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Isolated Clonal Cytogenetic Abnormalities after High-Dose Therapy

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A B S T R A C T

Therapy-related myeloid neoplasms (t-MN) are well-recognized complications of high-dose cytotoxic therapy (HDT), such as autologous stem cell transplantation (ASCT). Clonal marrow cytogenetic abnormalities (CMCA) in the setting of normal bone marrow pathology have also been reported after HDT, but their significance remains unclear. We retrospectively evaluated occurrences of CMCA and t-MN in 785 patients treated with HDT at Johns Hopkins University between 1997 and 2007. Most patients received ASCT, but 106 patients who received high-dose cyclophosphamide without ASCT were also included in this study, as this is our institutional standard for malignant and nonmalignant lymphoproliferative disorders in need of HDT. Twenty-two patients developed t-MN, with an estimated cumulative incidence of 3.5% at 4 years. Eleven patients developed isolated CMCA, either transient or persistent without pathologic evidence of t-MN. Altogether, only 20 of the patients with reported CMCA subsequently developed t-MN during the follow-up period. Therefore, in the absence of pathologic evidence of t-MN, CMCA should not be considered diagnostic of t-MN.

INTRODUCTION

Reported incidence rates of therapy-related myeloid neoplasms (t-MN) after autologous blood or marrow transplantation (ASCT), vary from 1% to 20% [1-9]. The reported incidence rates of t-MN after ASCT generally appear higher than those reported after multiple cycles of conventional-dose therapy [10]. Though t-MN are usually associated with clonal marrow cytogenetic abnormalities (CMCA) [11,12], it is not clear that isolated therapy-related CMCA, those that occur in the setting of normal bone marrow pathology, are always associated with t-MN. In fact, there are several reports of patients developing CMCA without other evidence of t-MN after ASCT [2,9,13-19], but the significance of this finding is uncertain. Several of our patients developed either transient or persistent isolated CMCA after high-dose therapy (HDT) without progression to t-MN over prolonged follow-up. As the prognosis of t-MN is extremely poor, with a median survival of less than 1 year unless cured with allogeneic stem cell transplantation [13,20-22], a better understanding of the significance of isolated CMCA after HDT is critical. Our aim was to evaluate occurrences of isolated CMCA and t-MN in patients who received HDT at Johns Hopkins Hospital between 1997 and 2006 via a retrospective review of medical records. One hundred and six patients who received high-dose cyclophosphamide (HiCy) without ASCT were also included in this study. This therapy is our institutional HDT for malignant lymphoproliferative disorders and severe aplastic anemia (SAA) [23,24].

MATERIALS AND METHODS

Subjects

We retrospectively identified all patients who underwent HDT at our institution between 1997 and 2006 (Table 1). Eligible patients were 18 years of age or older at time of treatment and had an initial diagnosis of indolent non-Hodgkin's lymphoma (iNHL), chronic myeloid leukemia (CML), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Hodgkin's lymphoma, diffuse large B cell lymphoma (DLBCL), acute lymphoblastic leukemia (ALL), or SAA. Clinical data were collected from the medical records of 785 consecutive patients. The information included age, diagnosis, status at time of HDT, date of treatment, date of last follow-up, disease status at follow-up, and results of bone marrow biopsy, cytogenetic analysis, and FISH studies. A subset of patients also had interphase FISH analysis for as part of their follow-up, as these tests came on-line clinically. Therefore, for patients with t-MN (Table 2) FISH results were included only if a patient had no cytogenetic analyses available. However, for patients with isolated CMCAs, all available FISH results were reported to depict the most complete portrayal available of the evolution of chromosome abnormalities. Acute leukemia that occurred after an original diagnosis of AML was only considered t-MN if there was not only a different karyotype, but also a distinctly different clinical presentation regarding dysplasia and white blood cell count. Among the records of patients with t-MN, abnormal cytogenetic analyses were further reviewed for details of previous cytotoxic therapy and other relevant clinical information. Our center's recommended follow-up includes periodic bone marrow examinations with routine morphology, flow cytometry, and cytogenetic analysis; however, the final decision regarding follow-up is left to the discretion of the attending physician and patient. Every available bone marrow biopsy result was included for the patients listed in Tables 2 and 3. All patients with CML received HDT between 1997 and 1999, before the standard use of imatinib. Patients were treated according to institutional review board–approved disease-specific ASCT or HiCy regimens. Preparative regimens for ASCT were Cy 200 mg/kg over 4 days with either 1200 cGy total body irradiation (CyTBI) or busulfan 16 mg/kg orally over 4 days, with dosing individualized based on first dose pharmacokinetics (BuCy) [25]. Cy 200 mg/kg alone (HiCy) was used for all 48 patients with SAA [23] as well as 58 patients with low-grade lymphoma or myeloma [24]. Approval for the analysis was

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Table 1
Patient Characteristics

Patient Characteristics	Total Patients	Patients with t-MN	Patients with Isolated CMCA
No. patients	785	22	11
Age, median, yr	51	58	56
Male	468	16	6
Female	317	6	5
Diagnosis			
AA	48	1	3
ALL	11	0	1
AML	36	1	0
CLL	28	2	1
CML	15	0	0
DLBCL	181	7	3
HL	100	0	1
MM	129	1	0
iNHL	237	10	2
Follow-up, median, yr	2.2	4.8	7.3

AA indicates aplastic anemia; HL, Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic lymphoma; ALL, acute lymphoblastic lymphoma; MM, multiple myeloma; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; t-MN, therapy-related myeloid neoplasms; CMCA, clonal marrow cytogenetic abnormalities.

obtained from the Johns Hopkins University internal review board. Data are reported up to August 2012.

Pathology

Standard French, American, and British and World Health Organization criteria were used for the diagnosis of t-MN criteria, myelodysplastic syndrome (MDS), AML, and ALL [26,27]. The time of diagnosis of t-MN after HDT was the first date when results of bone marrow pathology revealed a diagnosis of t-MN.

Cytogenetics

Cytogenetic analyses were performed as per routine post-transplantation follow-up. Abnormalities were described using International System for Human Cytogenetic Nomenclature (2009) criteria [28]. Cytogenetic abnormalities were considered clonal only if 2 or more cells had the abnormality. Cytogenetic abnormalities that are normal variants were not considered CMCA, including pericentric inversion of chromosome 9 and loss of the Y chromosome, which is commonly observed in older males without hematologic disease [29]. Of the entire cohort, this included 2 patients with a transient isolated loss of chromosome Y, 1 patient with a pericentric inversion of chromosome 9, and another with both inversion 9 and loss of Y. Cytogenetic abnormalities were considered isolated in the absence of bone marrow morphology consistent with pathologic diagnosis of MDS/AML. These isolated abnormalities were classified as transient if there were a subsequent analysis revealing a normal karyotype, whereas they were classified as persistent if there were no subsequent analyses demonstrating a normal karyotype. All cytogenetic analyses were done on-site, except the 5 results that are annotated “per note” in Tables 2 and 3.

Statistics

The aim of this study was to report discovered occurrences of isolated CMCA and estimate the cumulative incidence of t-MN among 785 patients after HDT. Patient characteristics were summarized by mean, median, standard deviation, range, and frequency. We estimated the cumulative incidence of discovered cases of isolated CMCAs to report a possible lower bound of the true incidence rate of these events. Cumulative incidence of t-MN and discovered cases of isolated CMCA were estimated via Kaplan-Meier approach. The time-to-event interval was defined from date of initial HDT. Patients who relapsed, progressed, or died before t-MN or isolated CMCA were treated as noninformative censoring to t-MN and CMCA events. In addition, patients who developed t-MN were no longer at risk of developing isolated CMCA. Therefore, patients who experienced t-MN before isolated CMCA was detected were censored at the time t-MN developed when estimating cumulative incidence of discovered cases of isolated CMCA. Patients with detected CMCA were still at risk of developing t-MN. Thus, for t-MN incidence estimation, an event was defined from time of HDT to diagnosis of t-MN. Patients who did not experience isolated CMCA or t-MN were censored at the time of last follow-up in the case of no prior occurrence of relapse, progression, or death. All analyses were performed in R 2.15.1 statistical software (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

The patient characteristics are displayed in Table 1. A total of 785 patients received HDT between 1997 and 2006, including 106 who received HiCy. Their diagnoses were as follows: 237 with 129 iNHL, 181 with DLBCL, 129 with MM, 100 with Hodgkin lymphoma, 48 with SAA, 36 with AML, 28 with CLL, 15 with CML, and 11 with ALL. The median age was 51 years and the median follow-up was 2.2 (range, 0 to 14.2) years for all patients and 3.5 (range, 0 to 14.2) years for those who have not died or relapsed.

t-MN

t-MN developed in 22 patients. The estimated 4-year cumulative incidence of t-MN was 3.5% (95% confidence interval [CI], 1.6% to 5.4%). The median follow-up for patients who developed t-MN was 4.8 (range, .8 to 15.2) years, and the median time to the diagnosis was 3.1 years (range, .8 to 12.9) from HDT (Table 2). These patients were older than the study population with a median age of 58. Of note, 73% were males, compared with 60% in the study population. The specific pathologic diagnosis was MDS in all but 4 patients, 4 of whom had a diagnosis of AML, 2 with dysplastic feature (Table 2, patient nos. 6 and 17), and 2 without (Table 2, patient nos. 14 and 18). One patient developed ALL after HDT (Table 2, patient no. 20). This patient initially developed complex karyotype 3 years after ASCT for NHL, but concurrent bone marrow pathology was unremarkable. Subsequently, the patient was lost to follow-up until 6.3 years from ASCT, when he presented with similar cytogenetic abnormalities and bone marrow pathology of unequivocal ALL absent any myeloid antigens. Six weeks later, during treatment for ALL, bone marrow pathology was consistent with MDS.

Of the patients who developed t-MN, 1 each had an initial diagnosis SAA, AML, or MM, 2 had CLL, 7 had DLBCL, and 10 had iNHL. Although iNHL only accounts for 31% of the study population, it accounts for 45% of patients with t-MN. The group with the largest proportion of patients with t-MN was CLL, with 9%. The only patient with t-MN with an original diagnosis of AML (Table 2, patient no. 2) originally presented with 47,XY+21 [3]/46,XY [17] and normal peripheral blood counts and no dysplasia. Before HDT, the patient was in complete remission with a normal karyotype. After HDT the patient developed cytopenias, marrow dysplasia and the cytogenetic abnormality 46,XY,+1,der(1;7)(q10;p10) [8]/46,XY [12], which was confirmed on subsequent evaluations. Therefore, this case was classified as t-MN as opposed to relapsed disease. Of the 34 patients with the initial diagnosis of AML, 17 relapsed after HDT, all but 3 within 1 year. In addition, 8 died of complications of HDT. Outcomes were similar with ALL, with 7 of the 11 patients dead or relapsed within 1 year. None of the 4 remaining patients developed t-MN.

Of the 22 patients who developed t-MN, only 6 patients were in first complete remission at time of HDT, 2 were in second complete remission, and the remainder had active disease. In addition, the majority were relatively heavily pretreated before HDT. The median number of cycles of chemotherapy administered was 6, and 13 patients were treated with more than 1 chemotherapy regimen. Only 1 patient, who had SAA, received no prior cytotoxic therapy. All but 3 patients received alkylating agents, 16 in combination