Isolated Clonal Cytogenetic Abnormalities after High-Dose Therapy

Margaret M. Showel, *Sidney Kimmel Comprehensive Cancer Center*
Robert A. Brodsky, *Johns Hopkins University*
Hua-Ling Tsai, *Sidney Kimmel Comprehensive Cancer Center*
Katlyn M. Briel, *Sidney Kimmel Comprehensive Cancer Center*
Jeanne Kowalski, *Emory University*
Constance A. Griffin, *Sidney Kimmel Comprehensive Cancer Center*
Richard J. Jones, *Sidney Kimmel Comprehensive Cancer Center*

Journal Title: Biology of Blood and Marrow Transplantation
Volume: Volume 20, Number 8
Publisher: Elsevier: 12 months | 2014-08-01, Pages 1130-1138
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.bbmt.2014.03.033
Permanent URL: https://pid.emory.edu/ark:/25593/tvwcr

Final published version: http://dx.doi.org/10.1016/j.bbmt.2014.03.033

Copyright information:

Published in final edited form as:
Biol Blood Marrow Transplant. 2014 August ; 20(8): 1130–1138. doi:10.1016/j.bbmt.2014.03.033.

Isolated Clonal Cytogenetic Abnormalities after High-Dose Therapy

Margaret M. Showel[1,*], **Robert A. Brodsky**[2], **Hua-Ling Tsai**[1], **Katlyn M. Briel**[1], **Jeanne Kowalski**[3], **Constance A. Griffin**[1], and **Richard J. Jones**[1]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland [2]Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland [3]Department of Biostatistics and Bioinformatics, Winship Cancer Institute of Emory University, Atlanta, Georgia

Abstract

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.

Keywords

Treatment-related myeloid neoplasms; Clonal cytogenetic abnormalities; Chromosomal alterations in myeloid neoplasms

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

[*]Correspondence and reprint requests: Margaret M. Showel, The Bunting-Blaustein Cancer Research Bldg, Room 12 285, 1650 Orleans St, Baltimore, MD 21231. mshowel1@jhmi.edu (M.M. Showel).

Conflict of interest statement: There are no conflicts of interest to report.

Financial disclosure: The authors declare no competing financial interests.

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 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 ormore 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 onsite, 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 with an anthracycline, 8 of whom also received etoposide. A total of 13 patients were treated with vinca alkaloids, all in combination with other agents. Five patients received fludarabine, 1 as monotherapy. Conditioning regimens in these patients consisted of CyTBI for 11 patients, BuCy in nine, and HiCy in 2 patients. Of 106 patients who received HiCy, 2 developed t-MN with initial diagnoses of AA and iNHL.

Chromosomal analysis was available in 21 of the patients who developed t-MN (Table 2). Of those, all but 1 patient had abnormal cytogenetics, all of which contained CMCA classified as unfavorable risk in the setting of t-MN [11, 30]. Eighteen patients had complex abnormalities, whereas 3 had a single cytogenetic abnormality. Abnormalities involving chromosome 7 were the most common. The abnormal clone involved a median of 83% of the cells analyzed. The median interval from HDT to initial CMCA detection was 3.1 (range, .8 to 12.9) years. Three of these patients (Table 2, patient nos. 12, 20 and 21) initially developed CMCA with normal bone marrow pathology, no change in blood counts, and no clinical signs or symptoms of t-MN, preceding the definitive morphologic diagnosis of t-MN by 1.2 to 3.2 years.

Isolated CMCA

Of the patients who had karyotype evaluation after HDT, isolated CMCA were found in 11 patients, who as of the last follow-up date have not shown bone marrow pathology consistent with MDS or AML (Table 3). The median age of 56 was older than that of the general population. With 6 males and 5 females, the gender distribution resembled that of the study population. The median time to the detection of the CMCA after HDT was 2.0 (range, .3 to 9.6) years. All but 1 of these patients (Table 3, patient no. 8) had at least 2 years of disease-free follow-up after detection of the cytogenetic abnormality, including normal bone marrow evaluations. The median follow-up from the date of first discovery of the CMCA was 4.2 (range, 1.0 to 9.3) years, with median follow-up from HDT of 7.3 years (range, 3 to 11.6) years. All of these patients were in complete remission with no histologic evidence of t-MN as of last follow-up at JHU. Patient no. 8 was in complete remission at last follow-up, but died 9 months later of unknown cause, per public records. Patient nos. 1 through 4 had isolated CMCA that were transient with normal karyotype on 1 or more subsequent analyses. Four patients had dysplasia in their marrow at some point that did not meet World Health Organization criteria for MDS morphology. All 3 patients with AA had cytopenias after HDT, but only 1 (Table 3, patient no. 1) had blood counts that were below the pretreatment values, which occurred transiently immediately after HDT. Of the remaining 8 patients, all of whom had normal blood counts before HDT, 4 had cytopenias briefly after HDT. Because of the nature and limitations of the data, it was not possible to estimate the rate at which these abnormalities occurred, but rather only at which they were discovered, with the premise that the incidence of occurrence is not likely to be lower this. The estimated cumulative incidence of discovering cases of isolated CMCA was 2.3% (95% CI, .8 to 3.8%) at 4 years.

Of the 11 patients in whom isolated CMCA were found, only 3 received more than 1 prior chemotherapy regimen and 3 patients with the initial diagnoses of SAA received no chemotherapy before HDT. Of the 8 previously treated patients, 5 were in remission at time of HDT. All those treated received alkylating agents. Seven patients received anthracyclines and vinca alkaloids, 2 of whom also received etoposide. One patient received fludarabine as part of combination therapy. Preparative regimens of CyTBI or HiCy were used in 4 patients each and BuCy in 3.

The CMCA in this group include anomalies that are often associated with t-MN, involving chromosomes 1, 5q, 7, 9q, and 20q [11, 30]. Cytogenetic abnormalities involving chromosome 7 were the most common, reported in 6 patients. Deletions or loss of chromosome 20 were reported in 4 patients. The abnormal clone involved a median of 39% of the cells analyzed. Of note, the t(8;21)(q22;p11.2) in patient no. 6 is not the classic t(8;21)(q22;q22) translocation seen in core-binding factor AML.

Of note, the patients with SAA represent over one quarter of the reported isolated CMCA cases but only about 5% of the total population. The 48 patients with SAA, which represent almost one half of the total HiCy cohort, had received no prior cytotoxic therapy. In contrast, almost all of the ASCT group had been treated before HDT. In addition, as part of their follow-up, the patients with SAA, and therefore the HiCY cohort in general, likely had more bone marrow and karyotype evaluations than the general population, enabling the discovery of more abnormalities than the general population. These factors and the small number of positive cases make it difficult to compare the 2 HDT groups. Therefore, the HiCy cohort was not evaluated separately.

DISCUSSION

This study reports the follow-up of 785 patients who received HDT at our institution. The estimated cumulative incidence of t-MN was 3.5% (95% CI, 1.6% to 5.4%) at 4 years. This incidence lies in the range of those previously reported; however, the true incidence is possibly higher. Although the median follow-up of all eligible patients who did not die or relapse was 3.5 years, t-MN can develop at least up to 10 years after cytotoxic therapy [1, 3, 31].

The most notable aspect of this analysis is the finding that in 11 patients, isolated CMCA were discovered, 4 of which were detected transiently. The isolated CMCA include anomalies that are often associated with t-MN.

There are several limitations to the interpretation of our data. Though follow-up after detection of the CMCA was at least 2 years in all but 2 patients, with median of over 4 years, it is possible that t-MN could still develop in these patients. Furthermore, although part of our recommended follow-up after HDT, routine bone marrow karyotype evaluation was not performed in all patients, and some returned to their home institution and were lost to follow-up, and consequently cases of isolated CMCA would have been missed. Therefore, within our reported time period, the number of cases of isolated CMCA after HDT +/− ASCT is very likely higher than reported here. Therefore, it is not possible to calculate a true

estimate of the cumulative incidence of this phenomenon. As the number of cases is likely higher than those discovered, the incidence of isolated CMCA is likely no lower than the estimated incidence of discovered cases of 2.3% (95% CI, .8% to 3.8%). Other groups have also reported rare instances of isolated clonal cytogenetic abnormalities after ASCT [2, 9, 13–19], but to our knowledge this is 1 of the largest single series of such patients. The only larger series was limited to patients with MM [9]. Moreover, the previous reports often included cytogenetic abnormalities that were not clonal or were normal variants. Table 4 summarizes the findings regarding only the isolated clonal cytogenetic abnormalities from these studies [2, 9, 14–19]. The largest series published reported 79 of 2418 patients who developed CMCAs without t-MN, two thirds of which were transient [9]. Imrie et al. reported findings comparable to ours: 6 of 62 patients treated with ASCT for AML developed isolated CMCA, including 2 which were transient [14]. Perot et al. reported 7 of 66 patients with persistent and 4 with transient isolated CMCA [17].

It is impossible to know if the isolated CMCA originated from hematopoietic progenitors that were damaged during conventional treatment before HDT or rather were damaged during high-dose conditioning. Regardless of when the damage occurred, the observed aberrant clones apparently lacked the ability to transform into malignant clones during the period of follow-up. Transient clonal hematopoiesis could be the result of mutations occurring in hematopoietic progenitors with limited self-renewal capacity. Moreover, normal hematopoietic progenitors acquire DNA mutations with age that are probably benign and not associated with malignant progression [32]. Therefore, perhaps it is not surprising that in patients who have been exposed to agents known to cause DNA damage and have frequent bone marrow analysis, gross genetic mutations (CMCA) that are not related to malignancy would be discovered.

The SAA group further highlights the importance of CMCA that may not represent t-MN. Of those 4 patients who developed cytogenetic abnormalities, only 1 has developed t-MN as of the last follow-up. Because of their reported increased risk of developing MDS/AML [14, 33], their increased incidence of clonal cytogenetic abnormalities [34], and the fact that these patients have cytopenias after HDT, patients with AA may be more likely to be diagnosed with MDS in the setting of isolated CMCA. Therefore, it would be particularly important in this population to note that all CMCA may not be associated with t-MN.

Though there were some differences between patients with t-MN and those with detected isolated CMCA, these differences did not definitively distinguish the 2 groups. Compared with those that developed t-MN, the cohort in whom CMCA were discovered received less cytotoxic therapy before and during HDT. The abnormal clone involved a median of only 39% of cells in patients with isolated CMCA compared with 83% of cells when the abnormality occurred with t-MN. Isolated CMCA were detected sooner after HDT than CMCA associated with t-MN, 2.0 (range, .3 to 9.6) versus 3.1 (range, .8 to 12.9) years respectively; however, there is significant overlap in these time intervals. In addition, 3 patients who developed t-MN initially had CMCA that presented with normal bone marrow pathology, preceding the definitive morphologic diagnosis of MDS/AML. The cytogenetic abnormalities in both groups were similar. Altogether, CMCA were found in 31 patients, only 20 of whom developed t-MN during the follow-up period. The proportion of CMCA

associated with t-MN cannot be calculated definitively for several reasons: as all patients did not have karyotype evaluation at all time points, all cases of isolated CMCA would not be discovered; undoubtedly some bone marrow biopsies were done because of peripheral blood count abnormalities or other clinical abnormalities, resulting in a higher likelihood that t-MN would be discovered; and those patients with identified isolated CMCA could still develop t-MN with longer follow-up. Despite these limitations, our data suggest that not all patients with isolated CMCA develop t-MN. Taken together, these findings have significant clinical implications, as the only curative treatment option for t-MN is allogeneic SCT with its high risk of morbidity and mortality. Moreover, early allogeneic SCT for t-MN would seem to be most effective. However, after HDT, the development of CMCA alone, even if persistent, should not be used as the sole criteria to diagnose t-MN. Morphologic changes in the bone marrow diagnostic of t-MN should also be present.

Acknowledgments

This work was supported in part by a grant from the National Institutes of Health (P01 306 CA15396).

REFERENCES

1. Del Cañizo M, Amigo M, Hernández JM, et al. Incidence and characterization of secondary myelodysplastic syndromes following autologous transplantation. Haematologica. 2000; 85:403–409. [PubMed: 10756367]
2. Lambertenghi Deliliers G, Annaloro C, Pozzoli E, et al. Cytogenetic and myelodysplastic alterations after autologous hemopoietic stem cell transplantation. Leuk Res. 1999; 23:291–297. [PubMed: 10071084]
3. Burns LJ. Late Effects after autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009; 15:21–24. [PubMed: 19147072]
4. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high- dose chemotherapy and autologous stem cell transplantation. Blood. 2000; 95:3273–3279. [PubMed: 10828005]
5. Tarella C, Passera R, Magni M, et al. Risk factors for the development of secondary malignancy after high-dose chemotherapy and autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol. 2011; 29:814–824. [PubMed: 21189387]
6. Hosing C, Munsell M, Yazji S, et al. Risk of therapy-related myelodysplastic syndrome/acute leukemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin's lymphoma. Ann Oncol. 2002; 13:450–459. [PubMed: 11996478]
7. Lillington DM, Micallef IN, Carpenter E, et al. Detection of chromosome abnormalities pre–high-dose treatment in patients developing therapy-related myelodysplasia and secondary acute myelogenous leukemia after treatment for non-Hodgkin's Lymphoma. J Clin Oncol. 2001; 19:2472–2481. [PubMed: 11331326]
8. Metayer C, Curtis RE, Vose J, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multi-center case-control study. Blood. 2003; 101:2015–2023. [PubMed: 12393427]
9. Barlogie B, Tricot G, Haessler J, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3000 patients treated since 1989. Blood. 2008; 111:94–100. [PubMed: 17895401]
10. Kollmannsberger C, Hartmann JT, Kanz L, et al. Risk of secondary myeloid leukemia and myelodysplastic syndrome following standard-dose chemotherapy or high-dose chemotherapy with stem cell support in patients with potentially curable malignancies. J Cancer Res Clin Oncol. 1998; 124:207–214. [PubMed: 9619748]

11. Armand P, Kim HT, DeAngelo DJ, et al. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. Biol Blood Marrow Transplant. 2007; 13:655–664. [PubMed: 17531775]
12. Godley LA, Larson RA. Therapy-related myeloid leukemia. Semin Oncol. 2008; 35:418–429. [PubMed: 18692692]
13. Hake CR, Graubert TA, Fenske TS. Does autologous transplantation directly increase the risk of secondary leukemia in lymphoma patients? Bone Marrow Transplant. 2007; 39:59–70. [PubMed: 17143301]
14. Imrie KR, Dubé I, Prince HM, et al. New clonal karyotypic abnormalities acquired following autologous bone marrow transplantation for acute myeloid leukemia do not appear to confer an adverse prognosis. Bone Marrow Transplant. 1998; 21:395–399. [PubMed: 9509975]
15. Laurenti L, Chiusolo P, Garzia MG, et al. Periodic morphologic, cytogenetic and clonality evaluation after autologous peripheral blood progenitor cell transplantation in patients with lymphoproliferative malignancies. Haematologica. 2002; 87:59–66. [PubMed: 11801466]
16. Martínez-Climent JA, Comes AM, Vizcarra E, et al. Chromosomal abnormalities in women with breast cancer after autologous stem cell transplantation are infrequent and may not predict development of therapy-related leukemia or myelodysplastic syndrome. Bone Marrow Transplant. 2000; 25:1203–1208. [PubMed: 10849534]
17. Perot C, Van den Akker J, Laporte JP, et al. Multiple chromosome abnormalities in patients with acute leukemia after autologous bone marrow transplantation using total body irradiation and marrow purged with mafosfamide. Leukemia. 1993; 7:509–515. [PubMed: 8464228]
18. Soligo DA, Lambertenghi Deliliers G, Servida F, et al. Haematopoietic abnormalities after autologous stem cell transplantation in lymphoma patients. Bone Marrow Transplant. 1998; 21:15–22. [PubMed: 9486489]
19. Basecke J, Podleschny M, Becker A, et al. Therapy-associated genetic aberrations in patients treated for non-Hodgkin lymphoma. Br J Haematol. 2008; 141:52–59. [PubMed: 18324966]
20. Goodman KA, Riedel E, Serrano V, et al. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. J Clin Oncol. 2008; 26:5240–5247. [PubMed: 18809615]
21. Anderson JE, Gooley TA, Schoch G, et al. stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy. Blood. 1997; 89:2578–2585. [PubMed: 9116305]
22. Kern W, Haferlach T, Schnittger S, et al. Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. J Clin Oncol. 2004; 22:2510–2511. [PubMed: 15197216]
23. Brodsky RA, Chen AR, Dorr D, et al. High-dose cyclophosphamide for severe aplastic anemia: long-term follow-up. Blood. 2010; 115:2136–2141. [PubMed: 20018919]
24. Gladstone DE, Bolaños-Meade J, Huff CA, et al. High-dose cyclophosphamide and rituximab without stem cell transplant: a feasibility study for low grade B-cell, transformed and mantle cell lymphomas. Leuk Lymphoma. 2011; 52:2076–2081. [PubMed: 21756035]
25. Kasamon YL, Jones RJ, Brodsky RA, et al. Immunologic recovery following autologous stem-cell transplantation with pre- and post-transplantation rituximab for low-grade or mantle cell lymphoma. Ann Oncol. 2010; 21:1203–1210. [PubMed: 19880437]
26. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51:189–199. [PubMed: 6952920]
27. Swerdlow, SH.; Campo, E.; Harris, NL. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2008.
28. Shaffer, L.; Slovak, ML.; Campbell, LJ. ISCN(2009): An international system for human cytogenetic nomenclature. Basel, Switzerland: Karger; 2009.
29. Herens C, Brasseur E, Jamar M, et al. Loss of the Y chromosome in bone marrow cells: results on 1907 consecutive cases of leukaemia and preleukaemia. Clin Lab Haematol. 1999; 21:17–20. [PubMed: 10197258]
30. Schoch C, Kern W, Schnittger S, et al. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in

comparison to 1091 patients with de novo AML. Leukemia. 2003; 18:120–125. [PubMed: 14586477]

31. Stone RM, Neuberg D, Soiffer R, et al. Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol. 1994; 12:2535–2542. [PubMed: 7989927]
32. Welch JS, Ley TJ, Link DC, et al. The origin and evolution of mutations in acute myeloid leukemia. Cell. 2012; 150:264–278. [PubMed: 22817890]
33. Tichelli A, Gratwohl A, Würsch A, et al. Late haematological complications in severe aplastic anaemia. Br J Haematol. 1988; 69:413–418. [PubMed: 3044440]
34. Appelbaum FR, Barrall J, Storb R, et al. Clonal cytogenetic abnormalities in patients with otherwise typical aplastic anemia. Exp Hematol. 1987; 11:1134–1139. [PubMed: 3315724]

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.

Table 2

Characteristics of Patients Who Developed t-MN after High-Dose Therapy

Patient No.	Dx	Previous Treatments	Status at HDT	HDT Prep	Years from HDT to t-MN	Outcome (years from HDT)	Time after HDT, yr	Cytogenetic Results
1.	AA	Prednisone	Active	HiCy	12.9	Alive with MDS (15.2)	Pre	46,XX[19]
							.5	46,XX[20]
							1	46,XX[10]
							2	46,XX[20]
							12.9	45,XX,−7[4]/45,idem,del(20)(q12)[4]/46,XX[2]
							13	45,XX,−7[9]/46,XX[11]
2.	AML	HDAC+	CR1	BuCy	2.2	Dead* (6.5)	Pre	46,XY[20]
		duano, HDAC+					.3, .6	46,XY[20]
		VP16					1, 1.4	46,XY[20]
							2.2	46,XY,+1,der(1;7)(q10;p10)[8]/46,XY[12]
							3	46,XY,+1,der(1;7)(q10;p10)[5]/46,XY[15]
							4	46,XY,+1,der(1;7)(q10;p10)[9]/47,idem,+8[11]
							5.8	47,XY,+8[1]/47,XY,+1,der(1;7)(q10;p10),+8[16]/46,XY[3]
3.	CLL	FluCy × 4	PR1	CyTBI	5.2	Dead (5.7)		NA
4.	CLL	Flu × 6	CR1	BuCy	3.1	Dead (6.6)	.1	46,XY[21]
		CHOP × 2 FluCy × 2					3.1	49–52,XY,+6,+8,+10,+11,i(17)(q10),+22[cp19]/46,XY[1]
5.	DLBCL	CHOP × 6	REL1	CyTBI	3.2	Dead (5.6)	3.2	−7 per note
		ESHAP × 2					3.5	−7 per note
							3.9	45,XX,−7[19]/46,XX[1]
							4.3	46,XX,−7,+21[2]/46,XX[7]
							4.6	46,XX,−7,+21[1]
							4.8	46,XX,−7,+21[11]/46,XX[9]
							5.1	46,XX,−7,+21[9]/46,XX[1]

Patient No.	Dx	Previous Treatments	Status at HDT	HDT Prep	Years from HDT to t-MN	Outcome (years from HDT)	Time after HDT, yr	Cytogenetic Results
6.	DLBCL	CHOP × 6	CR1	BuCy	2.8	Dead (2.9)	2.8	45,XY,−7[1]/44,XY,add(4)(q21),−7,add(18)(p11.3),−20, add(21)(q22)[19]
							2.9	44,XY,add(4)(q21),−7,add(18)(p11.3),−20, add(21)(q22)[15]/44,idem,add(19)(p13.3)[5]
7.	DLBCL	RCHOP × 6 RICE × 2	CR2	CyTBI	1.3	Dead (1.7)	1.3	−5q (66%) −20q(77%) FISH
8.	DLBCL	CVP × 8, RCHOP REPOCH	REL1	BuCy	2.7	Dead (3.6)	2.7	46,XX,−7[13]/45,idem,−6,add(10)(q11.2),add(12)(p12), add(20)(p13),+mar[7]
							2.8	44–45,XX,−6,−7,−12, add(20)(p13),+mar1,+mar2[cp5]/46,XX[5]
9.	DLBCL	RCHOP × 2 RESHAP	PR2	BuCy	2.1	Dead (2.9)	2.1	46,XY,del(7)(q22)[18]/46,XY[2]
							2.2	46,XY,del(7)(q22)[20]
							2.4	46,XY,del(7)(q22)[17]/46,XY[3]
10.	DLBCL	RCHOP × 6	PR2	CyTBI	8.8	CR (9.2)	8.8	47,XY,+8[2]/46,XY[18]
		ESHAP × 1					8.9	47,XY,+8[3]/46,XY[17]
		RT					9.2	46,XY[20]
11.	DLBCL	CHOP × 6	CR2	BuCy	4.3	Dead (4.8)	Pre	46,XY[20]
		ICE × 3					4.3	43,XY,der(5;17)(p10;q10),−7,der(19)t(19;20)(p13.1;p11.2),−20[3]/44,idem,+mar[6]/46,XY[11]
12.	MM	MP × 4	PR2	BuCy	2.5	Dead (3.0)	1.3	Complex including add(5),dup(6),del(11),del(15) per note
		VAD × 2					2.5	45,XX,−5,dup(6),dup(12)−18,−21 per note
							2.8	45,XX,−5,trp(6)(p12p21),ins(12;?)(q13;?),−18,+mar[14]/45,idem,11,der(18)t(1;18)(q12,q21)[3]/45,idem,del(20)(q12)[3]3/44,idem,t(X;21)(q2~4;q22)[2]
13.	iNHL	FluCy × 4	PR1	CyTBI	9.3	Dead (9.7)	9.3	48,XY,?inv(4)(p15.2q33),del(7)(q34),+8,+11[20]
14.	iNHL	FluCy × 4	CR1	CyTBI	4.0	Dead (4.7)	4	47,XY,+8[20]
15.	iNHL	ProMACE-CytaBOM, RT REPOCH × 2	REL1	BuCy	3.0	Dead (4.8)	3	46,XY,inv(14)(q11.2q32)[2]/46,idem,t(6;6)(p11.2;q25)[3]/46,XY,del(13)(q12q14)[2]/46,X,del(Y)(q11.2q12),add(12)(p12)[2]/46,XY[27]
							3.6	46,XY,add(6)(q25),−7,add(11)(p15),del(17)(q21)[2]/46,XY[15]
							4	46,XY[30]
16.	iNHL	RCHOP × 6	CR1	CyTBI	2.0	Dead (2.5)	.2, .5	46,XY[25]
							2	45,XY,add(1)(p36.1),add(5)(q15),−7,add(9)(p11),−19,+mar[17]/46,XY[3]
17.	iNHL	CVP × 8	REL2	HiCy	4.1	Dead (4.2)	1.0, 1.3	46,XX[26],[20]

Patient No.	Dx	Previous Treatments	Status at HDT	HDT Prep	Years from HDT to t-MN	Outcome (years from HDT)	Time after HDT, yr	Cytogenetic Results
		RCHOP × 3					1.5, 1.7	46,XX[20]
18.	iNHL	CHOP +	REL1	CyTBI	.8	Dead (.8)	.2	46,XY[25]
		HDMTX × 8 RT RESHAP × 2					.8	46–48,XY,t(1;21)(q12;q11.2),−7,der(7;10)(p10;q10),−10, add(11)(p14),der (12)t(1;12)(q21;q13), add(13)(p11.2), −17, add(19)(p13.3),+i(19)(q10),+14mar[cp9]
19.	iNHL	CHOP × 7	PR1	CyTBI	5.4	Dead (7.3)	3.6, 3.8	46,XY[20],[21]
							5.4	del(5),−7,−8,der(12),add(17)[11]/t(13;15)[2]/46,XY[7]per note
20.	iNHL	Flu × 5	PR1	CyTBI	6.3	Dead (7.9)	.1	46,XY[20]
							3.1	46,Y,t(X;1)(q26;q21),t(7;13)(p12;q32),del(10)(q22) [6]/46,Y,t(X;12)(q26;q13), der(7)del(7)(p11.2p14)add(7) (q22),inv(7)(q11.2q22)[2]/46,XY[16]
							6.3	t(X;1),t(7;13),del(10)[2/20] per note
							6.4	+2,del(5), del(7),inv(11),t(8;12) [2/20] per note
							7.3	46,Y,t(X;12)(q26;q13),der(7)del(7)(p11.2p14)add(7)(q22),inv(7)(q11.2q22) [6]/46,XY,del(7)(q22q32), inv(11)(p11.2q25),add(12)(q24)[2]/46,Y, t(X;1)(q26;q21),t(7;13)(p12;q32),del(10)(q22)[1]/46,XY[8]
21.†	iNHL	CHOP × 6	CR1	CyTBI	2.3	Dead (2.6)	Pre	46,XY[25]
							.2	46,XY[25]
							.8	46,XY,t(1;2)(p13;q31),t(5;18)(q33;q22),t(8;17)(q22;p13),inv(10) (p11.2q26)[8]/46,XY[12]
							1.0	46,XY,t(1;2)(p13;q31),t(5:18)(q33;q22),t(8;17)(q22;p13), inv(10) (p11.2q26)[16]/46,XY[9]
							2.0	46,XY,t(1;2)(p13;q31),t(5;18)(q33;q22),t(8;17)(q22;p13),inv(10) (p11.2q26)[20]
22.	iNHL	RCHOP × 3	PR1	BuCy	4.4	Dead (5.5)	.2, .5	46,XX[20]
		RICE × 2					1, 2	46,XX[20]
							4.4	complex per note
							4.8	45,XX,der(5;17)(p10;q10),−13,add(22)(q13),+mar[10]
							5.0	45,XX,der(5;17)(p10;q10),−13,add(22)(q13),+mar[6]/46,sl,+8[3]

Dx indicates diagnosis; HDT, high-dose therapy; Pre, before HDT; NA, not available; CR, complete remission; UNK, unknown; REL, relapse; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; RESHAP, Rituxan, etoposide, methylprednisolone, cytarabine, cisplatin; RT, radiation therapy; HCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; E2993, chemotherapy modeled after ECOG 2993 trial; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; HD, high dose; M, melphalan; P, prednisone; T, thalidomide; dauno, daunorubicin; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; CVP, cyclophosphamide, vincristine, prednisone; VAD, vincristine, doxorubicin, dexamethasone; Flu, fludarabine; ProMACE, prednisone, etoposide, doxorubicin, cyclophosphamide; CytaBOM, cytarabine, bleomycin, vincristine, methotrexate, leucovorin; AC,

cytarabine; PR, partial remission; RICE, rituximab, ifosfamide, carboplatin, etoposide; t-MN, therapy-related myeloid neoplasms; AA, aplastic anemia; iNHL, indolent non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic lymphoma; MM, multiple myeloma; AML, acute myeloid leukemia, MDS, myelodysplastic syndrome.

*Causes of death: Patient nos. 2, 5, 6, 15, 16, and 20 died of infection in the setting of refractory t-MN. Patient no. 3,4,7,8, 12–14, and 21 were discharged to home institutions or hospice for supportive care in the setting of active t-MN, and subsequently succumbed to their disease. Patient nos. 9 and 19 died of infection in the setting of refractory GVHD after allogeneic SCT for t-MN. Patients 11, 17, and 18 died of complications of relapsed NHL in the setting of active t-MN.

†Patient 21 had normal bone marrow pathology on all 4 biopsies listed. Then, at 2.3 years from HDT, a bone marrow biopsy performed at an outside hospital was consistent with t-MN, but those results were unavailable.

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2015 August 01.

Table 3

Characteristics of Patients Who Developed Isolated CMCA after High-Dose Therapy

Pt No.	Dx	Previous Treatments	Status at HDT	HDT Prep	Outcome (years from HDT)	Time after HDT, yr	Cytogenetic Results	WBC (10^3 per mm^3)	HCT (%)	PLT (10^3 per mm^3)
1.	AA	None	Active	HiCy	CR (5)	Pre	46,XX[20]	3.8	11.3	8
						3.4	−7[7/20] per note	3.8	34.6	62
						3.6	46,XX[20]	3.3	33.5	29
						3.8	46,XX[20] and FISH AML profile WNL	NA	NA	NA
2.	AA	None	Active	HiCy	CR (3.3)	Pre	NA	.43	15.8	2
						1	47,XX,+22[8]/46,XX[12]	1.7	27.3	10
						3.3	46,XX [26]	2.2	24.3	11
3.	DLBCL	RCHOP × 5	CR2	CyTBI	CR (8.5)	Pre	NA	4.8	26.2	167
		RICE × 5				1	46,XX [25]	4.6	37.2	93
						2	46,XX,del(7)(q31q35)[4]/46,XX[16]	5.8	33.8	134
						3	46,XX[20]	5.8	38.6	151
4.	HL	ABVD × 8	REL1	BuCy	CR (7.3)	pre	NA	3.8	28.1	134
		ESHAP × 3				.2	46,XY[20]	2.3	26.8	34
						.9	46,XY,t(1;9)(p22;p13)[2]/46,XY[29] FISH AML and MM profile WNL	1.7	25.6	21
						1, 2	46,XY[20]	5.5	38.1	51
						3	46,XY,t(1;9)(p22;p13)[1]/46,XY[19]	6.5	36.0	100
5.	AA	None	Active	HiCy	CR (7.2)	Pre	46,XX[1]	1.8	25.4	8
						3	46,XX,inv(7)(q11.2q22)[20]	3.0	33.7	55
6.	ALL	E2993	CR1	CyTBI	CR (9.9)	Pre	46,XY[20] and FISH BCR/ABL WNL	1.9	29.2	84
						.3	46,XY,add(1)(p32),t(2;8)(q12;p23),t(3;17)(p21;q22),t(7;8)(q32;q13), −12, del(13)(q12q14),+mar[3]/46,XY[8] and FISH wnl :BCR/ABL	2.4	32.1	23
						1.3	46,XY,t(8;21)(q22;p11.2)[4]/46,XY,add(1)(p32),t(2;8)(q12;p23), t(3;17)(p21;q22), t(7;8)(q32;q13),−12,del(13)(q12q14), +mar[6]/46,XY[9]	1.9	31.0	9
						2.5	46,XY,t(8;21)(q22;p11.2)[5]/46,XY,add(1)(p32),t(3;17)(p21;q22), del(5)(p11.2), t(6;12)(q21;q15),t(7;8)(q32;q13),−12,del(13) (q12q14), +mar[cp11]/46,XY[4] and FISH BCR/ABL negative	3.2	41.3	18
						9.1	46,XY,del(13)(q12q14)[4]/46,sl,t(2;8)(q12;p23),t(3;17)(p21;q22), t(7;8)(q32;q13),−12,+mar[2]/46,XY[8] and FISH BCR/ABL WNL	5.7	41.4	114

Pt No.	Dx	Previous Treatments	Status at HDT	HDT Prep	Outcome (years from HDT)	Time after HDT, yr	Cytogenetic Results	WBC (10^3 per mm^3)	HCT (%)	PLT (10^3 per mm^3)
						9.9	46,XY,del(13)(q12q14)[5]/46,XY,t(8;21)(q22;p11.2)[1]/46,XY, −1,add(3)(p21),add(12)(q24.3),−15,−20,+3mar[3]/46,XY,add(1)(p32), t(2;8)(q12;p23),t(3;17)(p21;q22),t(7;8)(q32;q13), −12,del(13)(q12q14),+mar[4]/46,XY[6] and FISH BCR/ABL WNL	5.7	37.3	124
7.	CLL	Flu × 3	PR1	CyTBI	CR (11.3)	Pre	NA	4.7	30.8	90
		Chlr × 6				6.3	46,X,t(Y;15)(p11.2;q11.2),t(11;12)(p15;q13),del(20)(q12)[9]/46,XY, t(2;7)(q33;p13),t(2,10;6)(q31;q22;q25),t(9;21;15)(q22;q22;q15), −20,del(20)(q11.2),+22[6]/46,XY[8]	3.2	38.9	112
						8.8	46,XY,t(2;7)(q33;p13),t(2;10;6)(q31;q22;q25),t(9;21;15) (q22;q22;q15),−20,del(20)(q11.2),+22[19]/46,X,t(Y;15) (p11.2;q11.2),t(11;12)(p15;q13),del(20)(q12)[2]/46,XY[1]	4.2	44.3	145
						10.2	46,X,t(Y;15)(p11.2;q11.2),t(11;12)(p15;q13),del(20)(q12) [14]/46,XY[6] and FISH AML profile del(20q) 48%	3.5	41.1	131
						11.2	del(20q) 37% FISH	4.3	41.8	146
8.	DLBCL	RT	CR2	BuCy	Dead (3)	Pre	NA	6.9	23.0	588
		CHOP × 6				.2	46,XX[20]	7.0	32.5	277
						.5	46,XX[20] and FISH BCR/ABL WNL	4.7	42.5	229
						1	46,XX[20]	5.8	37.4	271
						2	46,XX,del(7)(q22)[2]/46,XX[18]	6.0	36.1	412
9.	DLBCL	CHOP × 4	REL1	BuCy	CR (11.6)	Pre	NA	9.1	26.7	159
		RT				3.0	46,XY[21]	4.4	33.9	62
						9.6	del(20)(q11.2q13.3) [5/20] per note and FISH positive: del(20q) per note	4.2	21.0	97
						10	FISH AML profile WNL	4.0	35.8	97
10.*	iNHL	HCVAD × 5	CR1	CyTBI	CR (7.5)	Pre	NA	3.9	29.9	218
						.3	46,XY[25]	6.3	35.8	185
						.5	46,XY[25]	7.0	35.6	179
						1	45,X,−Y[7]/46,XY[18]	5.2	42.3	212
						2	45,X,−Y[6]/46,idem,+15[2]/46,XY[12]	6.5	40.7	276
						3	45,X,−Y[4]/46,X,−Y,+15[3]/46,XY[13]	6.9	39.5	268
						5	45,X,−Y[3]/46,idem,+15[4]/46,XY[18]	7.3	40.1	279
11.	iNHL	RCHOP × 6	CR1	HiCy	CR (5.3)	Pre	NA	7.5	37.9	231
						3.3	45,X,−Y[11]/46,XY,del(20)(q13.1)[10]	1.9	35.5	120
						5.3	46,XY,del(20)(q13.1)[14]/45,X,−Y[6]	5.0	33.8	139

Dx indicates diagnosis; HDT, high-dose therapy; HCT, hematocrit; PLT, platelet; Pre, before HDT; AML, acute myeloid leukemia; WNL, within normal limits; NA, not available; CR, complete remission; UNK, unknown; REL, relapse; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; RT, radiation therapy; HCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; E2993, chemotherapy modeled after ECOG 2993 trial; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; HD, high dose; M, melphalan; P, prednisone; T, thalidomide; dauno, daunorubicin; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; CVP, cyclophosphamide, vincristine, prednisone; VAD, vincristine, doxorubicin, dexamethasone; Flu, fludarabine; ProMACE, prednisone, etoposide, doxorubicin, cyclophosphamide; CytaBOM, cytarabine, bleomycin, vincristine, methotrexate, leucovorin; AC, cytarabine; RICE, rituximab, ifosfamide, carboplatin, etoposide; Chlr, chlorambucil; CMCA, clonal marrow cytogenetic abnormalities; AA, aplastic anemia; HL, Hodgkin lymphoma; iNHL, indolent non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; CLL, chronic lymphocytic lymphoma; PR1, first partial response; ALL, acute lymphoblastic lymphoma; MM, multiple myeloma; AML, acute myeloid leukemia.

Results denoted “per note” were only available from clinician notes, and the corresponding analyses were not done at our institution.

FISH results: In cases where more than 1 probe was tested, the name of the profile is stated and contain the following probes: AML FISH profile: 5p15.2, 5q31, 7cen, 7q31, 8cen, 11q23, 20pter, 20q12. Multiple myeloma (MM) FISH profile: 3cen, 7cen, 9cen, 15cen, 11q13, 14q32, 13q14, 13q34, 14q32, 17cen, 17p13.1 The MM profiles were not done at our institution.

* Patient 10: Loss of chromosome Y was considered a normal variant not a cytogenetic abnormality.

Table 4

Summary of Published Reports of Isolated CMCA after High-Dose Therapy

Author	No. Pts Evaluable of Total	Diagnoses	Pts with CMCA and Diagnosis		Follow-up Time from ASCT, mo		Months from ASCT to CMCA
			Transient	Persistent	Cohort, Median	Positive Pts	
Imrie	62 of 76	AML	2	4	39	4, median	20, median
Laurenti	66 of 225	NHL, MM, CML, HL	2 HL	0	25	67 and 49	32 and 16
Perot	66 of 114	AML, ALL	4	7	NA	46, median	20, median
Deliliers	83 of 109	NHL, HL, AML, ALL, MM	3 AML	0	47	NA	3–12
Soligo	31	NHL, HL	0	2	NA	18 and 18	12 and 18
Martinez-Climent	60 of 229	Breast	2	1	36	NA	12,12, and 18
Basecke*	53 of 56	DLCL, CLL	1 DLCL	1 CLL	48	45 and 12	12 and 12
Barlogie	2418 of 3077	MM	54	25	NA	NA	5–124

AML indicates acute myeloid leukemia; NHL, non-Hodgkin leukemia; MM, multiple myeloma; CMCA, clonal marrow cytogenetic abnormalities; CML, chronic myeloid leukemia; HL, Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; DLCL, diffuse large B cell lymphoma; ASCT, autologous blood or marrow transplantation, Pts, patients; HDT, high-dose therapy.

This table includes only patients who meet the same criteria for isolated CMCA used in our study. Patients without cytogenetic analysis at diagnosis who died of relapsed AML after HDT were not considered isolated CMCAs, as per our methodology.

*Though 3 patients were reported with aberrant clones, only 2 had completed HDT.