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Secondary Myeloid Leukemia and MDS in Patients Treated for Hodgkin Lymphoma – Experience of the German Hodgkin Lymphoma Study Group (GHSG)

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Depending on age and risk factors, more than 80% of patients with Hodgkin Lymphoma (HL) are currently being cured.[1] Long-term survivors, however, are at risk for treatment-related complications such as infertility, cardiac or pulmonary dysfunction or thyroid-related sequelae. Increased risk of secondary cancers has been observed after chemo- and radiotherapy. The malignancies most frequently associated with chemotherapy include acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[2-5]

Treatment-related AML and MDS generally respond poorly to therapy. Currently, there is no clear treatment strategy for secondary AML/MDS after HL, at least in part due to scarce data. Curative treatment strategies in second malignancies after HL are not yet standardized. Controversy exists about the value of hematopoietic stem cell transplantation. High-dose chemotherapy (HDCT) with allogeneic stem cell transplantation (ASCT) has been attempted resulting in some responses.[7-9] However, review of the literature reveals little information about the long-term clinical outcome of treatment-related AML or MDS after treatment for HL.

Therefore, we retrospectively analyzed patients with secondary AML/MDS registered in the database of the German Hodgkin's Lymphoma Study Group (GHSG) in a total of 5411 patients.10 The purpose of the present analysis is to determine incidence and treatment outcome in particular in respect to long-term results.

Results

Patient selection and characteristics

Between 1981 and 1998, 5411 HL patients registered in the GHSG database were enrolled into three generations of clinical trials (HD 1- HD 9) (Table 1). Of these, a total of 46 patients with secondary AML/MDS were identified. Patient characteristics are listed in Table 2. Six of the 46 patients with AML/MDS (13%) had early stage disease, 16 (35%) intermediate stage and 24 patients (52%) advanced stage at first diagnosis of HL. Primary treatment for HL consisted of radiotherapy alone in 4 patients (9%) and combined modality in 36 patients (78%). Twelve patients (26%) developed secondary AML/ MDS after salvage therapy for relapsed HL including 4 patients (9%) who were treated with HDCT and autologous SCT. At the time of diagnosis of secondary AML or MDS the median age was 47 years, ranging from 22-79 years. Thirty-six (78%) were diagnosed as AML and ten (22%) as MDS.

In 15 of 46 patients a cytogenetic evaluation was performed (Table 3). Clonal chromosome aberrations were found in all 15 patients (abnormalities of chromosome 5 or 7 [n=6], rearrangements on chromosome 11 [n=6]). Chromosome analysis revealed a complex aberrant karyotype in 6 patients and 45XO in one patient.

Time of occurrence and relative risk of secondary AML or MDS

After a median observation time for the 5411 patients of 55 months the cumulative risk of secondary AML/MDS was 1% (95% CI: 0.7-1.3). The median interval between the end of HD therapy and the diagnosis of secondary AML/MDS was 12,5 months (range: 0-128 months). 89% of secondary AML or MDS occurred within the first 5 years after completion of the initial therapy for HL. Secondary AML or MDS occurred within less than 12 months in ten patients and in five patients after five years.

Table 1. Clinical Trials of the German Hodgkin's Lymphoma Study Group between 1981 and 1998.

Trial	*Trial design*	*No. of Patients Included*	*No. of Patients With MDS/AML*
1978-1988		506	5
HD 1	2 x COPP/ABVD + EF 40 Gy *versus* 2 x COPP/ABVD + EF 20 Gy		
HD 3	3 x COPP/ABVD + 1 x COPP/ABVD versus 3 x COPP/ABVD + IF 20 Gy		
1988-1994		2,035	19
HD 4	EF 40 Gy *versus* EF 30 Gy + IF 10 Gy		
HD 5	2 x COPP/ABVD + EF 30 Gy (Bulk 10 Gy) *versus* 2 x COPP/ABV/IMEP + EF 30 Gy (Bulk 10 Gy)		
HD 6	4 x COPP/ABVD + IF Bulk/residual mass *versus* 4 x COPP/ABV/IMEP + IF Bulk/residual mass		
1994-1998		2,865	22
HD 7	EF 40 Gy *versus* 2 x ABVD + EF 40 Gy		
HD 8	2 x COPP/ABVD + EF 30 Gy (Bulk 10 Gy) *versus* 2 x COPP/ABVD + IF 30 Gy (Bulk 10 Gy)		
HD 9	4 x COPP/ABVD + IF Bulk/residual mass *versus* 8 x BEACOPP baseline + IF Bulk/residual mass *versus* 8 x BEACOPP escalated + IF-RT Bulk/residual mass		

HD, Hodgkin's disease; AML, acute myeloid leukemias; MDS, myelodysplastic syndromes; COPP, cyclophosphamide, procarbazine, and prednisone; ABVD, adriamycin, bleomycin, vincristine, and dacarbazine; EF, extended field; IF, involved field; IMEP, ifosfamide, methotrexate, etoposide, and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, and procarbazine, and prednisone.

Treatment of secondary AML/MDS

The different treatments applied upon diagnosis of secondary AML/ MDS are shown in Table 4. Twenty-four patients patients received only palliative supportive treatment. Eleven patients received high-dose Ara-C containing regimens. Nine patients received an allogeneic SCT.

Outcome of secondary AML/MDS

Median surival after the diagnosis of AML/MDS was 4 months (range: 0-76 months) in the whole group of patients and 10 months in the subgroup of transplanted patients (range: 3-28 months) (Figure 1). 10 patients (22%) died within a month after the diagnosis of secondary AML or MDS, 18 patients died within 6 months and 11 patients within a year. Altogether 39 patients (85%) did not survive one year after the diagnosis. Two patients of 46 survived more than 5 years. These patients were diagnosed with AML M3 and MDS RAEB. The majority of patients (n=34; 74%) died of secondary AML or MDS itself. Seven patients died of transplant related complications (pneumonia after allogeneic SCT n=5, acute GVHD n=2). Two patients had therapy-related mortality (pneumonia).

After 24 months of observation FFTF and OS were 2% and 8%, respectively (Figure 1). There was no difference in the overall survival rate between patients who developed AML versus patients who developed MDS (Figure 2). The OS for patients having received allogeneic SCT and for patients having received conventional or no therapy was very similiar (Figure 3).

Discussion

Although several reports exist about the incidence and risk factors for developing a secondary AML or MDS after primary HL, little is known about treatment outcome and prognostic factors for these patients. The incidence of secondary AML/MDS following conventional chemotherapy of HL ranges from 0.8% to 6.3% after 6 to 20 years.[3,4,11-13] The cumulative probability of AML or MDS after stem cell transplantation for lymphoma varies from 4.3% to 14.2% at 5 years.[6,14,15] The comparatively low incidence in our cohort (1% at 5 years) may result from different treatment regimes and the different leukemogenic potential of cytotoxic drugs used in our trials. For example mustargen was replaced by cyclophos-

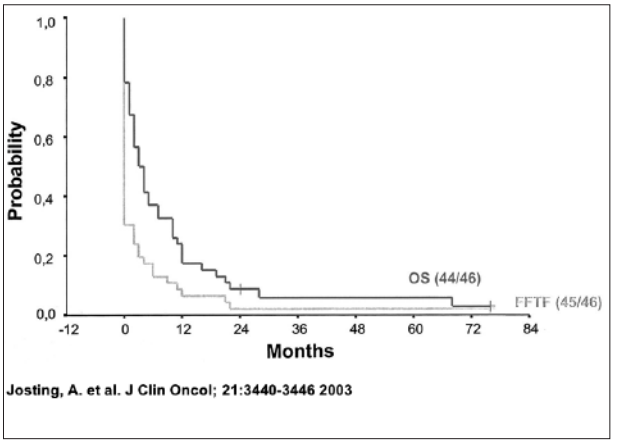

Figure 1. Overall survival (OS) and freedom from treatment failure (FFTF) after diagnosis of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

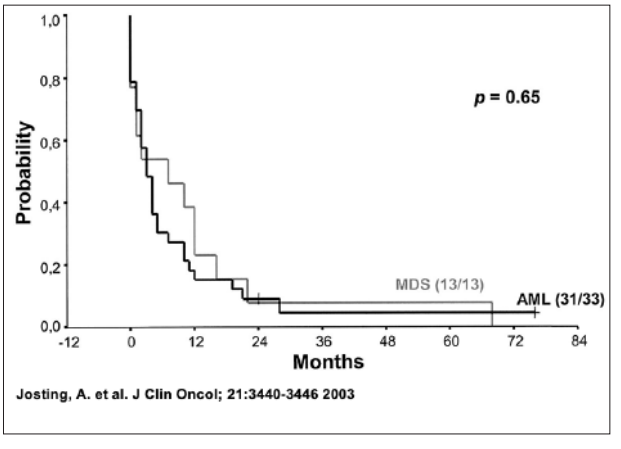

Figure 2. Overall survival (OS) in acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients.

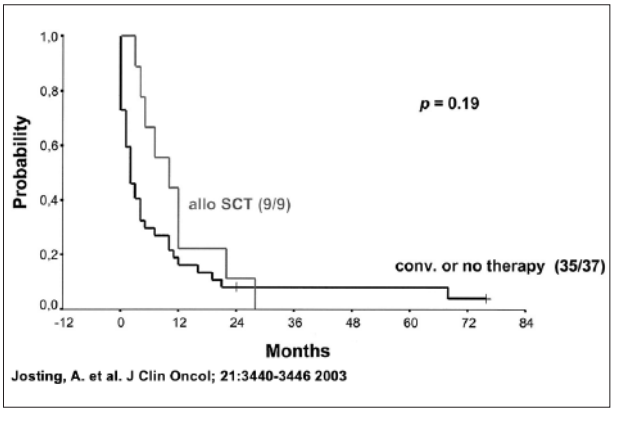

Figure 3. Overall survival (OS) after allogeneic stem-cell transplantation (SCT) versus conventional and no supportive therapy.

Table 2. Patient Characteristics.

	No.	*%*
Total	46	100
Sex		
Male	22	48
Female	24	52
Prior Therapy		
Radiotherapy alone	4	10
ABVD	1	2
COPP/ABVD	24	52
COPP/ABV/IMEP	6	13
BEACOPP (baseline)	2	4
BEACOPP (escalated)	9	19
Combined therapy	36	78
Salvage chemotherapy (+ HDCT)	12 (4)	26 (9)
AML/MDS		
AML	36	78
M1	4	9
M2	7	15
M3	1	2
M4	9	20
M4eo	1	2
M5	6	13
M7	2	4
Not classified	6	13
MDS	10	22
Radiotherapy alone	1	2
RAEB	3	7
RARS	1	2
RAEB-t	2	4
CMMoL	1	2
Not classified	2	4

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ABVD, adriamycin, bleomycin, vincristine, and dacarbazine; COPP, cyclophosphamide, procarbazine, and prednisone; ABV, adriamycin, bleomycin, and vincristine; IMEP, ifosfamide, methotrexate, etoposide, and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; HDCT, high-dose chemotherapy. M4eo, eosiniphils; CMMoL, chronic myelo-monocytic leukemia.

phamide in all GHSG trials. Historically the actuarial risk has decreased in recent studies.[16,17] A variety of risk factors for the development of secondary AML/MDS were found, especially after high-dose therapy. Older age, the number and type of prior courses of chemoradiotherapy, exposure to radiotherapy prior to transplantation and the use of total body irradiation in the conditioning regimen have been related to the development of secondary AML/MDS.[4,6]

Certain cytogenetic abnormalities and the latency period between previous anti-cancer treatment and secondary AML/MDS development both depend upon the use of chemotherapeutic drugs. The latency period is shorter after topoisomerase II inhibitors (2-3 years) and longer after alkylating agents (3-8 years). Although our data confirm that most of the sec-

Table 3. Cytogenetics.

Patient No.	*Study arm*	*FAB*	*Cytogenetic Abberations*
1	HD9C	M2	46XX, del 3p, der (4), t(4;21), -5, -13, der (14), t (14;22), 16p,17p+, -18, -21, -22[16]43XX, -3, -5, der (13;15) -15, 16p+, 17p+, -18, 21q+43XX, del (3)p, -5, -13, -14, 16p+, 17p+, -18, 21q+, -2244XX, -5, der (7), +12, -13, -15, -16, -17, -22
2	HD9C	M4eo	46XX [11]53XX, +1, -2, +3, +4, +7, +15, +17, +19, +22 [1]
3	HD9C	M4eo	47XY, inv (16)(p13q22), add (17)(q25)
4	HD9C	M5	45XX, t(3;12)(q22;q11), -7, -10, del (11)(q22), +21 cp
5	HD5B	M4	Complex abberations at position (4; 16; 17; 21)
6	HD5B	M7	Complex abberation with del 5, del 7
7	HD9C	M5a	46XX, t(9;11)(p21;q23)
8	HD9C	M5b	47XY, t(9;11)(p22;q23), +19
9	HD9B	M2	46XX, t(10; 11)(10p14; 11q21)
10	HD8B	M4	46XX, t(9;11)(p22q23)
11	HD7B	RAEB-t	46XY (t(1;11)(q25; p13)
12	HD5A	CMMoL	45XX,-7
13	HD9C	M2	46XX, t(9; 11)(p21;q23)
14	HD9C	M4	45XO
15	HD4A	M1	45XX, t(3;3), -7

HD9C: 8 cycles BEACOPP esc. ± RT bulk or residual; HD9B: 8 cycles BEACOPP baseline ± RT bulk or residual; HD5A: 2 cycles COPP/ABVD + extended field RT; HD5B: 2 cycles COPP/ABV/IMEP + extended field RT; HD8B: 2 cycles COPP/ABVD + involved field RT; HD7B: 2 cycles ABVD + extended field RT; HD4A: extended field RT; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; RT, radiotherapy; COPP, cyclophosphamide, procarbazine, and prednisone; ABVD, adriamycin, bleomycin, vincristine, and dacarbazine; IMEP, ifosfamide, methotrexate, etoposide, and prednisone; FAB, French-American-British; M4eo, eosinophils; RAEB-t, refractory anemia with excess of blasts in transformation; CMMoL, chronic myelo-monocytic leukemia.

ondary AML/MDS occurr within the first years after completion of the initial therapy for HL, further alkylating agents- induced secondary neoplasias must be expected.

Patients with secondary AML/MDS are frequently referred for allogeneic stem cell transplantation, if donor availability, age and medical condition permit. However the feasibility of allogeneic transplantation in treatment-related AML or MDS seems to be overestimated. In our analysis transplantation was only practicable in a small percentage of all patients with secondary leukemia or MDS. Less than 35% of patients would have been eligible in this setting for transplantation taking into account that 28 patients died within 6 months after the diagnosis of AML and additional three patients were older than 60 years. Although different authors report 5-year disease-free survival of 16% and 24.4% after stem cell transplantation, these patients may only represent a small selected subgroup of all patients with secondary AML/MDS.[19,20]

Some authors claim tailor-made protocols with regard to the cytogenetic findings. Patients with a favourable karyotype (inv (16), t (8;21) should be treated as for de-novo AML whereas palliative treatment or experimental approaches ought to be considered for patients with a complex aberrant karyotype.[8,21] In our cohort only 15 cytogenetic analysis of 46 patients were available. This relatively low number might be due to the fact that patients have been treated since the early 1980s where cytogenetic analysis have not been common. Striking, however, is the fact that favourable karyotypes have not been found in this cohort which might be an additional explanation for the poor outcome in this group. A better outcome is seen in patients with favourable risk cytogenetics.[19]

In our analysis, the 2-year FFTF and OS for all patients were 2% and 8% respectively. The poor OS of the cohort of the GHSG does not allow to detect differences in the outcome of transplanted versus conventionally treated patient or between AML or MDS. The dismal outcome of these patients, even with HDCT and ASCT, underlines the need to evaluate new treatment strategies. Currently untreatable patients should be identified at an early stage and lead to palliative treatment or alternatively to new therapeutic options. Allogeneic *minitransplant* might be an investigational alternative seeking to exploit graft-versus-tumor reaction. New agents, such as farnesyl transferase inhibitors (ras inhibitors) or drug-antibody conjugates should be explored with minimal compromise of quality of life.

In conclusion, the application of tailor-made protocols holds the greatest promise to treat patients according to their prognosis. Whereas remission can be achieved in a few secondary AML/MDS, our analysis suggests a palliative treatment approach for those with unfavourable subtypes.

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