Therapy-related Myelodysplastic Syndrome Following Primary Breast Cancer

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Abstract

Background: Therapy-related myelodysplastic syndrome (t-MDS) is a serious clinical disease occurring after breast cancer treatment.

Methods: A cohort of 11,684 invasive breast cancer (BC) patients from 1990-2014 were followed for incidence of t-MDS through institutional and the Surveillance, Epidemiology and End Results (SEER) Program registries. t-MDS cases were identified using ICD-O SEER registry codes, pathology and chart reports. Treatment, cytogenetics, and time from BC diagnosis to t-MDS and t-MDS diagnosis to last follow up or death were obtained. Incidence rate ratios were calculated using SEER national incidence rates for comparison.

Results: 27 cases of t-MDS post BC treatment were confirmed. 96% of cases were breast cancer stage I-II at diagnosis. All patients had received radiation treatment and 59% received adjuvant chemotherapy. Two patients were alive with no evidence of disease after treatment with stem cell transplantation (age 33 and 46). t-MDS incidence was 30 times the expected population rate among patients < 55 years (RR 31.8, 95% CI 15.0, 60.8) with shorter time from t-MDS diagnosis to death (median survival time: <55: 8 months, 55-74: 26 months, 75+: 23 months).

Conclusion: We found elevated t-MDS risk especially among younger BC patients with stem cell transplantation the only observed curative treatment.

Keywords: therapy-related myeloid neoplasm, breast cancer, therapy-related myelodysplasia, prognosis, survival, t-MDS

Background

Therapy-related myelodysplastic neoplasias (tMN) represent clonal hematopoietic stem cell disorders resulting in abnormal hematopoiesis including both myelodysplasia (tMDS) and acute myelogenous leukemia (tAML) [1]. The term therapy-related myelodysplastic syndrome (t-MDS) is used to describe treatment-related MDS based on a patient's history of exposure to cytotoxic agents in the form of either chemotherapy or radiation [2]. Even though t-MDS is rare the outcome is often lethal and incidence post treatment may increase over time with improved breast cancer survival due to early diagnosis and clinical advances [3]. The number of invasive breast cancer patients potentially affected by treatment related myeloid neoplasms could be as much as .54% 8 year cumulative incidence depending on patient age and treatment received [4]. However the epidemiology of t-MDS following breast cancer treatment as distinct from t-AML is not fully characterized with the latency period between primary diagnosis and therapy-related disease ranging from several months to several years [5].

Risk of t-MN's among breast cancer survivors varies by age [6], treatment with cytotoxic radiation and chemotherapy either separately or in combination [7-9], and use of granulocyte colony-stimulating factors (G-CSF) [10]. Clinical and cytogenetic associations with t-MN's following cancer treatment have been documented across different cancer sites. Characteristics include clonal abnormalities involving loss of all or part of chromosome 5 and/or 7 with alkylating agents, translocations involving chromosome bands 11q23 or 21q22 with anthracyclines, and other balanced rearrangements that can also occur with de novo leukemia [11].

There is no agreed upon standard treatment approach for patients with t-MDS following breast cancer treatment. Subsequent t-MDS treatment options vary considerably and will depend on the severity of disease, cytogenetic abnormalities, and patient's performance status [12]. The range of possible treatments include supportive care when life expectancy is limited, active treatment such as azacytidine, lenalidomide or cytosine arabinoside and allogeneic stem cell transplantation (SCT) when the intent of t-MDS treatment is curative [13, 14].

In this report, we expand on our previously published study of therapy-related myeloid neoplasm incidence following breast cancer diagnosis [7] but are intentionally reporting on t-MDS specifically as opposed to the broader categories that include t-AML or t-MN in general. We conducted a retrospective cohort study using our dedicated institutional breast cancer registry database to identify and describe t-MDS cases, treatment and outcomes from 1990 and 2014.

Methods

A breast cancer registry of patients seen at our institution was created in 1990 containing detailed information on diagnosis, staging, surgery, chemotherapy, radiation therapy, tumor markers, and follow up status. Incident cases of breast cancer are entered into the system in real time as the patients present to the institution and are followed for all treatment and subsequent outcomes related to their breast cancer diagnosis. Registry follow up is updated on an annual basis by a certified cancer registrar with information on recurrence, subsequent treatment and vital status, current through 2014. Vital and disease status information is obtained from electronic chart review if the patient is still seen at the institution, or through physician directed follow up

letter if follow up care is provided elsewhere. Patients not under the care of a managing physician are contacted by mail using an IRB approved letter from their diagnosing physician requesting annual follow up information. If no response is received, the institution's cancer registry and the SEER Seattle-Puget Sound Registry are reviewed for patient's vital and disease status [15]. IRB approved methods were used for patient follow up and data was input and stored in a password protected HIPAA compliant database. This project was reviewed and approved by the Institutional Review Board at our community based regional cancer center. All analyses were conducted using de-identified data as per IRB and HIPAA guidelines.

The cohort of all female breast cancer patients from 1990 to 2014 at our community based cancer center were reviewed for incidence of blood disorders (myeloid neoplasms) of any type by our registry follow up system and by linkage to the Surveillance, Epidemiology and End Results (SEER) registry for our area [15]. All cases of post breast cancer leukemia were reviewed for incidence of t-MDS. Coding of cases was assigned by our registrar and the SEER registry using International Classification of Diseases for Oncology (ICD-O-3) diagnosis codes for type of leukemia from pathology reports and physician chart notes [16]. We included all cases of MDS and MDS→AML (histologic type ICD-O-3 codes 9861, 9895, 9920, 9975, 9980, 9982-9987, 9989). A single patient with cytogenetic abnormality t(8:21)(q22;q22) was diagnosed in 2000 with MDS, treated for MDS and died of MDS as per death certificate. In 2008 the WHO classification changed to AML for patients with this particular cytogenetic abnormality regardless of blast count. As the patient was diagnosed, treated, and died per diagnostic criteria of the time in the year 2000, the case is

included in the cohort as an MDS patient [1]. Information on cytogenetic testing was included if performed and available (N=14). Two patients had cytogenetic testing summarized in the chart as complex karyotype.

Cases of t-MDS were identified by registry follow up and confirmed with SEER coding for MDS. One hundred percent follow up was completed on all t-MDS cases as of 2014 if they were alive or earlier if the patients had died. Death certificates were obtained on all patients that died during the follow up period and were reviewed for cause of death. Registry data includes demographic data such as age and race and disease specific information including diagnosis date, stage at diagnosis, surgery, adjuvant chemotherapy and radiation treatment, recurrence, treatment for recurrence, time interval from breast cancer diagnosis and treatment to leukemia diagnosis and time from leukemia diagnosis to follow up or death.

Population based background MDS rates were calculated for all women ages 20+ years and by age groups (20-54, 55-74 and 75+ years) from the SEER Seattle-Puget Sound cancer registry. Stratified age adjustment (5-year intervals) was performed to standardize incidence rates of expected MDS cases to the reference population. The adjusted background rates are based on cases representative of a population with the same age distribution as our cohort of women with breast cancer. Rates of incident MDS in the cohort were compared to background rates of MDS reported as a first primary cancer in the group overall and by age stratum. Age-standardized rate ratios (RRs) and 95% confidence intervals (CIs) were calculated using Poisson regression. We examined survival following diagnosis of MDS post-breast cancer using the Kaplan-Meier method. Women were followed from diagnosis of MDS until date of death or end

of the study period (December 31, 2014). We performed tests for the equality of survivor functions and trend across groups of age (20-54, 55-74, 75+ years) and type of MDS (MDS, MDS→AML) using stratified log-rank tests. Determination of statistical significance was based on a 2-sided P value < 0.05. SPSS v23 and Stata were used for statistical and survival analysis [17, 18].

Results

From our community cancer center cohort of 11,684 patients diagnosed with invasive breast cancer from 1990 to 2014 with 82,400 person years of follow up, we identified and confirmed 27 cases of t-MDS following diagnosis and treatment for breast cancer [cumulative incidence = .23, rate = .33 per 1000 person years]. Median age at breast cancer diagnosis was 63 years (range: 33-88 years) (table 1). Most cases were diagnosed with stage I (41%) or stage II (56%) primary breast cancer.

Initial breast cancer treatments were surgery plus radiation only (43%) and surgery plus radiation and chemotherapy (50%) with two patients treated with only surgery initially. All but one chemotherapy treated cases received standard cyclophosphamide-containing regimens and 75% of regimens included doxorubicin. Four of the t-MDS cases had recurrent breast cancer treated with radiation and chemotherapy, two of whom had not received either radiation or chemotherapy previously with their initial breast cancer diagnosis. Therefore, prior to t-MDS diagnosis all 27 invasive breast cancer patients were treated with surgery, radiation and/or chemotherapy.

Breast cancer treatment varied significantly by age with all cases less than age 55 receiving chemotherapy and radiation, eight of 12 age 65-74 receiving chemotherapy

and radiation and three of the six patients age 75 and older receiving both treatments (p=.037). Of the 27 cases diagnosed with t-MDS, five transformed from t-MDS to t-AML (t-MDS→t-AML) (19%). Three of the transformed leukemias were in patients age less than 55 with two age 55 to 65 and all had been treated with both radiation and chemotherapy for their BC.

Among 16 patients with cytogenetic reports, two patients had normal karyotypes. Twelve cases had chromosomal abnormalities of 3, 5, 6, 7, 8, 11, 12, 13, 20, or X (75%) (table 2). Eight patients had complex karyotypes with three or more cytogenetic abnormalities (47%), all of whom died except for the two transplanted patients. Clonal abnormalities were observed involving chromosome 5, 7 or both (n=6), chromosome 11q deletion (n=3), chromosome 11q23 or 21q22 (n=2), chromosome 20q deletion (n=2), trisomy 8 (n=1), chromosome 3 abnormalities (n=2) and one with a partial X deletion. Two cases had reports of complex karyotypes without specific cytogenetics ('multiple cytogenetic abnormalities unspecified' and 'complex karyotype consistent with secondary MDS') (table 2). The single patient (age 57) with isolated 5q deletion syndrome has been treated successfully with lenalidomide.

Treatment specific for post breast cancer t-MDS included stem cell transplantation (n = 2, 7%), supportive treatment with hematopoietic growth factors and transfusions (n = 6, 22%), and chemotherapy (n = 12, 44%) with agents including cytosine arabinoside, azacitidine, hydroxyurea, and lenalidomide (Table 3). Six patients did not receive treatment due to stable disease or imminent mortality (22%). Only two patients were treated with stem cell transplantation (SCT) and both achieved cure (age 33 and 46). The other patients age less than 55 patients treated for MDS with

chemotherapy agents did not achieve stable disease and survival time was short (n = 7). Only three of twelve patients treated with chemotherapy or immunomodulatory treatment were alive with stable disease, one treated with lenalidomide (age 57) and two on hydroxyurea (age 59, age 84). The three patients with stable disease not requiring treatment were age 70, 72, and 78, one with abnormal chromosome 20 and one with trisomy 12. Patients older than age 65 were more likely to have untreated stable disease and were less likely to receive stabilizing therapy (p = .15).

Median latency to t-MDS from breast cancer diagnosis was 78 months (range 25-205 months), including patients treated for breast cancer recurrence. Overall survival among t-MDS cases at 5 years was 26% with 7 of 27 cases alive at five years follow up (figure 1). Median survival following t-MDS diagnosis was 19 months (range = 1.5-115, n = 20) and 15 months among cases with deaths directly attributed to t-MDS or t-MDS→t-AML (range = 1.5-115, n = 19).

Nineteen of the 20 patients died of t-MDS or t-MDS→t-AML and one died of other causes. Time from MDS diagnosis to death from t-MDS/t-MDS→t-AML and survival were both shorter for younger patients (p = .119, p = .132) [age <55: 8 months (range 3-25), age 55-74: 26 months (range 1.5-83), age 75+: 40.5 months (range 3-115)] (figure 2 and 3) although neither was statistically significant at the .05 level. Death rate from t-MDS or t-MDS→t-AML was not significantly different by age (<55 = 78%, 55-74 = 58%, 75+ = 67%, p = .867). The death rate was 50% among the 22 t-MDS cases (deaths = 11) and 80% among the five t-MDS→t-AML transformed cases. Median time to death from t-MDS diagnosis was 19 months (range 1.5-115) for t-MDS cases and 14.5 months (range 9-38) for t-MDS→t-AML transformed cases without significant

difference at the .05 level by survival analysis (p=.367) (figure 5). 3 of the 5 t-MDS→t-AML cases were less than age 55 years and 2 were age 58 and 63.

t-MDS incidence risk post breast cancer diagnosis and treatment among younger patients (< 55 years) was 30 times the expected population rate (RR 31.8, 95% CI 15.0, 60.8) (table 4). BC patients age 55-74 also had a significantly increased incidence of t-MDS post BC treatment than that expected in the general population (RR = 4.29, 95% CI = 2.41, 7.63). The incidence rate among patients in the oldest age group was double the expected rate (RR= 2.06, 95% CI .98, 4.34).

Discussion

We observed an increased risk of therapy-related MDS post invasive breast cancer diagnosis especially among younger patients. The only curative treatment observed in our group of community treated patients was bone marrow transplantation. We observed a high death rate from t-MDS with a significant number of t-MDS cases transforming rapidly to t-AML and an even higher death rate among transformed cases. Patients less than age 55 had 30 times the expected incidence of t-MDS with three of nine cases progressing to t-AML.

Patients treated with cytotoxic agents or radiation therapy are at risk of developing both myelodysplastic syndrome (t-MDS) and acute myeloid leukemia (t-AML). These conditions lie along a continuum of disease categorized by the 2008 WHO classification system as therapy-related myeloid neoplasms (t-MN) [1, 19]. t-MDS is a heterogeneous and poorly defined disease with a shorter median survival than de novo AML, MDS, or MDS/MPN and a high risk of evolution to acute myeloid leukemia [2]. t-MDS post breast cancer diagnosis presents with a trajectory and outcome similar

to that observed in treatment-related myelodysplasia occurring post treatment for Non-Hodgkin's Lymphoma [20].

In a study of 306 patients with therapy-related myelodysplasia and myeloid leukemia, Smith et al found a median survival time of 8 months and 5 year survival rate of 10% [11]. In a Danish study of secondary and therapy-related AML an increased risk of death was observed in patients less than age 60 with t-AML [21]. Morton et al in a review of treatment related AML from 9 U.S. population-based cancer registries (1975-1980) found standardized incidence ratios were highest among younger age patients [22]. In our own review of SEER registry data, we found a 30 fold increased risk of MDS post breast cancer diagnosis among women age 20-49 [6].

Two of our patients had normal karyotypes. All patients with chromosome abnormalities or recurring balanced rearrangements or both had karyotypes that have been reported in the literature to be associated with either t-MDS, t-AML, MDS or AML [19, 23-32]. The most common cytogenetic abnormalities observed were abnormalities in chromosome 5 (-5), or 7 (-7) or both and were found in 38% of patients. Chromosome 5 and/or 7 abnormalities are associated with treatment with alkylating agents or radiation therapy and have an unfavorable prognosis [11, 23]. Three patients had abnormalities in chromosome 11 with or without q21q23. All three had been treated for breast cancer with doxorubicin which has a well documented critical association with t-MDS and this chromosome abnormality [33, 34]. Five of the 27 MDS cases transformed to AML. One of the five MDS→AML cases had a chromosome 3 abnormality and died within nine months of diagnosis. This rapid transformation and dire

prognosis has been seen previously in the presence of a chromosome 3 abnormality [25].

It has been noted that both MDS and t-MDS patients present with complex and diverse karyotypes making stratification for treatment by presentation characteristics difficult [35, 36]. Overall our t-MDS patients presented with diverse karyotypes with no single or combination of cytogenetic abnormalities unifying their t-MDS presentation or outcome. In our cohort of patients even those with lesser risk prognostic cytogenetics died of t-MDS (normal, partial del(X)).

There are three types of treatment for t-MDS, curative (SCT), stabilizing (azacytidine, cytosine arabinoside, hydroxyurea, lenalidomide) and supportive (erythropoietin, transfusions) [13, 14, 37]. It is recommended that treatment-related myelodysplasia patients be considered for SCT early in the course of disease due to a very high risk of rapid progression and mortality with or without transformation to AML [38]. Although SCT has curative potential it is not without risk of failure [39]. In de novo MDS patients, azacytidine has shown overall survival advantage compared to patients treated with best supportive care, low-dose cytosine arabinoside, or intensive chemotherapy in a randomized clinical trial which did not include t-MDS patients [40]. Stable disease was obtained in a single patient in our cohort, age 57 years, treated with lenalidomide for t-MDS with 5q deletion syndrome. Lenalidomide has been approved for treatment of del5q MDS patients and clinical trials are ongoing [41].

The primary strength of our study is real time detailed data collection by a dedicated registrar and complete follow up of our registry cohort for recurrence and identification of incident myeloid neoplasms such as t-MDS, a disease not routinely

reported or followed in registries. The small number of t-MDS cases is a limitation as we are not able to evaluate the association between patient and treatment characteristics and outcomes due to small numbers or zero cells when data are stratified. We are able to estimate the risk of t-MDS by age group compared to U.S. population rates and identify disease risk by age. We are unable to evaluate treatment efficacy from a retrospective cohort study. Cytogenetic studies were not done on all patients and less often on patients age 65 years and older.

t-MDS is a clinically and pathologically complex disease with the same force of mortality as t-AML in most cases. The potential for rapid disease progression is combined with limited effective treatment options post treatment for a prior neoplasm. The Revised International Prognostic Scoring System for untreated myelodysplastic syndromes includes age as a significant additive feature for survival [12]. Prognostic classifications based on karyotype exist to help predict outcomes post SCT for de novo and treatment related MDS and AML [42]. It appears from our study, young age and/or multiple cytogenetic abnormalities may be overriding predictors of poor outcome in t-MDS post breast cancer treatment. The large variation of cytogenetic abnormalities in treatment related myelodysplasia is not understood and risk stratification by karyotype may not be relevant in treatment related cases. We did not observe a heterogeneous prognosis in t-MDS patients less than age 55 in relation to disease karyotype.

Evaluation and enumeration of t-MDS incidence post breast cancer treatment may provide insight into the puzzling and diverse biology of therapy-related myelodsyplastic syndromes. Larger studies with adequate power to conduct multivariate analysis to evaluate age and cytogenetic influence on outcome may be

useful to guide treatment as well as continued clinical trials. In the absence of adequately powered studies and given our observation of 100% fatality without stem cell transplantation in our younger patients, stem cell transplantation appears to be a compelling choice for eligible patients in this group.

Conclusions

t-MDS is a disease with inherent adverse prognosis and limited clinical options due to its' association with prior radiation and/or chemotherapy treatment. Early breast cancer detection and use of commercially available genetic risk testing for treatment decisions could reduce the number of breast cancer patients exposed to chemotherapy and radiation thus reducing t-MDS risk [43]. Given the insidious onset of t-MDS, inclusion of annual complete blood counts for monitoring younger invasive breast cancer patients for post treatment blood neoplasms may be warranted.

Our results confirm previous observations of therapy-related MDS post breast cancer diagnosis as an uncommon but rapidly progressive and deadly disease especially in younger women. From our study results, incidence at younger age and presence of multiple cytogenetic abnormalities appear to add challenging complexity to a therapy-related MDS diagnosis.

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References

[1] S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, J.W. Vardiman, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (IARC WHO Classification of Tumours), Fourth Edition, World Health Organization, Lyon, France, 2008.

[2] M.J. Thirman, R.A. Larson, Therapy-related myeloid leukemia, Hematol Oncol Clin North Am 10(2) (1996) 293-320.

[3] H.G. Kaplan, J.A. Malmgren, M.K. Atwood, G.S. Calip, Effect of treatment and mammography detection on breast cancer survival over time: 1990-2007, Cancer 121(15) (2015) 2553-61.

[4] A.C. Wolff, A.L. Blackford, K. Visvanathan, H.S. Rugo, B. Moy, L.J. Goldstein, K. Stockerl-Goldstein, L. Neumayer, T.S. Langbaum, R.L. Theriault, M.E. Hughes, J.C. Weeks, J.E. Karp, Risk of marrow neoplasms after adjuvant breast cancer therapy: the national comprehensive cancer network experience, J Clin Oncol 33(4) (2015) 340-8.

[5] S.M. Matesich, C.L. Shapiro, Second cancers after breast cancer treatment, Semin Oncol 30(6) (2003) 740-8.

[6] H.G. Kaplan, J.A. Malmgren, C.I. Li, G.S. Calip, Age related risk of myelodysplastic syndrome and acute myeloid leukemia among breast cancer survivors, Breast cancer research and treatment 142(3) (2013) 629-36.

[7] H.G. Kaplan, J.A. Malmgren, M.K. Atwood, Increased incidence of myelodysplastic syndrome and acute myeloid leukemia following breast cancer treatment with radiation alone or combined with chemotherapy: a registry cohort analysis 1990-2005, BMC Cancer 11 (2011) 260.

[8] H. Kaplan, J. Malmgren, A.J. De Roos, Risk of myelodysplastic syndrome and acute myeloid leukemia post radiation treatment for breast cancer: a population-based study, Breast cancer research and treatment 137(3) (2013) 863-7.

[9] A.J. De Roos, H.J. Deeg, S. Davis, A population-based study of survival in patients with secondary myelodysplastic syndromes (MDS): impact of type and treatment of primary cancers, Cancer Causes Control 18(10) (2007) 1199-208.

[10] G.S. Calip, J.A. Malmgren, W.J. Lee, S.M. Schwartz, H.G. Kaplan, Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer, Breast cancer research and treatment 154(1) (2015) 133-43.

[11] S.M. Smith, M.M. Le Beau, D. Huo, T. Karrison, R.M. Sobecks, J. Anastasi, J.W. Vardiman, J.D. Rowley, R.A. Larson, Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series, Blood 102(1) (2003) 43-52.

[12] P.L. Greenberg, H. Tuechler, J. Schanz, G. Sanz, G. Garcia-Manero, F. Sole, J.M. Bennett, D. Bowen, P. Fenaux, F. Dreyfus, H. Kantarjian, A. Kuendgen, A. Levis, L. Malcovati, M. Cazzola, J. Cermak, C. Fonatsch, M.M. Le Beau, M.L. Slovak, O. Krieger, M. Luebbert, J. Maciejewski, S.M. Magalhaes, Y. Miyazaki, M. Pfeilstocker, M. Sekeres, W.R. Sperr, R. Stauder, S. Tauro, P. Valent, T. Vallespi, A.A. van de Loosdrecht, U. Germing, D. Haase, Revised international prognostic scoring system for myelodysplastic syndromes, Blood 120(12) (2012) 2454-65.

[13] Benesch M, Deeg HJ. Hematopoietic cell transplantation for adult patients with myelodysplastic syndromes and myeloproliferative disorders. Mayo Clin Proc 2003;78:981-990.

[14] S.D. Nimer, Myelodysplastic syndromes, Blood 111(10) (2008) 4841-51.

[15] Cancer Surveillance System (contract No. N01-CN-67009), Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, Bethesda MD http://www.fhcrc.org/en/labs/phs/projects/cancer-surveillance-system.html.

[16] A.G. Fritz, International classification of diseases for oncology : ICD-O, Third edition, First revision. ed., World Health Organization, Geneva, 2013.

[17] IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

[18] StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

[19] J.W. Vardiman, J. Thiele, D.A. Arber, R.D. Brunning, M.J. Borowitz, A. Porwit, N.L. Harris, M.M. Le Beau, E. Hellstrom-Lindberg, A. Tefferi, C.D. Bloomfield, The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes, Blood 114(5) (2009) 937-51.

[20] J.O. Armitage, P.P. Carbone, J.M. Connors, A. Levine, J.M. Bennett, S. Kroll, Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients, J Clin Oncol 21(5) (2003) 897-906.

[21] L.S. Granfeldt Ostgard, B.C. Medeiros, H. Sengelov, M. Norgaard, M.K. Andersen, I.H. Dufva, L.S. Friis, E. Kjeldsen, C.W. Marcher, B. Preiss, M. Severinsen, J.M.

Norgaard, Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study, J Clin Oncol 33(31) (2015) 3641-9.

[22] L.M. Morton, G.M. Dores, M.A. Tucker, C.J. Kim, K. Onel, E.S. Gilbert, J.F. Fraumeni, Jr., R.E. Curtis, Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008, Blood 121(15) (2013) 2996-3004.

[23] G. Flandrin, Classification of myelodysplasic syndromes, Atlas Genet Cytogenet Oncol Haematol 6(3) (2002) 220-5.

[24] H. Hirai, Molecular mechanisms of myelodysplastic syndrome, Jpn J Clin Oncol 33(4) (2003) 153-60.

[25] W. Cui, J. Sun, C.V. Cotta, L.J. Medeiros, P. Lin, Myelodysplastic syndrome with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) has a high risk for progression to acute myeloid leukemia, American journal of clinical pathology 136(2) (2011) 282-8.

[26] S.K. Ma, T.S. Wan, W.Y. Au, L.F. Fung, C.K. So, L.C. Chan, Chromosome 11q deletion in myeloid malignancies, Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K 16(5) (2002) 953-5.

[27] C. Bilhou-Nabera, del(20q) in myeloid malignancies, Atlas Genet Cytogenet Oncol Haematol 5(1) (2001) 33-4.

[28] J. Musilova, K. Michalova, M. Jarosova, Chromosomes in myelodysplastic syndrome: structural abnormalities of chromosome 11. Czechoslovak MDS Cooperative Group, Ann Genet 32(1) (1989) 43-6.

[29] M.J. Thirman, H.J. Gill, R.C. Burnett, D. Mbangkollo, N.R. McCabe, H. Kobayashi, S. Ziemin-van der Poel, Y. Kaneko, R. Morgan, A.A. Sandberg, et al., Rearrangement of the MLL gene in acute lymphoblastic and acute myeloid leukemias with 11q23 chromosomal translocations, N Engl J Med 329(13) (1993) 909-14.

[30] B. Johansson, R. Billstrom, U. Kristoffersson, M. Akerman, S. Garwicz, T. Ahlgren, C. Malm, F. Mitelman, Deletion of chromosome arm 3p in hematologic malignancies, Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K 11(8) (1997) 1207-13.

[31] B. Johansson, R. Billstrom, N. Mauritzson, F. Mitelman, Trisomy 19 as the sole chromosomal anomaly in hematologic neoplasms, Cancer Genet Cytogenet 74(1) (1994) 62-5.

[32] Y.V. Olshanskaya, A.I. Udovichenko, L.A. Vodinskaya, E.N. Glasko, E.N. Parovitchnikova, Y.Y. Lorie, V.N. Dvirnik, V.G. Savchenko, E.V. Domracheva, Myelodysplastic syndromes with isolated deletion of the long arm of the chromosome X as a sole cytogenetic change, Cancer Genet Cytogenet 167(1) (2006) 47-50.

[33] J. Pedersen-Bjergaard, M. Pedersen, D. Roulston, P. Philip, Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia, Blood 86(9) (1995) 3542-52.

[34] J. Pedersen-Bjergaard, P. Philip, S.O. Larsen, G. Jensen, K. Byrsting, Chromosome aberrations and prognostic factors in therapy-related myelodysplasia and acute nonlymphocytic leukemia, Blood 76(6) (1990) 1083-91.

[35] A. Orazi, M.B. Czader, Myelodysplastic syndromes, American journal of clinical pathology 132(2) (2009) 290-305.
[36] D. Haase, U. Germing, J. Schanz, M. Pfeilstocker, T. Nosslinger, B. Hildebrandt, A. Kundgen, M. Lubbert, R. Kunzmann, A.A. Giagounidis, C. Aul, L. Trumper, O. Krieger, R. Stauder, T.H. Muller, F. Wimazal, P. Valent, C. Fonatsch, C. Steidl, New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients, Blood 110(13) (2007) 4385-95.
[37] R.P. Witherspoon, H.J. Deeg, B. Storer, C. Anasetti, R. Storb, F.R. Appelbaum, Hematopoietic stem-cell transplantation for treatment-related leukemia or myelodysplasia, J Clin Oncol 19(8) (2001) 2134-41.
[38] J.E. Anderson, T.A. Gooley, G. Schoch, C. Anasetti, W.I. Bensinger, R.A. Clift, J.A. Hansen, J.E. Sanders, R. Storb, F.R. Appelbaum, Stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy, Blood 89(7) (1997) 2578-85.
[39] P. Armand, H.T. Kim, E. Mayer, C.S. Cutler, V.T. Ho, J. Koreth, E.P. Alyea, J.H. Antin, R.J. Soiffer, Outcome of allo-SCT for women with MDS or AML occurring after breast cancer therapy, Bone Marrow Transplant 45(11) (2010) 1611-7.
[40] P. Fenaux, G.J. Mufti, E. Hellstrom-Lindberg, V. Santini, C. Finelli, A. Giagounidis, R. Schoch, N. Gattermann, G. Sanz, A. List, S.D. Gore, J.F. Seymour, J.M. Bennett, J. Byrd, J. Backstrom, L. Zimmerman, D. McKenzie, C. Beach, L.R. Silverman, M.D.S.S.S.G. International Vidaza High-Risk, Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic

syndromes: a randomised, open-label, phase III study, Lancet Oncol 10(3) (2009) 223-32.

[41] P. Fenaux, A. Giagounidis, D. Selleslag, O. Beyne-Rauzy, G. Mufti, M. Mittelman, P. Muus, P. Te Boekhorst, G. Sanz, C. Del Canizo, A. Guerci-Bresler, L. Nilsson, U. Platzbecker, M. Lubbert, B. Quesnel, M. Cazzola, A. Ganser, D. Bowen, B. Schlegelberger, C. Aul, R. Knight, J. Francis, T. Fu, E. Hellstrom-Lindberg, M.D.S.L.d.q.S. Group, A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q, Blood 118(14) (2011) 3765-76.

[42] P. Armand, H.T. Kim, D.J. DeAngelo, V.T. Ho, C.S. Cutler, R.M. Stone, J. Ritz, E.P. Alyea, J.H. Antin, R.J. Soiffer, Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation, Biol Blood Marrow Transplant 13(6) (2007) 655-64.

[43] S.M. Stemmer, S.H. Klang, N. Ben-Baruch, D.B. Geffen, M. Steiner, L. Soussan-Gutman, S. Merling, C. Svedman, S. Rizel, N. Lieberman, The impact of the 21-gene Recurrence Score assay on clinical decision-making in node-positive (up to 3 positive nodes) estrogen receptor-positive breast cancer patients, Breast cancer research and treatment 140(1) (2013) 83-92.

Table 1. Characteristics of MDS post BC treatment patients (n=27)		
	n	(%)
Age, years (median, range)	63	(33-88)
<55	9	(33.3)
55–74	12	(44.4)
75+	6	(22.2)
BC stage at diagnosis		
I	11	(40.7)
II	15	(55.6)
III	1	(3.7)
Lymph node status		
Positive	8	(29.6)
Negative	17	(63.0)
Missing	2	
Tumor size, cm (mean, SD)	2.0	(1.7)
<2 cm	17	(63.0)
≥2 cm	10	(37.0)
Missing		
Initial BC treatment		
Surgery only	2	(7.1)
Surgery plus radiation	12	(42.9)
Surgery plus radiation and chemotherapy	14	(50.0)
Patients with recurrence		
(Treated with radiation and chemotherapy)	4	(14.8)
Latency time (years) to MDS diagnosis		
Mean interval from BC diagnosis (range)	7.1	(2.1-17.1)
Mean interval from last BC treatment (range)	5.8	(1.0-12.6)
Histology and behavior (ICD-O code)		
9861 Acute myeloid leukemia NOS	1	(3.7)
9895 Acute myeloid leukemia with myelodysplasia	1	(3.7)
9920 Therapy-related myeloid neoplasms	2	(7.4)
9975 Myelodysplastic/myeloproliferative neoplasm, unclassifiable	3	(11.1)
9980 Myelodysplastic syndromes, refractory anemia	1	(3.7)
9982 Myelodysplastic syndromes with ringed sideroblasts	2	(7.4)
9983 Myelodysplastic syndromes with excess blasts	5	(18.5)
9986 Myelodysplastic syndromes with 5q deletion	3	(11.1)
9987 Therapy-related myelodysplastic syndrome	4	(14.8)
9989 Myelodysplastic syndrome, unclassifiable	5	(18.5)
Vital status		
Alive with disease	5	(18.5)
Alive NED (bone marrow transplant cases)	2	(7.4)
Died (due to MDS or MDS-->AML)	19	(70.3)
Died (due to other cause)	1	(3.7)

Table 2. Cytogenetic abnormalities by age with latency period and outcomes (n=16)			
Months, BC to MDS diagnosis	Age at BC diagnosis	Cytogenetic abnormalities	Vital status
25	33	t(9,11),-7,del(6)	Alive NED (SCT)
162 (138)*	37	46 XX[20] Normal	Died MDS
85	38	t(11)(q21q23) (t-MDS→t-AML)	Died AML
122 (94)*	41	-5, -7, +19,del(3p),del(12p)	Died MDS
92 (12)*	50	t(8;21)(q22;q22)	Died MDS
104	50	Complex karyotype consistent with secondary MDS**	Died MDS
53	57	del(5q)	Alive w/ MDS (Lenolidamide)
146	62	del (5q),del(7q)	Died MDS
85 (27)*	63	46,XX [20] Normal	Died MDS
32	63	inv(3)(q11.2q26),del(5q), -7 (t-MDS→t-AML)	Died AML
129	66	del (20q),+8	Died MDS
43	72	del(20q)	Alive w/ MDS (no tx)
186	73	Multiple cytogenetic abnormalities**	Died MDS
43	76	partial del(X)	Died MDS
69	78	trisomy 12 (+12)	Alive w/ MDS (no tx)
63	82	del(5q),-13,-18	Died MDS

*(months) time post chemotherapy for breast cancer recurrence to MDS
** report from chart without exact cytogenetics, pathology was not available.

Table 3. t-MDS treatment by age (n=27)			
	Age < 65	Age 65+	Total
	N (%)	N (%)	N (%)
Treatment category			
Stable disease, no treatment	0	3 (27%)	3 (11%)
Patient mortally ill, no treatment	1 (6%)	2 (18%)	3 (11%)
Supportive treatment only	4 (25%)	2 (18%)	6 (22%)
Stabilizing therapy treatment	8 (50%)	4 (36%)	12 (44%)
Stem cell transplant	2 (13%)	0	2 (7%)
Unknown treatment	1 (6%)	0	1 (4%)
	16 (59%)	11 (41%)	27 (100%)
Treatment regimens			
Supportive treatment			
hematopoietic growth factors*	3 (11%)	3 (27%)	6 (22%)
transfusions	2 (13%)	2 (18%)	4 (15%)
prednisone	1 (6%)	0	1 (4%)
splenectomy	1 (6%)	0	1 (4%)
Stabilizing treatment: chemotherapy*			
azacytidine	5 (31%)	0	5 (19%)
cytosine arabinoside	2 (13%)	0	2 (7%)
cytosine arabinoside /idarubicin	1 (6%)	0	1 (4%)
fludarabine	1 (6%)	0	1 (4%)
hydroxyurea	2 (13%)	3 (27%)	5 (19%)
Immunomodulatory agent treatment			
lenalidomide	1 (6%)	0	1 (4%)

*patients may have received multiple treatments

Table 4. Observed MDS cases and age-standardized expected MDS incidence from the Seattle-Puget Sound SEER registry								
	Age-standardized expected rate per 100,000	Person-years	Observed rate per 100,000	Expected cases	Observed cases	Age-standardized rate ratio	(95% CI)	*P* value
All ages	6.0	82,400	32.8	4.9	27	5.46	(3.47, 8.60)	<0.001
20-54 years	1.1	39,954	22.5	0.3	9	31.71	(14.98, 60.80)	<0.001
55-74 years	10.2	34,748	34.5	2.8	12	4.29	(2.41, 7.63)	<0.001
75+ years	43.4	7,699	77.9	3.3	6	1.80	(0.80, 4.02)	0.149

Figure 1. Overall Survival for MDS post breast cancer patients (n=27)

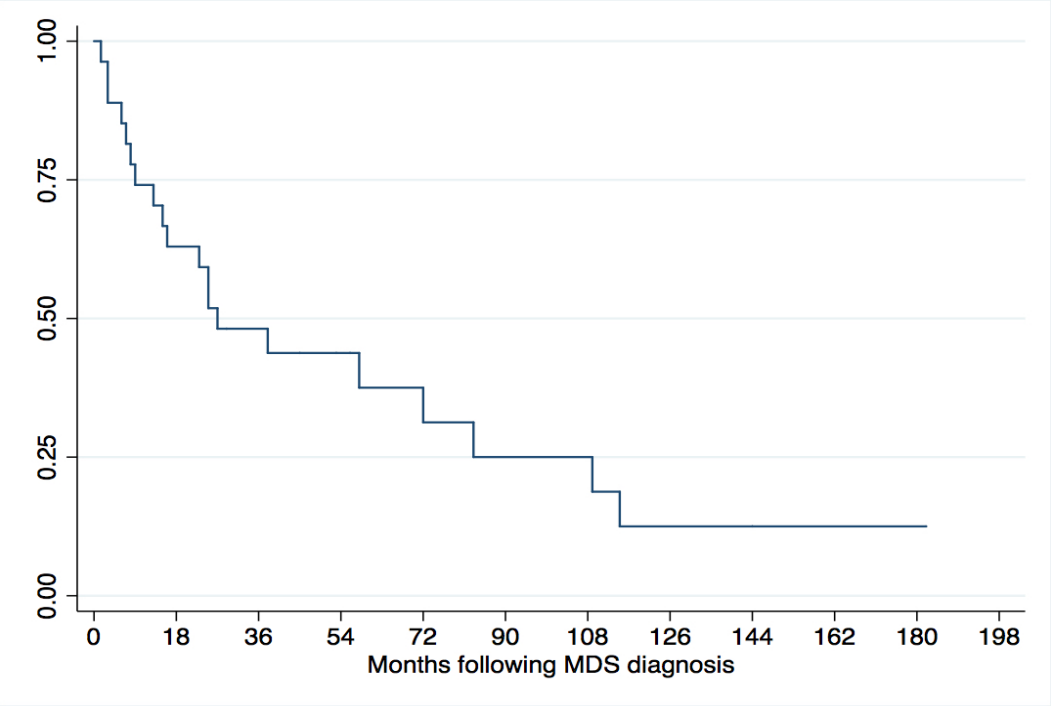

Figure 2. Median time (vertical line) with interquartile range (box) from MDS diagnosis to MDS-specific death by age group (n=27)

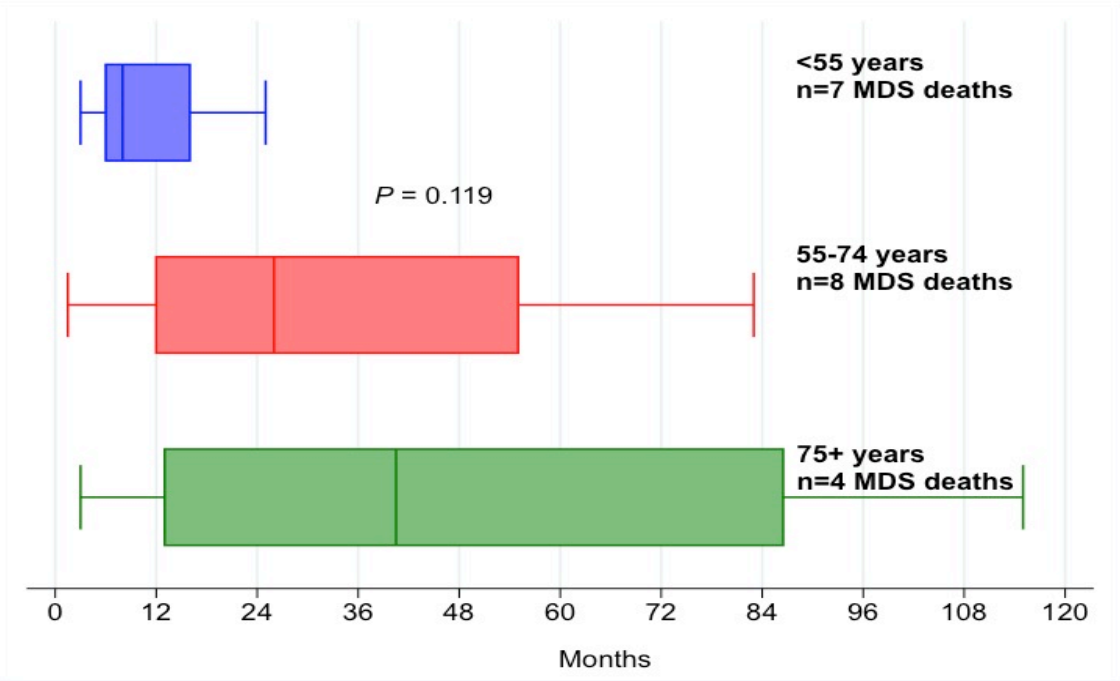

Figure 3. Kaplan-Meier survival function for MDS-specific death by age at BC diagnosis (≤55, 56-74, 75+ years)

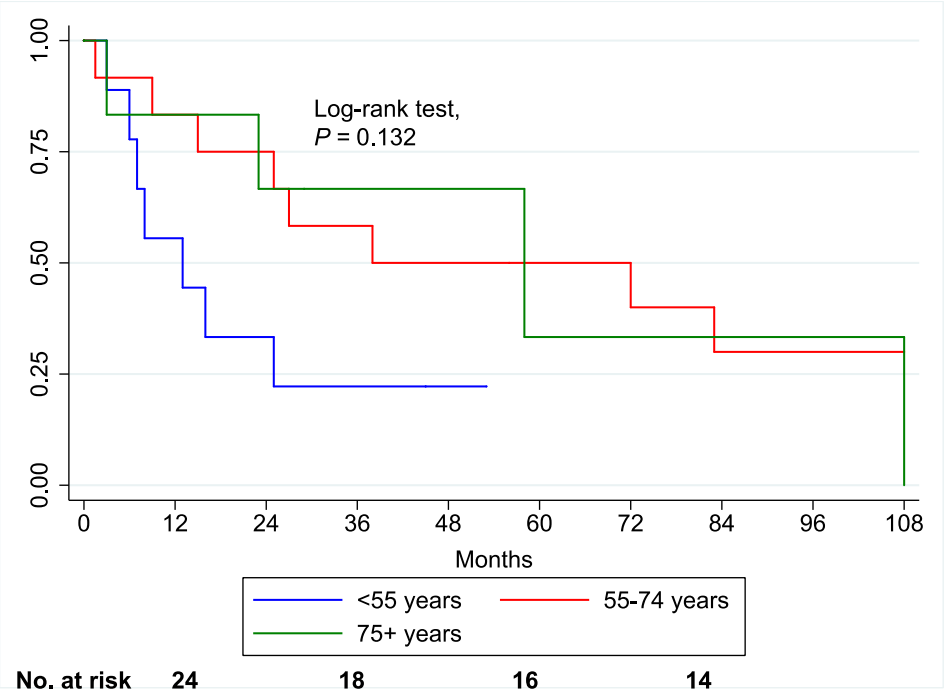

Figure 4. Survival time for MDS vs MDS→AML cases (n=19)