Therapy-related myeloid neoplasms following treatment with radioiodine

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ABSTRACT

Background
Few data are available on therapy-related myelodysplastic syndromes and acute myeloid leukemia developing after radioiodine treatment.

Design and Methods
We retrospectively analyzed 39 patients with myeloid neoplasms following radioiodine treatment, whose data were reported to the Duesseldorf Myelodysplastic Syndromes Register (8 of 3814 patients) and five other German Myelodysplastic Syndromes centers (n=31) between 1982 and 2011. These data were compared with those from 165 patients from our Myelodysplastic Syndromes Register with therapy-related myeloid neoplasms following chemotherapy (n=90), radiation (n=30), or radiochemotherapy (n=45).

Results
With a median latency of 79 months, 18 patients developed therapy-related acute myeloid leukemia and 21 presented with therapy-related myelodysplastic syndromes (8 refractory anemia with excess blasts I/II, 6 refractory anemia with multilineage dysplasia, 3 myelodysplastic syndromes with del(5q), 1 refractory anemia, 1 refractory anemia with ring sideroblasts, 1 chronic myelomonocytic leukemia II, 1 myelodysplastic/myeloproliferative neoplasm unclassifiable). Risk assessment according to the International Prognostic Scoring System was low-risk in 23%, intermediate-1 in 29%, intermediate-2 in 35%, and high-risk in 13%. Karyotype was abnormal in 68%, with chromosomes 7 (30%), 5 (26%), 8 (26%) and 3 (17%) being most frequently affected. No differences in the distribution of gender, World Health Organization subtype, acute myeloid leukemia progression, International Prognostic Scoring System score, and cytogenetic risk were observed between patients with therapy-related myeloid neoplasms following radioiodine or other treatment modalities. Of 17 patients who received induction chemotherapy, 71% were refractory to this treatment or died from treatment-related toxicity. The median overall survival in the entire group was 21.7 months (95%-CI 10.5-33 months) and did not differ significantly in comparison to the survival of patients with therapy-related myeloid neoplasms following other cytotoxic treatments. Patients with therapy-related acute myeloid leukemia had significantly inferior overall survival (12.4 *versus* 28.7 months, P=0.002).

Conclusions
Patients developing a therapy-related myeloid neoplasm after radioiodine treatment usually present with biological characteristics similar to those seen in patients with therapy-related myeloid neoplasms following other cytotoxic treatment modalities, associated with a low response rate to induction chemotherapy and poor prognosis.

Key words: therapy-related, myelodysplastic syndromes, acute myeloid leukemia, radioiodine, thyroid, secondary.

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Introduction

Myelodysplastic syndromes (MDS), acute myeloid leukemia (AML) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) arising as late complications following cytotoxic treatment are summarized as 'therapy-related myeloid neoplasms' within the current World Health Organization (WHO) classification.[1] They account for approximately 10% to 20% of all cases of MDS and AML and their incidence is likely to rise, given the increasing number of cancer survivors at risk.[2-4] Therapy-related myeloid neoplasms are preferentially observed following treatment with cytostatic drugs such as alkylating agents, topoisomerase II inhibitors and antimetabolites, as well as following radiotherapy, but have also been described in patients receiving intensive immunosuppressive treatment.[5,6]

The majority of patients with therapy-related MDS (tMDS) or AML (tAML) have cytogenetic aberrations most of which assign the patients to a high-risk category, causing inferior outcome compared with *de novo* myeloid malignancies.[7-11] Traditionally, therapy-related myeloid neoplasms were subdivided into two subgroups according to the type of causative therapy.[2,8] The first subtype, following treatment with alkylating agents, is characterized by a latency period of 5 to 10 years, is frequently preceded by a MDS phase, and is associated with unbalanced chromosomal aberrations often involving chromosomes 5 and 7 and/or a complex karyotype. The other subtype occurs after treatment with topoisomerase II inhibitors, has a shorter latency period, generally without a MDS prephase, and is associated with balanced translocations.[2,8]

Although myeloid neoplasms induced by therapeutic or accidental exposure to ionizing radiation do not exhibit a unique pattern, they often share characteristics with leukemia following alkylating agents.[3,12] Radioiodine (^{131}I) is a β emitter used for the treatment of non-malignant thyroid diseases as well as in thyroid cancer.[13,14] As the occurrence of tMDS/tAML after radioiodine treatment has been considered to be rather uncommon, such cases have been reported only sporadically so far or are often summarized under the term radiation in the context of tMDS/tAML.[15,16] Data about the clinical presentation, treatment and outcome of patients with tMDS/tAML following radioiodine therapy are, therefore, scarce.

In this retrospective study we evaluated the clinical characteristics and cytogenetic and molecular data of 39 patients with tMDS/tAML following radioiodine treatment, and report on their response to treatment and probability of survival.

Design and Methods

Patients

From 1982 to 2011, 3814 patients were entered into the Duesseldorf MDS Register. Of these, 263 patients (6.6%) had tMDS/tAML and detailed information about the preceding treatment modalities was available for 173 patients. Eight of these patients were diagnosed as having a therapy-related myeloid neoplasm (tMDS/tAML according to the WHO 2008 classification) as a consequence of preceding radioiodine therapy, and their data were analyzed together with the data of 31 additional patients with tMDS/tAML following radioiodine identified by a questionnaire sent to others centers (Goettingen, Hannover, Dresden, Hamburg and Ulm) participating in the German-Austrian-Swiss MDS Working Group. These results were compared with the data of the remaining 165 patients from the Duesseldorf MDS Register with tMDS/tAML following chemotherapy (n=90), radiation (n=30), or radiochemotherapy (n=45).

Since patients were part of the MDS databases of the respective centers, regular follow-up was available. The median follow-up time was 12 months (range, 1 to 160 months). The collection and retrospective analysis of patients' data were approved by the respective institutional review boards.

Patients were evaluated for the underlying disease requiring radioiodine treatment, its dosage and the latency between the diagnosis of the primary disease and the occurrence of the therapy-related myeloid neoplasm. Hematologic parameters including AML and MDS subtype, proportion of blast cells in the blood and bone marrow, blood cell counts and lactate dehydrogenase (LDH) concentration were noted at the time of diagnosis of tMDS or tAML.

Cytogenetic analyses were performed as part of the routine diagnostic procedures at the respective centers and karyotypes were reported in accordance with the International System for Human Cytogenetic Nomenclature. In a subgroup of patients samples had been analyzed for mutations in the *FLT3* (n=9), *NPM1* (n=9), *CEBPA* (n=6), *AML1/RUNX1* (n=1), *NRAS* (n=1) as well as *ASXL1* (n=1) genes.

In patients with tMDS, cytogenetics were graded as low-, intermediate- and high-risk according to the International Prognostic Scoring System (IPSS) score, while in patients with tAML cytogenetic and molecular genetic data were reported as recently proposed.[17]

Data were gathered regarding the type of treatment patients received for tMDS/AML, and the response to treatment was recorded. In the case of tMDS progressing to a more advanced type of tMDS or tAML, time to progression and time to overt tAML, respectively, were calculated from the date of initial diagnosis to the date of disease progression.

Statistics

Medians and ranges were calculated to describe patients' characteristics. Overall survival and time to AML evolution were estimated according to the Kaplan-Meier method. The log-rank test was used for comparison of overall survival between subgroups, whereas cross-tabulation and the χ^2 test or Fisher's exact test was employed for comparison of biological variables. Statistical analyses were carried out using Excel (Microsoft) and SPSS for Windows (SPSS Inc. Chicago, IL, USA).

Results

Patients' characteristics and hematologic parameters

We identified 39 patients (20 female and 19 male) with a myeloid neoplasm (tMDS n = 21, tAML n=18) following treatment with radioiodine. Since databases of the other MDS centers are more heterogeneous, for example, some only cover patients with tAML but not with tMDS and others only record patients undergoing allogeneic stem cell transplantation, the proportion of tMDS and tAML following radioiodine within all tMDS/AML collected in these centers could not be determined exactly. Nevertheless, out of 3814 patients with MDS and AML following MDS in the Duesseldorf MDS Register 263 patients (6.6%) have tMDS/tAML and detailed information about the preceding treatment modalities was available for 173 of them. The percentage of tMDS/tAML fol-

lowing radioiodine therapy was 5% (8 of 173) in the Duesseldorf MDS Registry. The median age at the time that the diagnosis of tMDS or tAML was made was 63 years (range, 19-80 years). With regard to their primary disease, 19 patients (46%) had received radioiodine for the treatment of thyroid cancer, while 16 patients (41%) had benign thyroid diseases including five suffering from Graves' disease. One patient (3%) had a mesenteric carcinoid tumor. In four patients (10%) we were unable to ascertain the indication for radioiodine therapy. Except the patient with the carcinoid tumor, who had received ^{131}I-metaiodobenzylguanidine (MIBG), all other patients had been treated with 131-Iodine (^{131}I). The median time between diagnosis of the primary disease and the onset of tMDS/tAML was 79 months (range, 6-440 months) and did not differ significantly between patients with tMDS and tAML (77.5 *versus* 89 months, *P*=0.67).

The exact ^{131}I dose was known only for nine patients (23%). In these, the mean dose of injected activity was 1216 mCurie (range, 16-3351 mCurie). To address the question of a relationship between the dose of ^{131}I and the development of tMDS/tAML we compared those patients who had received radioiodine for benign diseases, thereby being more likely to have received lower doses, with patients having received radioiodine for malignant diseases. No differences in the frequency of chromosomal abnormalities, disease-risk and the time to development of tMDS/tAML were found between these two subgroups.

Detailed hematologic parameters of the patients at the time of diagnosis of tMDS and tAML are given in Table 1.

According to the WHO classification, eight (39%) of the 21 patients with tMDS presented with a refractory anemia with excess blasts I or II (RAEB I 2 patients, RAEB II 6 patients), six patients (28%) with a refractory cytopenia with multilineage dysplasia (RCMD), one patient (5%) each with a refractory anemia (RA) without or with ring sideroblasts (RARS), three patients (14%) with a myelodysplastic syndrome with isolated del(5q), and two patients (9%) with a MDS/MPN (1 chronic myelomonocytic leukemia type II and 1 MDS/MPN unclassifiable). The IPSS was applicable to 17 of the 21 MDS patients (81%) at the time of diagnosis, while four patients (19%) could not be classified because of missing cytogenetics. Four patients (23%) belonged to the IPSS low-risk group, five patients (29%) to the intermediate I-, six patients (35%) to the intermediate II-, and two patients (13%) to the high-risk group.

In seven (33%) of the patients with tMDS the disease transformed into AML within a median time of only 7.9 months (range, 1-11 months), while in three other patients it progressed to an advanced type of MDS (RCMD to RAEB-I in 2 patients, RARS to RAEB-I in 1 patient) within a median time of 4 months (range, 1-21 months).

One patient, who presented with a tAML, had a history of a polycythemia vera. The time from diagnosis of polycythemia vera to evolution into AML was 12.75 months and the polycythemia vera had been treated only with phlebotomies.

Cytogenetic and molecular genetic features

Cytogenetic data were available for 34 patients (88%) with tMDS and tAML: 23 of those 34 patients (68%) had an abnormal karyotype. The median number of aberrant chromosomes was one (range, 0-10). Twelve patients (52%) had one, and three patients (13%) had two chromosomal abnormalities, while two patients (9%) had a complex karyotype and six patients (26%) had a monosomal karyotype according to the definition of Breems *et al.*[23] The chromosomes most frequently affected were chromosomes 7 (30%), 5 (26%), 8 (26%) and 3 (17%).

Patients with tMDS had a significantly higher frequency of karyotype anomalies than patients with primary MDS in the Duesseldorf MDS Registry (80% *versus* 51%, *P*=0.024).

Mutation analyses were not performed routinely but were available in a subgroup of patients: mutations of the *FLT3* gene were found in three patients (2 ITD, 1 TKD), while four patients had an *NPM1* mutation either isolated (n=3) or in association with a *FLT3*-TKD mutation (n=1). A mutation in the *AML1/RUNX1*, the *ASXL1*, or the *NRAS* gene was found as a single molecular alteration in three respective patients. A *CEBPA* mutation was not detected in any of the six patients who were investigated for this alteration. Detailed information on cytogenetic and molecular genetic features is given in Table 2.

Based on cytogenetic data MDS patients were stratified to a low-risk (9 patients, 52%), intermediate-risk (4 patients, 24%) or high-risk group (4 patients, 24%) according to the IPSS. In comparison, patients with *de novo* MDS and available cytogenetic data in the Duesseldorf MDS Registry (n=2286) had low-risk (n=1444, 63%), intermediate-risk (n=401, 18%) and high-risk (n=441, 19%) cytogenetics. Thus, there was a trend to a higher proportion of intermediate- and high-risk cytogenetic abnormalities in patients with tMDS following radioiodine treatment (48% *versus* 37%), but the number of patients with radioiodine-associated tMDS was too small for the difference to reach statistical significance.

Applying the recently proposed risk stratification of the European Leukemia Network[17] to the patients with tAML, three patients (16%) belonged to the favorable genetic risk group, nine patients (50%) to an intermediate group and five patients (34%) to an adverse genetic risk group (data missing for 1 patient).

Treatment

Data on the treatment of tMDS/tAML were available for

Table 1. Hematologic parameters in patients with tMDS or tAML following radioiodine treatment at the time of diagnosis.

	tMDS	tAML
Patients, n (%)	21 (54)	18 (46)
White cell count, $\times 10^9$/L	3.1	20.5
Median (range)	0.8-31.2	0.42-111
Hemoglobin, g/dL	9.1	9.4
Median (range)	4.0-15.1	5.7-11.3
Platelets, $\times 10^9$/L	57.0	52.0
Median (range)	9-308	22-146
Peripheral blood blasts (%)	0	29
Median (range)	0-19	0-91
Bone marrow blasts (%)	4	61
Median (range)	1-18	16-90
Lactate dehydrogenase, U/L	184	369
Median (range)	117-636	192-1168

34 (88%) of the 39 patients. Following the diagnosis of tMDS/tAML, 13 patients (38%) received best supportive care only (including transfusions, iron chelation, and hematopoietic growth factors), or low dose chemotherapy (n=2, 1 patient with low-dose cytarabine, 1 patient with hydroxyurea) or immunosuppressive therapy (using antithymocyte globulin and cyclosporine A) or farnesyltransferase inhibitors, or valproate with or without all-*trans* retinoic acid.

Intensive induction chemotherapy using various cytarabine/anthracycline-based regimens was employed as first-line therapy in 17 patients (50%) with available information, while upfront allogeneic hematopoietic stem cell transplantation was performed in two patients (6%). The remaining two patients (6%) received epigenetic treatment with a DNA methyltransferase inhibitor (5-azacitidine) as first treatment.

Following induction chemotherapy only five (29%)

Table 2. Cytogenetic and molecular features detected in patients with therapy-related myeloid neoplasms following radioiodine treatment at the time of diagnosis. In most patients the correct karyotype formula according to the ISCN is displayed. In a few patients only the specific karyotype aberration could be given because of the retrospective character of this analysis.

UPN	WHO	Cytogenetics	Molecular genetics
1	RA	46,XX	
2	RARS	45,XX,-7 [12], 46,XX [8]	
3	MDS del 5q	46,XX,del(5)(q31)	
4	MDS del 5q	46,XX,del(5)(q14q34) [17]/46XX [3]	
5	MDS del 5q	46,XX,del(5)(q13q33) [4]/ 46,XX[1]	
6	RCMD	46,XX,del(5)(q), -7,del18q, t15,+mar	
7	RCMD	46,XX,t(15;18)(q26;q21) [7]/46, XX [12]	
8	RCMD	46XY,del(20)(q11) [19]/46,XY [3]	
9	RCMD	46,XY,del(20)(q12) [3]/45,idem,-7 [5]/46,XY [7]	
10	RCMD-RS	46,XX,t(3;3)(q21;q26) [5]/47,idem,+mar [2]	
11	RCMD-RS	missing	
12	CMML-II	46,XY	
13	MDS/MPN-u	46,XY [25]	ASXL1+
14	RAEB I	missing	
15	RAEB I	missing	
16	RAEB II	47,XY,+8 [2]/ 46,XY[21]	
17	RAEB II	missing	
18	RAEB II	46,XY,t(6,7)(p12;q11),t(9;13)(q34;q14) [19]/46,XY [1]	
19	RAEB II	45,XX,t(3;3)(q21;q26), -7 [17]/46 XX [3]	
20	RAEB II	46,XX	
21	RAEB II	46,XX	FLT3-TKD +, NPM1 +
22	tAML	46,XX,del(12)(p11)	
23	tAML	46,XX	NPM1 +
24	tAML	45,XY,t(3;7)(q27/29;q22),-5	
25	tAML	45,XY,-17,-19,+mar[1]/46,XY,-8,+mar[1]/46,XY[5]	
26	tAML	47,XY,+8[12], 47,XY,t(3 ;22)(q27 ;q13),+8[10]	FLT3-ITD +
27	tAML	46,XY,del(12)(p11)[4]/47,XY,del(12)(p11)+19[3]/48,idem,+13[4]/49, idem,+X,+8[12]/46,XY[1]. nuc ish(ETV6x1)[197/235]/D8Z1x3)[118/224]/(D13S319,TEL13q)x3[38/266]	RUNX1
28	tAML	46,XY [20]	
29	tAML	46,XY [26]	
30	tAML	46,XY [30]	
31	tAML	46,XY [22]	NPM1 +
32	tAML	45,XY,-13[2]/46,XY [19].nuc ish 11q23(MLLx2(spx0,13q14(RB1x1))	
33	tAML	46,XY, t(8;16)	
34	tAML	46,XY,t(14;21)(q24,q22)[4]/46,XY,add(9)(p22), t(14;21)(q24;q22) [14]/47,XY,idem,+22 [2]	
35	tAML	46,XX, del6	NPM1 +
36	tAML	46,XX	FLT3-ITD +
37	tAML	43- 44,XX,add(4q),del(5)(q11),del(7)(q22),-9,del(11)(p11),-13,-17,-19,-19,+2-3mar	
38	tAML	46, XX, inv(16)(p13q22) [20]	NRAS +
39	tAML	missing	

patients reached a complete remission. Refractory disease was observed in ten patients (59%), while two patients (12%) died as a consequence of toxicity during induction therapy. Among patients who received induction chemotherapy, no differences were found in karyotype abnormalities between responders and non-responders (*data not shown*). Both patients who received low-dose chemotherapy for cytoreduction had intermittent stabilization of their leukocyte counts. Of the two patients treated with 5-azacitidine, one achieved a partial remission and the other had disease stabilization and proceeded to allogeneic hematopoietic stem cell transplantation as salvage therapy. The other two patients who underwent upfront allogeneic hematopoietic stem cell transplantation reached complete remission but died from complications (1 GVHD, 1 transplantation-associated thrombotic microangiopathy).

Survival

The median overall survival in the entire group of patients with therapy-related myeloid neoplasms following radioiodine treatment was 21.7 months (95%-CI 10.5 to 33 months Figure 1A). There was no significant difference in overall survival between patients with tMDS following radioiodine therapy and patients with primary MDS in our registry (28.7 months *versus* 29.9 months). However, patients with post-radioiodine tAML had a significantly inferior overall survival compared to patients with post-radioiodine tMDS (28.7 months *versus* 12.4 months, P=0.002, Figure 1B). No survival differences were observed among patients receiving induction therapy, best supportive care, and low intensity treatment. Furthermore, there was no difference in overall suvival between patients who underwent allogeneic hematopoietic stem cell transplantation or not (*data not shown*).

Comparison between therapy-related neoplasms related to different treatment modalities

In a next step, we compared the patients with tMDS/tAML following radioiodine treatment with 165 patients with tMDS/tAML recorded in the Duesseldorf MDS Register, who had available information on antecedent treatment modalities (chemotherapy, radiation, and radiochemotherapy).

As indicated in *Online Supplementary Table S1*, we did not find any differences in the distribution of gender, WHO subtype, AML transformation rate, IPSS, and cytogenetic risk between these groups of patients. The only differences, we observed, were that: (i) patients with tMDS/tAML following radioiodine were significantly younger than patients with tMDS/tAML following radiotherapy (63 years *versus* 71 years, P<0.001), and (ii) that time between primary disease and onset of tMDS/tAML was longer following radioiodine (79 months) than following chemotherapy (70 months, P=0.026) and radiochemotherapy (61 months, P=0.006).

Next, we compared the overall survival of the aforementioned groups. There were no statistically significant differences between patients with therapy-related myeloid neoplasms following radioiodine as well as following other treatment modalities. This also applied when we looked only at patients with tMDS related to radioiodine treatment (Figure 1C).

Discussion

By collecting and analyzing data from 39 individuals from the Duesseldorf MDS Registry and five other German MDS centers we have been able to analyze to the best of our knowledge the largest group of patients with therapy-related myeloid neoplasms following radioiodine treatment that has been described so far.

Ionizing radiation induces chromosomal aberrations frequently found in secondary leukemias, and its causal contribution to leukemogenesis is generally established.[2] Nevertheless, the link between radioiodine treatment for malignant and non-malignant thyroid diseases and the evolution of tMDS/tAML has long been a matter of debate, because early epidemiological studies yielded conflicting results.[18-21]

In a comprehensive review and meta-analysis of the currently available literature covering 16,502 patients with

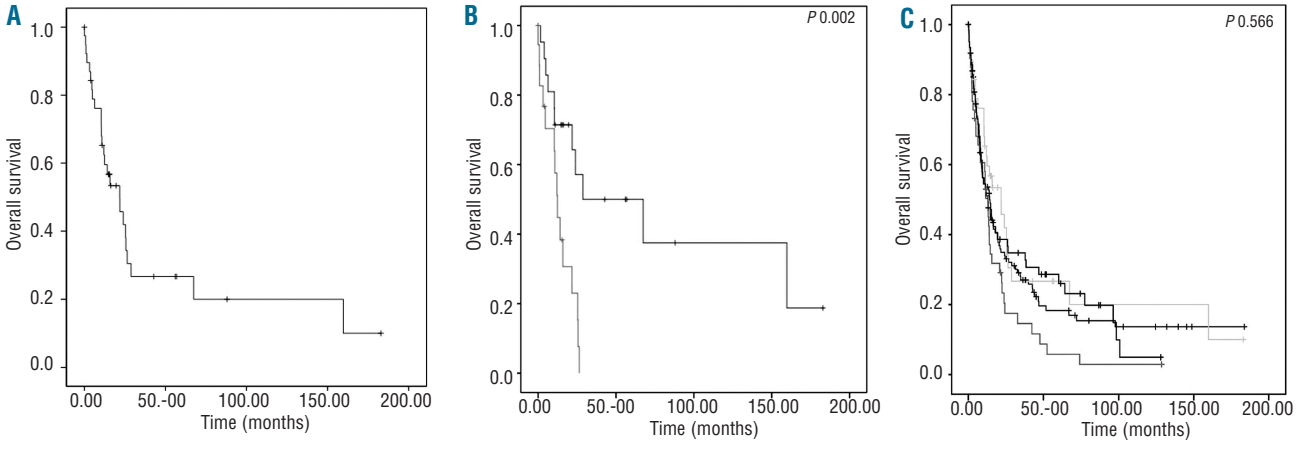

Figure 1. (A) Overall survival of all patients (n=39) with therapy-related neoplasms following radioiodine treatment. (B) Overall survival in patients with tAML (n= 18, gray curve) in comparison to patients with tMDS (n=21, black curve) following radioiodine treatment. (C) Overall survival of patients with therapy-related myeloid neoplasms following radioiodine (n=39) and following other treatment-modalities (n=165): lower black curve chemotherapy, dark grey curve radiotherapy, light grey curve radioiodine, upper black curve radiochemotherapy.

thyroid cancers, the relative risk for the development of leukemia was increased 2.5-fold in patients treated with radioiodine.[22] In line with this, thyroid cancer was also identified as the second most common primary neoplasm arising in patients who developed tAML following treatment for solid cancers.[7] Still, data on patients with therapy-related myeloid neoplasms following radioiodine treatment have been scarce so far, comprising case reports on a total of only 33 patients.

Our analysis shows that the great majority of patients developing therapy-related myeloid neoplasms following radioiodine treatment already present with AML or high-risk MDS as reflected by blast count, karyotype, IPSS or rapid disease progression. These patients do, therefore, share major biological characteristics with patients with tMDS/tAML following chemotherapy, radiation or radiochemotherapy, as indicated by the comparison with an additional set of 165 patients out of our MDS Register.

Regarding cytogenetics, 68% of the patients had an abnormal karyotype with up to ten aberrations per patient and 35% of these patients had a complex or monosomal karyotype, which carries an even worse prognosis.[23] Our findings are in line with data from two large series of patients suffering from tMDS or tAML, which showed an abnormal karyotype in 75% und 92% of the cases, while an abnormal karyotype was observed in only 51% and 52% of patients with *de novo* AML and primary MDS, respectively.[7,9,24] The most frequently affected chromosomes in our series, i. e. chromosomes 7, 5, 8 and 3, and the median latency between primary disease and onset of tMDS/tAML of 6.58 years are in accordance with the usual phenotype of tMDS/tAML induced by alkylating agents or external radiotherapy. This similar biological phenotype supports the idea of a causal relationship between radioiodine treatment and evolution of tMDS/tAML in these patients.[3,11,25]

The finding of gene mutations has become an important prognostic factor in patients with *de novo* AML. Although knowledge about gene mutations could also be relevant to pathogenesis and prognosis of patients with therapy-related myeloid neoplasms, there are only few studies on this topic.[7,25]

We found a *FLT3* and/or a *NPM1* mutation in three and four patients, respectively. Both mutations have been described in patients with tMDS/tAML, but at lower frequencies than in patients with *de novo* AML and primary MDS.[7,25,26] Of interest, *FLT3* mutations were associated with radiation therapy in a series of patients with tAML, but this was not confirmed in another study.[7,27] Furthermore, we found one patient with a *RUNX1* mutation, which has frequently been observed in MDS secondary to atomic bomb radiation exposure and is associated with resistance to chemotherapy and an inferior outcome.[25,28-29] However, the retrospective character of our analysis and the availability of molecular data for just a subgroup of patients does not allow us to draw valid conclusions regarding the frequency of such gene mutations and their potential contribution to leukemogenesis in patients with tMDS/tAML.

The diagnosis 'tMDS/tAML' is associated *per se* with an unfavorable outcome, and karyotype has also proven to be an independent prognostic parameter in these patients.[7,10] Since the majority of patients with therapy-related myeloid neoplasms following radioiodine reported here had high-risk characteristics such as tAML, an adverse karyotype or an advanced MDS subtype, we were interested to see whether this influenced their response to induction therapy and survival.

Despite the small number of patients receiving intensive induction therapy, it is still worth noting that 71% of the patients were either refractory to induction therapy or died as a consequence of toxicity. While treatment-related mortality in patients with t-MDS/t-AML is generally ascribed to cumulative toxicity of previous and current cytotoxic therapies and is generally accepted to affect the outcome negatively, there is controversy regarding the likelihood of response to induction therapy.[7,30-31] In our series, both treatment-related mortality and a low remission rate contributed to short survival. As no difference regarding karyotype abnormalities was found between responders and non-responders, the fact that these were therapy-related neoplasms seemed to override the prognostic impact of cytogenetics in our group of patients. In addition, treatment intensification by induction therapy and/or allogeneic stem cell transplantation did not improve the prognosis of these patients.

Several authors have shown that overall survival in patients with tAML is worse than that of patients with *de novo* AML, despite various treatment options.[7-8,10] This was also true in our series of patients with tAML following radioiodine treatment, who had a median overall survival of 12.4 months (Figure 1B). Our finding that there was no statistically significant difference in overall survival between the group of patients with tMDS and patients with *de novo* MDS is probably due to the small number of patients. The survival curves illustrate that the majority of patients with tMDS also died soon after diagnosis. However, some patients, in particular the five patients with a low-risk type of MDS, that is, RARS (n=1), MDS with isolated del 5q (n=2) and RCMD (n=2), favorably influenced the overall survival of the whole tMDS group. Nevertheless, when we compared the overall survival of patients with therapy-related myeloid neoplasms following radioiodine treatment with the overall survival of patients with tMDS/tAML following other treatment modalities, we found no statistically significant difference, and this also applied when looking at tMDS separately. This finding again underlies the biological similarity between patients with tMDS/tAML following radioiodine and other cytotoxic therapies, but larger numbers of patients would be required to provide a more reliable estimate of the likelihood of survival in patients with tMDS/tAML following radioiodine therapy.

In conclusion, tMDS/tAML after radioiodine treatment is a devastating late complication, usually associated with an advanced disease stage, adverse chromosomal changes, a low response rate to induction chemotherapy, and a poor prognosis similar to that seen in patients with tMDS/tAML following cytotoxic treatment modalities other than radioiodine.

Authorship and Disclosures

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