized for patients with documented resistance or intolerance to IM therapy. Patients were followed according to ELN treatment guidelines [8], including a complete blood count at least once per month and cytogenetic analysis from BM specimens every 3 to 6 months thereafter. Starting in 2004, quantitative reverse transcriptase polymerase chain reaction (QPCR) of BCR-ABL transcripts on peripheral blood (PB) specimens was performed every 3 months starting from diagnosis and was reported as log reductions, as determined by comparison of the measured value to the log value obtained at diagnosis or an averaged baseline value (+.1), as adapted by Hughes and Branford [10]. Once QPCR monitoring became readily available and molecular equivalents to cytogenetic responses were established, routine BM tests with cytogenetic analysis were no longer performed for monitoring purposes, provided the response to therapy was satisfactory according to the ELN treatment guidelines. For patients who did not achieve the treatment milestones per the ELN guidelines, or who later developed progression (resistance) after an initial response, a BM aspirate and biopsy with a full karyotype was performed to establish current disease status and to determine whether progression to AP or BP was present. Before the availability of the second-generation TKIs, transplantation-eligible patients with IM resistance or intolerance were offered allogeneic HSCT if a suitable donor was available. Second-generation TKIs became available at our institution on November 1, 2007, and after this time, patients with IM resistance or intolerance were generally offered a trial of treatment with these newer agents if still in CP, and HSCT was reserved for those patients with an unsatisfactory therapeutic response or if progression to AP or BP had occurred.

For those patients presenting with CML in advanced phase (AP or BP) who were deemed transplantation eligible, treatment with IM therapy with or without concomitant conventional chemotherapy as a bridge to HSCT was undertaken in an attempt to achieve CP status while awaiting donor confirmation.

From 2006 onwards, mutational analysis by bidirectional sequencing of the ABL kinase domain of the BCR-ABL fusion transcript using a nested RT-PCR technique was also undertaken for those patients developing resistance or with an unsatisfactory treatment response.

Conditioning Regimens and Stem Cell Source

Details of the conditioning regimens and stem cell source are shown in Table 1. All chemotherapy doses were based on the lesser of the corrected body weight (.5 kg [ideal body weight + actual body weight]) or the actual body weight. The preparative regimen utilized was dependent on disease status at transplantation, the donor type (related or unrelated), patient age, and comorbidities. All transplantations were myeloablative (total body irradiation [TBI] 1200 cGy and i.v. cyclophosphamide 150 mg/kg or i.v. busulfan 12.8 mg/kg and i.v. cyclophosphamide 120 mg/kg), with the exception of 3 patients who received reduced-intensity conditioning regimens (i.v. fludarabine 150 mg/m^2, i.v. busulfan 6.4 mg/kg, and i.v. alemtuzumab 100 mg [n = 2] or fludarabine 90 mg/m^2 and TBI 200 cGy [n = 1]).

The stem cell source varied over the time period of the study. Eight patients received BM and 43 patients received PB from an HLA-matched sibling or an unrelated donor. HLA matching for unrelated donors was based on molecular typing for HLA-A, -B, -C, and -DRB1. Standard supportive care techniques and graft-versus-host disease (GVHD) prophylaxis were employed as previously described [11].

Post-Transplantation Therapy and Monitoring

The standard monitoring practice after transplantation included a BM analysis with standard karyotyping and XY FISH for gender-mismatched transplantations 100 days after transplantation. For reduced-intensity transplantations, patient and donor lymphoid and myeloid chimerism were also performed on fractionated PB specimens from day 60 and day 100 after transplantation, utilizing microsatellite analysis of genomic DNA by comparison of the averaged amplification of donor and recipient alleles of informative microsatellite markers, as determined from pretransplantation specimens. In addition, institutional guidelines recommended molecular analysis of BCR-ABL on PB on a 3-monthly basis for the first 2 years, then every 6 months if complete molecular remission (CMR) was achieved. In the event of molecular relapse, a BM analysis and karyotype were performed, and molecular analysis continued every 3 months or more frequently at physician discretion. Therapeutic intervention was typically undertaken based on cytogenetic or hematologic relapse or for increasing molecular BCR-ABL transcripts in the event of molecular relapse only. TKI therapy or any other chemotherapy was not given as a maintenance treatment after HSCT in an attempt to decrease the risk of relapse.

Definitions

CML CP was defined as <10% blasts and <20% basophils in PB or BM without extramedullary disease. *CML AP* was defined as 10% to 20% blasts, >20% basophils, platelet count < 100 × 10^9/L unrelated to therapy, or cytogenetic clonal evolution. *CML BP* was defined by >20% blasts in PB or BM or extramedullary leukemic involvement. *Complete hematologic response* (CHR) was defined as normalization of PB count and absence of all signs and symptoms of disease. Cytogenetic responses were classified as *complete* if there were no Ph+ metaphase cells in BM or a 2-log reduction in PB BCR-ABL transcripts compared with baseline, *minor* (35% to 95% Ph+ metaphases), or *major* (1% to 34% Ph+ metaphases), or a 1-log reduction in PB BCR-ABL transcripts compared with baseline (MCR). *Hematologic relapse* was defined by the reappearance of a leukocytosis in PB or BM with an abnormal differential typical of CML with confirmation by cytogenetic analysis. Cytogenetic relapse involved the reappearance of 1 or more Ph+ metaphases on cytogenetic analysis. *Major molecular response* (MMR) was defined as a 3-log reduction in PB BCR-ABL transcripts compared with baseline. The threshold for CMR was based on the level below which BCR-ABL transcripts