Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Allogeneic Hematopoietic Stem Cell Transplantation In Therapy-Related Myeloid Neoplasms (t-MN) of the Adult: Monocentric Observational Study and Review of the Literature

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Competing interests: The authors have declared that no competing interests exist.

Abstract. ***Background:*** **Therapy related myeloid neoplasms (t-MN) occur due to direct mutational events of chemotherapeutic agents and radiotherapy. Disease latency, mutational events and prognosis vary with drugs categories.**

Methods: **We describe a cohort of 30 patients, 18 females and 12 males, with median age of 52.5 years (range, 20 to 64), submitted to allogeneic stem cell transplantation (HSCT) in our department between September 1999 and March 2017. Patients had a history of solid tumour in 14 cases, haematological disease in 15 cases and both of them in one case. After a median of 36.5 months (range, 4 to 190) from first neoplasm, patients developed t-AML in 19 cases and t-MDS in 11 cases. Molecular abnormalities were detected in 5 patients, while karyotype aberrations were found in 17 patients. Patients received conventional chemotherapy in 14 cases, azacitidine in 10 cases and both of them in one case. Five patients were submitted to HSCT without previous treatment except for supportive therapy.**

Results: **Seventeen patients obtained sustained CR after SCT, while 8 patients showed resistant or relapsed disease. The remaining five patients died early after SCT. At follow up time (May 2017) 13 patients were alive with a median OS of 48 months (range 3-195), while 17 patients died after a median of 4 months (range 1-27) by relapse mortality in 6 cases and non-relapse mortality in the other 11 patients.**

Conclusions: **Global OS was 43%. After SCT, 72.2% of patients with t-MN maintained a sustained CR.**

Keywords: Therapy-related myeloid neoplasm, Hematopoietic stem cell transplantation, Secondary leukemia.

Citation: Metafuni E., Chiusolo P., Laurenti L., Sorà F., Giammarco S., Bacigalupo A., Leone G., Sica S. Allogeneic hematopoietic stem cell transplantation in therapy-related myeloid neoplasms (t-MN) of the adult: monocentric observational study and review of the literature. Mediterr J Hematol Infect Dis 2018, 10(1): e2018005, DOI: http://dx.doi.org/10.4084/MJHID.2018.005

Published: January 1, 2018 **Received: October 10, 2017** **Accepted: December 1, 2017**

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Introduction. Therapy-related myeloid neoplasms are recognized as a separate entity in the World Health Organization (WHO) classification of haematological diseases.[1] The incidence of therapy-related myeloid neoplasms (t-MN) continue to rise due to the relative prolongation of survival and cure related to chemo- and radio-therapy for primary malignancies, mostly breast cancer and lymphoproliferative diseases.[2-7] The peak occurrence time of therapy-related acute myeloid leukemia/myelodysplastic syndrome is 3 to 5 years after prior cytotoxic treatment, while the risk decreases markedly after the first decade.[8] At present, t-MN account for 10–20% of all malignant myeloid diseases.[9] Factors associated with an increased risk of t-MN include exposure to alkylating agents, topoisomerase II inhibitors, radiation therapy,[10-15] and older age at treatment, in addition to genetic susceptibility.[16-21] t-MN after anthracyclines and/or topoisomerase II inhibitors are associated with occurrence of MLL translocation at 11q23 or RUNX1/AML1 at 21q22 after a median latency of 1 to 3 years without a prodromal phase. t-MN after alkylating agents have a median latency of 4 to 10 years and are often preceded by myelodysplasia. It is associated with unbalanced chromosome 5 and 7 abnormalities, complex karyotypes, and/or TP53 mutations. After radiation treatment, the highest risk for t-MN occurrence is registered at 2 years and appears to normalize after 10 to 15 years.[22-24] Particularly, patients who received radiation to chest, pelvis and vertebrae for stomach, colorectal, liver, breast, endometrial, prostate, and kidney cancers seem to be at a significantly higher risk of developing t-MN.[24,25] More recently, it came to light the potential role of various germline genetic factors in an individual's susceptibility to t-MN, particularly for those variants that alter drug metabolism such as gene NQ01, glutathione-S-transferase,[9,18,19,26] as well as those involved in DNA repair pathway such as BRCA, TP53 and MDM2.[20,21]

Clonal cytogenetic abnormalities are found in 75–90% of t-MN, and 46-70% of them are adverse karyotype including complex karyotype, deletion or loss of chromosome 5 and/or 7.[3,4] Cytogenetics assessment is the principal prognostic factor for relapse rate and overall survival (OS).[27-29] The heterogeneous treatments of therapy-related myeloid neoplasms, ranging from best supportive care to intensive chemotherapy, hypomethylating agents, and allogeneic stem cell transplantation, do not allow definite conclusions on the best treatment choice, particularly for elderly patients.[30,31] Treatment of t-MN with conventional therapy is associated with a poor outcome in terms of survival (6 months),[8,32] remission rate (28% to 50%) and duration of the remission.[33-35] On the other hand, conventional chemotherapy might be a reasonable option for t-MN with favourable karyotype such as inv(16), t(16;16), t(15;17) or t(8;21), since the reported remission rate and the disease free survival are similar to those seen for the *de novo* counterpart.[35,36] The introduction of new drugs such as azacitidine and decitabine has shown promising results in the management of t-MN with an acceptable toxicity profile also for frail patients, and with an overall response rate of approximately 40%.[4,30,31,37,38-44]

Allogeneic Stem Cell Transplantation for t-MN. Allogeneic haematopoietic stem cell transplantation (HSCT) represents the only potentially curative strategy, but it is not feasible for all patients due to age, comorbidities in elderly patients, poor organ reserve and high non-relapse mortality (NRM).[4,45] The haematopoietic cell transplantation-specific comorbidity index (HCT-CI) was developed as a sensitive tool to measure the burden of comorbidities before HSCT and to predict both the risks of NRM and the probabilities of survival after HSCT.[46] As reported by ElSawy et al.[47] in the HCT-CI validation study, the three HCT-CI risk groups with score 0, 1–2, and ≥3 result in a NRM of 14%, 23%, and 39% with a survival of 74%, 61%, and 39%, respectively. Therefore, HSCT should be offer as a reliable option to fit patients with good performance status, intermediate and poor risk karyotype with suitable and available donor.[9,27,28,48-50] With particularly interest to t-MN, the Center of International Bone Marrow Transplantation Research (CIBMTR) and the European Group for Bone and Marrow Transplantation (EBMT) extrapolated pre-transplant factors predicting post-HSCT outcome in these patients from larges study cohorts. CIBMTR conducted a large study cohorts on t-MN and proposed a prediction model of survival after allogeneic HSCT using the following four risk factors: age older than 35 years, poor-risk cytogenetics, t-AML not in remission or advanced t-MDS, donor other than an HLA-identical sibling or a partially or well-matched unrelated donor. Five-year survival for subjects with none, 1, 2, 3, or 4 of these risk factors was 50%, 26%, 21%, 10%, and 4%, respectively.[27] Also the EBMT group[28] reported that disease stage at transplant different from complete remission, abnormal cytogenetics (excluding t(8;21), inv(16) and t(15;17)) and patients' age >40 years are the most significant factors predicting survival, relapse rate, disease-free survival (DFS) and NRM dividing patients into three risk groups: low, intermediate and high. Overall survival for the above-mentioned groups was 62%, 33% and 24%,

Table 1. Results of the review: outcomes of patients with therapy-related AML/MDS submitted to HSCT.

Author and year	N° of patients	Poor karyotype (%)	OS	NRM	Relapse rate	Median follow-up
Finke et al, 2016[51]	79	53%	38%	23%	42%	7.5 ys
Tang et al, 2016[52]	16	43%	66%	13%	20%	3.3 ys
Alam et al, 2015[2]	65	50%	34%	31%	30-36%	5.9 ys
Liu et al, 2015[53]	30	-	33%	-	34%	2 ys
Spina et al, 2012[54]	29	59%	37%	32%	33%	3.7 ys
Zinke-Cerwenka et al, 2011[55]	17	47%	47%	30%	24%	2.6 ys
Armand et al, 2010[56]	24	50%	41%	17%	38%	2.8 ys
Litzow et al, 2010[27]	868	26%	22%	48%	31%	5 ys
Kröger et al, 2009[28]	461	42%	35%	37%	31%	1.8 ys
Nevill et al, 2008[57]	24	46%	33%	30%	38%	4.5 ys
Chang et al, 2007[38]	257	51%	33%	54%	33-36%	3.8 ys
Witherspoon et al, 2001[58]	111	-	-	52-58%	26-40%	5 ys
de Witte et al, 2000[59]	67	-	35%	46%	36%	5 ys
Yacoub-Agha et al, 2000[60]	70	-	30%	49%	42%	7.9 ys
Anderson et al, 1997[61]	46	25%	26%	44%	33%	5 ys
Ballen et al, 1997[62]	18	50%	28%	50%	22%	3 ys
This report, 2017	30	32%	41%	44%	27%	2 ys

respectively; DFS was 58% (low), 32% (intermediate) and 20% (high); NRM was 22% (low), 37% (intermediate) and 38% (high); finally, relapse rate was 20% (low), 31% (intermediate) and 32% (high) respectively.

We performed a review of the literature on therapy-related AML/MDS submitted to allogeneic stem cell transplantation excluding AML secondary to MDS progression. Detailed results concerning cohort size, median follow up, overall survival, NRM incidence, and relapse rate are depicted in **Table 1**. The reported outcomes for patients submitted to HSCT for therapy-related AML/MDS are very heterogeneous. Median OS ranges from 22% to 66%, with a NRM of 21 to 58% and a relapse rate of 26% to 42%.[2,27,28,38,51-62]

Monocentric Observational Study. *Patients and disease characteristics.* We retrospectively analyzed patients submitted to HSCT in our department and identified 30 patients with a diagnosis of therapy-related myeloid neoplasm (t-MN) transplanted between September 1999 and March 2017. Patients were 18 females (60%) and 12 males (40%) with a median age of 52.5 years (range, 20 to 64). Secondary neoplasm was acute myeloid leukemia (t-AML) in 19 cases (63%) and myelodysplasia (t-MDS) in 11 cases (37%). Data were collected through retrospective chart review and after institutional review board approval. The median time occurred from primary disease to t-MN occurrence was of 36.5 months (range, 4 to 190). Primary disease was hematologic in 15 cases (50%): Hodgkin's disease (n=2), non-Hodgkin's lymphoma (n=9), acute lymphoblastic leukemia (n=1), chronic lymphocytic leukemia (n=2) and acute myeloid leukemia (n=1). Fourteen patients (50%) had a previous diagnosis of solid tumor: medulloblastoma (n=1), breast (n=8), Ewing sarcoma (n=1), thyroid (n=1), bladder (n=2) and vagina/anus (n=1). One patient had a history of both haematological (non-Hodgkin's lymphoma) and solid tumor (breast). Twelve patients (40%) had been previously treated with chemotherapy, 8 patients (26.7%) with chemotherapy and autologous transplantation, 2 (6.7%) patients with radiotherapy, one patient (3.3%) with radioiodine therapy and 7 patients (23.3%) with a combination of chemo- and radiotherapy. At t-MN diagnosis all patients had received a median of 2 lines of therapy (range, 1 to 6) for their primary malignancy. All patients were free of their primary malignancies at the time of transplantation.

Revised International Prognostic Scoring System (IPSS-R)[63] was used to classify cytogenetics of t-MDS, while European Leukemia Net AML risk stratification by cytogenetics was used for AML.[64] Karyotype was available for 28 out of 30 patients. Eleven patients (36.7%) had normal karyotype, three patients (10%) had a favourable karyotype, 5 patients (16.7%) had an intermediate-risk karyotype and 9 patients (30%) had an adverse-risk karyotype. Molecular cytogenetics analyses were available for 14 out of 30 patients: FLT3/ITD+ (n=2), CBFB/MYH11 (n=1), NPM1+ (n=1), NPM1 and FLT3/ITD double positivity (n=1), no abnormalities (n=9). A detailed description of primary neoplasms, treatment for primary neoplasm and t-HN is reported in **Table 2**. Transplant features and outcomes are depicted in **Table 3**.

Table 2. Detailed report of patients, primary and therapy-related disease and treatment.

Patients n.	Sex	Age	First neoplasia	Treatment for first neoplasm	Time to t-MN (months)	t-MN	Blasts count %	Molecular marker	Karyotype	Pre-HSCT treatment
1	Female	60	NHL	CHT+ASCT	18	t-MDS	20	N.A.	46,XX	Aza
2	Female	53	Breast cancer	CHT+RT	33	t-AML	20	N.A.	Hyperploid (93-94, XX), +G, -F, +C*	None
3	Female	49	Breast cancer	CHT	32	t-AML	23	Inv (16)	46, XX, Inv (16)	SD-CHT
4	Female	62	NHL	CHT+ASCT	120	t-MDS	N.A.	N.A.	46, XX, (-7)	Aza
5	Female	29	Breast cancer	CHT+RT	24	t-AML	N.A.	N.A.	46, XX	LD-CHT
6#	Male	33	AML	CHT+ASCT	72	t-MDS	N.A.	N.A.	45, XY, (-7)	Aza
7	Male	30	NHL	CHT+ASCT	60	t-MDS	15	N.A.	N.A.	None
8	Female	57	Breast cancer	RT	180	t-AML	58	NPM1+	46, XX	SD-CHT
9	Male	48	CLL	CHT	37	t-AML	20	None	46, XY, (-7)	SD-CHT
10	Female	36	Breast cancer	CHT+RT	48	t-AML	90	None	46, XX	Aza
11	Female	56	Breast cancer and NHL	CHT+RT	108	t-MDS	N.A.	N.A.	46, XX, (-7)	Aza
12	Female	48	Thyroid cancer	RIT	4	t-AML	20	NPM1+, FLT3+	N.A	SD-CHT
13	Male	48	Bludder cancer	CHT	48	t-AML	34	None	46, XY, t(3;3), (-7), (+8)	SD-CHT
14	Female	55	HL	CHT	36	t-AML	N.A.	N.A.	N.A.	SD-CHT
15	Male	55	NHL	CHT+ASCT	144	t-MDS	4	N.A.	46, XY	Aza
16	Female	57	Breast cancer	RT	24	t-AML	9	N.A.	46, XX, (+8)	None
17	Male	40	ALL	CHT	29	t-MDS	5	N.A.	45, XY (-7)	None
18	Female	53	Breast cancer	CHT+RT	120	t-AML	N.A.	N.A.	47, XY, (-11)(q14q23)	LD-CHT
19	Female	56	NHL	CHT+ASCT	24	t-MDS	6	None	N.A.	Aza
20	Female	41	Ewing sarcoma	CHT	17	t-AML	85	None	46, XX	SD-CHT
21	Male	62	NHL	CHT	61	t-MDS	5	N.A.	48, XXY (+8)	Aza
22	Female	39	Breast cancer	CHT+ASCT	30	t-AML	N.A.	N.A.	Hypoploid (42-44, XX)	SD-CHT
23	Female	55	NHL	CHT+RT	16	t-AML	91	None	46, XX, (-16), (+13)	SD-CHT
24	Male	53	NHL	CHT	39	t-AML	20	None	46, XY	Aza
25	Male	57	Bludder cancer	CHT	12	t-AML	30	FLT3+	N.A.	SD-CHT
26	Male	20	Medulloblastoma	CHT	190	t-MDS	8	None	46, XX, (-7p), (-1p), (-5q)	Aza
27	Male	59	NHL	CHT	12	t-AML	40	FLT3+	46, XY	SD-CHT
28	Male	64	CLL	CHT+ASCT	48	t-MDS	3	N.A.	46, XY (-20)	SD-CHT
29	Female	50	HL	CHT	17	t-AML	43	None	46, XX	SD-CHT+Aza
30	Female	52	Vagina-anus cancer	CHT+RT	100	t-AML	16	N.A.	N.A.	SD-CHT

Abbreviations: t-AML=therapy-related acute myeloid leukemia; t-MDS=therapy-related myelodysplastic syndrome; NHL=non-Hodgkin lymphoma; CLL=chronic lymphocytic leukemia; HL=Hodgkin lymphoma; ALL=acute lymphoblastic leukemia; CHT=chemotherapy; RT=radiotherapy; ASCT=autologous stem cell transplantation; Aza=azacitidine; SD-CHT=standard dose chemotherapy; LD-CHT=low dose chemotherapy; RIT: radioiodine therapy. N.A.=not available; *not otherwise specified deletion in the F group and duplication in the G and C group. # [Patients in question had an AML with t(8;21) as first neoplasia. Seven years after the last therapy (autologous stem cell transplantation), he developed a myelodysplasia with deletion of chromosome 7, while t(8;21) was not detected].

Table 3. Transplant for t-MN: features and outcomes.

Patient n.	Status at HSCT	HCT-CI	Time from t-HN to HSCT (months)	HSCT year	Donor	Stem cells source	Conditioning	GvHD prophylaxis	Disease response	DFS months	GvHD (acute or chronic)	Outcome	Cause of death	Survival months
1	refractory	9	13	2013	REL	PB	RIC	CSA+MTX	relapse	5	chronic	alive		48
2	untreated	4	2	2002	REL	PB	MAC	CSA+MTX	remission	173	chronic	alive		173
3	CR	3	6	2001	REL	PB	MAC	CSA+MTX	remission	195	both	alive		195
4	refractory	6	11	2014	REL	PB	RIC	CSA+MFA	refractory	0	acute	dead	NRM	3
5	refractory	3	3	1999	REL	PB	MAC	CSA+MTX	relapse	6	none	dead	RRD	6
6	PR	4	5	2013	MUD	PB	RIC	CSA+MFA+ATG	N.A.	1	acute	dead	NRM	1
7	untreated	4	4	2006	MUD	CB	RIC	CSA+MFA+ATG	remission	135	chronic	alive		135
8	CR	5	19	2015	REL	PB	MAC	CSA+MTX	remission	18	chronic	alive		18
9	refractory	7	4	2013	MUD	PB	RIC	CSA+MTX+ATG	refractory	0	none	dead	RRD	5
10	CR	4	9	2012	MUD	PB	MAC	CSA+MTX+ATG	remission	4	both	dead	NRM	4
11	CR	5	11	2012	MUD	PB	RIC	CSA+MFA	N.A.	1	none	dead	NRM	1
12	CR	3	19	2009	MUD	PB	MAC	CSA+MTX+ATG	N.A.	1	none	dead	NRM	1
13	refractory	3	3	2007	REL	PB	RIC	CSA+MFA	remission	6	acute	dead	NRM	6
14	CR	3	16	2009	REL	PB	MAC	CSA+MFA	remission	98	chronic	alive		98
15	CR	4	26	2011	MUD	PB	MAC	CSA+MTX+ATG	remission	8	both	dead	NRM	8
16	untreated	3	2	2016	REL	PB	MAC	CSA+MTX+ATG	remission	14	both	alive		14
17	untreated	5	4	2014	MUD	BM	MAC	CSA+MFA+ATG	remission	37	both	alive		37
18	refractory	3	7	2004	MUD	PB	MAC	CSA+MTX+ATG	relapse	12	none	dead	RRD	12
19	refractory	7	8	2016	HAPLO	BM	MAC	CSA+MFA+Cy	N.A.	1	none	dead	NRM	1
20	CR	3	7	2017	HAPLO	BM	MAC	CSA+MFA+Cy	remission	3	acute	alive		3
21	PR	4	12	2015	MUD	PB	MAC	CSA+MTX+ATG	remission	19	both	alive		19
22	refractory	3	9	2009	REL	PB	MAC	CSA+MTX	refractory	0	none	dead	RRD	4
23	CR	3	6	2009	REL	PB	MAC	CSA+MTX	remission	92	none	alive		92
24	CR	5	11	2013	MUD	PB	MAC	CSA+MTX+ATG	relapse	15	both	dead	RRD	16
25	refractory	3	6	2009	REL	PB	MAC	CSA+MTX	relapse	3	acute	dead	RRD	4
26	PR	6	14	2014	HAPLO	BM	MAC	CSA+MFA+Cy	remission	32	none	alive		32
27	CR	3	6	2011	REL	PB	RIC	CSA+MFA	remission	68	both	alive		68
28	untreated	3	36	2006	MUD	PB	RIC	CSA+Alemtuzumab	remission	27	chronic	dead	NRM	27
29	refractory	5	16	2011	MUD	PB	RIC	CSA+MTX+ATG	N.A.	1	acute	dead	NRM	1
30	CR	3	7	2011	MUD	PB	RIC	CSA+MFA	remission	4	acute	dead	NRM	4

CR=complete remission; PR=partial remission; REL=match related donor; MUD=match unrelated donor; Haplo=related haploidentical donor; PB=G-CSF-primed peripheral blood stem cells; BM=un-manipulated bone marrow stem cells; CB=un-manipulated cord blood stem cells; MAC=myeloablative conditioning; RIC=reduced intensity conditioning; CSA=cyclosporine A; MTX=methotrexate; MFA=mycophenolate mofetil; ATG=anti-lymphocytes globulin; Cy=post-transplant cyclophosphamide.

Statistical analysis. Overall survival and disease-free survival (DFS) were estimated using Kaplan-Meier product method, while for curves comparison log-rank test was applied. χ^2 test and Fisher's exact test were used to assess associations between categorical variables and OS, NRM, RRD, DFS. A competing risk analysis was performed to calculate the cumulative incidence of relapse-related death (RRD) and non-relapse mortality (NRM). For NRM, relapse was the competing event, and for relapse, NRM was the competing event. Fine and Gray's method for cumulative incidence of RRD and NRM were used to compare different groups. Statistical analysis was realized using NCSS 10. A p-value ≤ 0.05 was considered statistically significant.

Results. *Engraftment and GvHD.* White blood cells count of $\geq 1.0 \times 10^9$/L and stable platelets count $\geq 20.0 \times 10^9$/L were reached at median day +21 (range, 11 to 130) and median day +15 (range, 10 to 45), respectively. Three patients died early before achieving stable engraftment.

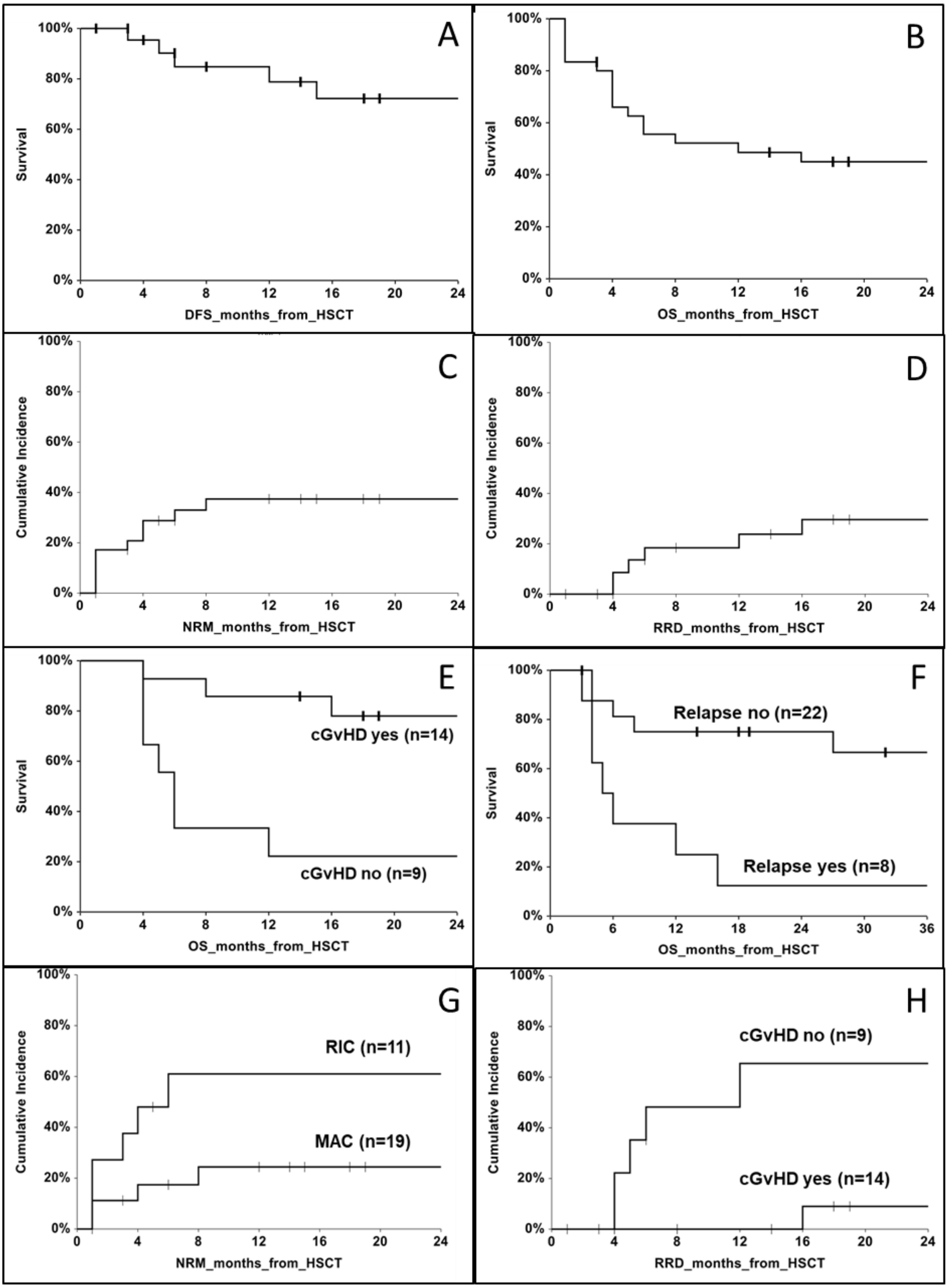
Acute GvHD (aGvHD)[65] occurred in 15 patients (50%) and global grading was as follows: grade I (n=3), grade II (n=5), grade III (n=6), and grade IV (n=1). Among them, three patients died because of aGvHD. Chronic GvHD (cGvHD)[66] was diagnosed in 14 out of 23 patients surviving after day +100 (65%) and global scoring was as follows: mild (n=3), moderate (n=7) and severe (n=4). One of them died for cGvHD-related complications.

Response. Morphological bone marrow cytology was performed on day +30 after HSCT only in 25 patients because of early death in the others five. Three patients (12%) had a persistence of the underlying disease, whereas twenty-two patients achieved a CR (88%) on day +30. Among them, 5 patients (22.7%) experienced a relapse after a median time of 6 months (range, 3 to 15), while 17 patients (77.3%) maintained a CR after a median time of 27 months (range, 3 to 195). Median 2-ys DFS after HSCT was of 72.2% (95% CI 51.1 to 93.3) (**Figure 1A**).

Overall survival, NRM and RRD. At the follow up data fixed on May 2017, 13 patients were alive after a median time of 48 months (range, 3 to 195), while 17 patients died after a median time of 4 months (range, 1 to 27). The causes of death were as follows: underlying disease (n=6), GvHD (n=3), EBV-related post-transplant lymphoproliferative disease (PTLD) (n=1) and infectious complications (n=7). The overall survival at 2 years after HSCT was of 40.5% (95% CI 22.1 to 58.9), whereas the cumulative incidence of NRM and RRD at 2 years was of 44.4% (95% CI 27.6 to 71.2) and 29.6% (95% CI 15 to 58.6), respectively (**Figures 1B, 1C** and **1D**). No differences in terms of OS, NRM, RRD and DFS were seen stratifying patients according to underlying disease, disease status at transplant, previous treatment received, karyotype risk, patients and donor characteristics, stem cell source. An association was identified between OS and cGvHD development after HSCT, as well as between OS and relapse occurrence. Overall survival was higher in the group with cGvHD than those detected in the group without this complication (68% vs. 22%, p=0.018). Median OS was of 6 months (range, 4.6 to 7.4) in the group without cGvHD, while it was not reached in the group with cGvHD (p=0.0002, **Figure 1E**). An higher mortality was recorded in the group of patients who experienced a relapse of the underlying disease as compared with patients who did not relapsed after HSCT (67% vs. 13%, p=0.011). Median OS in the group relapsed after HSCT was of 5 months (range, 2.2 to 7.8) as compared to patients without relapse, for whom a median OS was not reached (p=0.004, **Figure 1F**). Relatively to NRM, an association was identified with the conditioning regimen: surprisingly, NRM was higher for patients who had received a reduced intensity conditioning as compared to those who had received a myeloablative one (p=0.046). Two-years cumulative incidence of NRM was of 74% (95% CI 49 to 100) after RIC transplant and 24% (95% CI 10 to 58) after ABL transplant (p=0.022, **Figure 1G**). Finally, also for RRD an association was found with cGvHD development after HSCT: among patients with cGvHD, a minor number of RRD was recorded as compared to patients who had not developed this complication (p=0.018). The cumulative incidence of RRD at 2 years after HSCT was of 9% (95% CI 1 to 59) for patients with cGvHD and 65% (95% CI 38 to 100) for patients without cGvHD (p=0.004, **Figure 1H**).

Two patients (6.7%) experienced a third tumor, in particular a breast cancer occurred thirteen years after HSCT and an EBV-related PTLD of the brain occurred eight months after HSCT.

Figure 1. Five-years outcomes of therapy-related AML/MDS after HSCT: **1A**) Kaplan Meier for DFS; **1B**) Kaplan Meier for OS; **1C**) cumulative incidence of NRM; **1D**) cumulative incidence of RRD; **1E)** Kaplan Meier for OS according to cGvHD development; **1F**) Kaplan Meier for OS according to relapse occurrence; **1G**) cumulative incidence of NRM according to transplant conditioning regimen; **1H**) cumulative incidence of RRD according to cGvHD development.



Discussion. In the last two decades, many authors published results concerning different cohorts of patients with therapy-related acute myeloid leukemia or myelodysplasia submitted to allogeneic stem cell transplantation. An high heterogeneity in the percentage of OS (22% to 66%), NRM (21% to 58%) and relapse rate (26% to 42%) come to light from these experience.[2,27,28,38,51-62] Each of these studies highlighted a different key point in this transplant setting, which might affect outcome after HSCT. The mainly predicting factor for OS resulted the karyotype and the recipient performance status at transplant.[38,54,56] Patients achieving a CR before transplantation showed better outcomes, whereas multiple therapy lines increase organ damage as well as the incidence of neutropenia, infection events and the immunosuppression of the patient increase TRM.[54,60,61] Patients at risk for treatment-related myeloid neoplasms should be followed closely and be considered for stem-cell transplantation early in the course of myelodysplasia.[38,58,61] Considering the incremented risk of relapse according to blasts percentage, patients with secondary MDS should be direct to transplantation before the progression into AML, and if secondary AML occurs, they should be transplanted as soon as possible.[61] For patients who did not achieved a CR pre-transplant, rapid transplantation, also considering alternative donor, could offer a reasonable outcome, reducing the risk of deterioration of the patient's performance status. OS after HSCT in patients aged 60 years or above was very poor.[50,51,67,68] Reduced intensity conditioning and conditioning with targeted busulphan dose[38,51,58] might reduce TRM, especially for those patients with a reduced organ reserve. As reported for patients with de novo MDS,[69] pre-transplant disease stage, cytogenetic risk group,[57,56] type of therapy given for the original disease, transplant conditioning regimen, and patient age[61] significantly affect relapse-free survival among patients with secondary MDS/t-AML.[38] Concerning to stem cell source, peripheral blood instead of bone marrow appeared to reduce NRM[38] and relapse rate[38,57] and to improve OS.[38] On the other hand, controversial data were reported relative to donor source impact on OS.[2,27,38,53,70]

In our cohort, global OS appeared to fit with those reported from several authors (40.5% vs 22-66%), whereas NRM appeared the major cause of death, even if the NRM rate was comparable to others data (44% vs 21-58%).[2,27,28,38,51-62] Surprisingly, we observed an high DFS (72.2%) perhaps attributable to high cGvHD rate after HSCT, corresponding to an enhanced GvL effect. In fact, among patients with cGvHD a reduced RRD and an increased OS were registered. Graft-versus leukemia (GvL) effect, especially associated with chronic GvHD, improved DFS and OS also in adverse karyotype t-MN submitted to HSCT.[71] Probably due to the small size of our study group, no differences in terms of post-transplant outcomes emerged dividing patients according to recipient age, previous treatment, disease status at transplant, karyotype, donor or stem cell source. Unexpectedly, we found a higher NRM among patients who had received a RIC transplant as compared to ABL, but no differences in performance status, pre-transplant risk score or disease status existed between the two groups.

An interesting feature revealed by our curves was that DFS reached a plateau approximately after the first year post HSCT, while OS reached its prolonged plateau after the second one. In fact, no relapse was ascertained after the first year post-HSCT, so that eighteen patients (56.7%) obtained and maintained a complete remission after HSCT. On the other hand, no deaths were recorded after the second year post-HSCT, with an OS of 40.5% at the follow up time.

Conclusions. The incidence of t-MN is increasing as more individuals survive treatment for a primary cancer diagnosis. At t-MN diagnosis,[72] physicians should evaluate molecular and cytogenetic risk of the disease, performance status, age and comorbidities of patients, and should start HLA-typing to timely detect a suitable donor. Older patients with poor performance status should be offered clinical trials or best supportive care. For fit patients, molecular and cytogenetics stratification is crucial. t-APL might benefit from standard first line protocols. Favorable karyotype t-MN should be treated with standard induction chemotherapy followed by high dose cytarabine consolidation course. Normal karyotype t-MN could receive standard induction chemotherapy followed by HSCT while poor molecular karyotype t-MN should be encouraged to participate in prospective clinical trials specifically designed and they should be considered early for allogeneic HCT.[51] Upfront HSCT could be offered to patients with low blast count and poor performance status.

Acknowledgements. This study was supported by Centro di Ricerca sulle Cellule Staminali Emopoietiche e le Terapie Cellulari, Università Cattolica del Sacro Cuore in Rome.

References:

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. doi: 10.1182/blood-2016-03-643544. Review. https://doi.org/10.1182/blood-2016-03-643544
2. Alam N, Atenafu EG, Kuruvilla J, Uhm J, Lipton JH, Messner HA, Kim DH, Seftel M, Gupta V. Outcomes of patients with therapy-related AML/myelodysplastic syndrome (t-AML/MDS) following hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50:1180-6. doi: 10.1038/bmt.2015.151. Epub 2015 Jun 29. https://doi.org/10.1038/bmt.2015.151
3. Kayser S, Döhner K, Krauter J, Köhne CH, Horst HA, Held G, von Lilienfeld-Toal M, Wilhelm S, Kündgen A, Götze K, Rummel M, Nachbaur D, Schlegelberger B, Göhring G, Späth D, Morlok C, Zucknick M, Ganser A, Döhner H, Schlenk RF; German-Austrian AMLSG. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011 Feb 17;117(7):2137-45. doi: 10.1182/blood-2010-08-301713. Epub 2010 Dec 2. https://doi.org/10.1182/blood-2010-08-301713
4. Smith SM, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, Vardiman JW, Rowley JD, Larson RA. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood. 2003 Jul 1;102(1):43-52. Epub 2003 Mar 6. https://doi.org/10.1182/blood-2002-11-3343 PMid:12623843
5. Ornstein MC, Mukherjee S, Mohan S, Elson P, Tiu RV, Saunthararajah Y, Kendeigh C, Advani A, Kalaycio M, Maciejewski JP, Sekeres MA. Predictive factors for latency period and a prognostic model for survival in patients with therapy-related acute myeloid leukemia. Am J Hematol. 2014 Feb;89(2):168-73. doi: 10.1002/ajh.23605. Epub 2013 Nov 21. https://doi.org/10.1002/ajh.23605
6. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R; SEARCH collaborators., Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schürmann P, Dörk T, Tollenaar RA, Jacobi CE, Devilee P, Klijn JG, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MW, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X; kConFab.; AOCS Management Group., Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BA. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007 Jun 28;447(7148):1087-93. https://doi.org/10.1038/nature05887 PMid:17529967 PMCid:PMC2714974
7. Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47. doi: 10.1093/annonc/mdq683. Epub 2011 Feb 2. https://doi.org/10.1093/annonc/mdq683
8. Bhatia S. Therapy-related myelodysplasia and acute myeloid leukemia. Semin Oncol. 2013 Dec;40(6):666-75. doi: 10.1053/j.seminoncol.2013.09.013. https://doi.org/10.1053/j.seminoncol.2013.09.013
9. Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. Best Pract Res Clin Haematol. 2013 Dec;26(4):309-17. doi: 10.1016/j.beha.2013.09.001. Review. https://doi.org/10.1016/j.beha.2013.09.001
10. Krishnan A, Bhatia S, Slovak ML, Arber DA, Niland JC, Nademanee A, Fung H, Bhatia R, Kashyap A, Molina A, O'Donnell MR, Parker PA, Sniecinski I, Snyder DS, Spielberger R, Stein A, Forman SJ. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood. 2000 Mar 1;95(5):1588-93. PMid:10688812
11. Govindarajan R, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B, Tricot G. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. Br J Haematol. 1996 Nov;95(2):349-53. https://doi.org/10.1046/j.1365-2141.1996.d01-1891.x PMid:8904891
12. Pedersen-Bjergaard J, Pedersen M, Myhre J, Geisler C. High risk of therapy-related leukemia after BEAM chemotherapy and autologous stem cell transplantation for previously treated lymphomas is mainly related to primary chemotherapy and not to the BEAM-transplantation procedure. Leukemia. 1997 Oct;11(10):1654-60. https://doi.org/10.1038/sj.leu.2400809 PMid:9324285
13. Gilliland DG, Gribben JG. Evaluation of the risk of therapy-related MDS/AML after autologous stem cell transplantation. Biol Blood Marrow Transplant. 2002;8(1):9-16. https://doi.org/10.1053/bbmt.2002.v8.pm11846355
14. Milligan DW, Ruiz De Elvira MC, Kolb HJ, Goldstone AH, Meloni G, Rohatiner AZ, Colombat P, Schmitz N. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. Br J Haematol. 1999 Sep;106(4):1020-6. https://doi.org/10.1046/j.1365-2141.1999.01627.x PMid:10520006
15. Wheeler C, Khurshid A, Ibrahim J, Elias A, Mauch P, Ault K, Antin J. Incidence of post-transplant myelodysplasia/acute leukemia in non-Hodgkin's lymphoma patients compared with Hodgkin's disease patients undergoing autologous transplantation following cyclophosphamide, carmustine, and etoposide (CBV). Leuk Lymphoma. 2001 Feb;40(5-6):499-509. https://doi.org/10.3109/10428190109097649 PMid:11426523
16. Bhatia S, Ramsay NK, Steinbuch M, Dusenbery KE, Shapiro RS, Weisdorf DJ, Robison LL, Miller JS, Neglia JP. Malignant neoplasms following bone marrow transplantation. Blood. 1996 May 1;87(9):3633-9. PMid:8611687
17. André M, Henry-Amar M, Blaise D, Colombat P, Fleury J, Milpied N, Cahn JY, Pico JL, Bastion Y, Kuentz M, Nedellec G, Attal M, Fermé C, Gisselbrecht C. Treatment-related deaths and second cancer risk after autologous stem-cell transplantation for Hodgkin's disease. Blood. 1998 Sep 15;92(6):1933-40. PMid:9731050
18. Larson RA, Wang Y, Banerjee M, Wiemels J, Hartford C, Le Beau MM, Smith MT. Prevalence of the inactivating 609C>T polymorphism in the NAD(P)H:quinone oxidoreductase (NQO1) gene in patients with primary and therapy-related myeloid leukemia. Blood. 1999 Jul 15;94(2):803-7. PMid:10397748
19. Ellis NA, Huo D, Yildiz O, Worrillow LJ, Banerjee M, Le Beau MM, Larson RA, Allan JM, Onel K. MDM2 SNP309 and TP53 Arg72Pro interact to alter therapy-related acute myeloid leukemia susceptibility. Blood. 2008 Aug 1;112(3):741-9. doi: 10.1182/blood-2007-11-126508. Epub 2008 Apr 21. https://doi.org/10.1182/blood-2007-11-126508
20. Link DC, Schuettpelz LG, Shen D, Wang J, Walter MJ, Kulkarni S, Payton JE, Ivanovich J, Goodfellow PJ, Le Beau M, Koboldt DC, Dooling DJ, Fulton RS, Bender RH, Fulton LL, Delehaunty KD, Fronick CC, Appelbaum EL, Schmidt H, Abbott R, O'Laughlin M, Chen K, McLellan MD, Varghese N, Nagarajan R, Heath S, Graubert TA, Ding L, Ley TJ, Zambetti GP, Wilson RK, Mardis ER. Identification of a novel TP53 cancer susceptibility mutation through whole-genome sequencing of a patient with therapy-related AML. JAMA. 2011 Apr 20;305(15):1568-76. doi: 10.1001/jama.2011.473. https://doi.org/10.1001/jama.2011.473
21. Schulz E, Valentin A, Ulz P, Beham-Schmid C, Lind K, Rupp V, Lackner H, Wölfler A, Zebisch A, Olipitz W, Geigl J, Berghold A, Speicher MR, Sill H. Germline mutations in the DNA damage response genes BRCA1, BRCA2, BARD1 and TP53 in patients with therapy related myeloid neoplasms. J Med Genet. 2012 Jul;49(7):422-8. doi: 10.1136/jmedgenet-2011-100674. Epub 2012 May 31. https://doi.org/10.1136/jmedgenet-2011-100674
22. Abou Zahr A, Kavi AM, Mukherjee S, Zeidan AM. Therapy-related myelodysplastic syndromes, or are they?. Blood Rev. 2016 Nov 24. pii: S0268-960X(16)30111-4. doi: 10.1016/j.blre.2016.11.002. [Epub ahead of print] Review. https://doi.org/10.1016/j.blre.2016.11.002
23. Leone G, Fianchi L, Pagano L, Voso MT. Incidence and susceptibility to therapy-related myeloid neoplasms. Chem Biol Interact.

2010;184:39 – 45. https://doi.org/10.1016/j.cbi.2009.12.013 PMid:20026017
24. Cristy M. Active bone marrow distribution as a function of age in humans. Phys Med Biol. 1981;26:389–400. https://doi.org/10.1088/0031-9155/26/3/003 PMid:7243876
25. Sun LM, Lin CL, Lin MC, Liang JA, Kao CH. Radiotherapy- and chemotherapy-induced myelodysplasia syndrome: a nationwide population-based nested case-control study. Medicine. 2015;94:e737.
26. Allan JM, Wild CP, Rollinson S, Willett EV, Moorman AV, Dovey GJ, Roddam PL, Roman E, Cartwright RA, Morgan GJ. Polymorphism in glutathione S-transferase P1 is associated with susceptibility to chemotherapy-induced leukemia. Proc Natl Acad Sci U S A. 2001 Sep 25;98(20):11592-7. Epub 2001 Sep 11.
27. Litzow MR, Tarima S, Pérez WS, Bolwell BJ, Cairo MS, Camitta BM, Cutler CS, de Lima M, Dipersio JF, Gale RP, Keating A, Lazarus HM, Luger S, Marks DI, Maziarz RT, McCarthy PL, Pasquini MC, Phillips GL, Rizzo JD, Sierra J, Tallman MS, Weisdorf DJ. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. Blood. 2010 Mar 4;115(9):1850-7. doi: 10.1182/blood-2009-10-249128. https://doi.org/10.1182/blood-2009-10-249128
28. Kröger N, Brand R, van Biezen A, Zander A, Dierlamm J, Niederwieser D, Devergie A, Ruutu T, Cornish J, Ljungman P, Gratwohl A, Cordonnier C, Beelen D, Deconinck E, Symeonidis A, de Witte T; Myelodysplastic Syndromes Subcommittee of The Chronic Leukaemia Working Party of European Group for Blood and Marrow Transplantation (EBMT). Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic stem cell transplantation. Haematologica. 2009 Apr;94(4):542-9. doi: 10.3324/haematol.2008.000927. https://doi.org/10.3324/haematol.2008.000927
29. Chang MC, Chen TY, Tang JL, Lan YJ, Chao TY, Chiu CF, Ho HT. Leukapheresis and cranial irradiation in patients with hyperleukocytic acute myeloid leukemia: no impact on early mortality and intracranial hemorrhage. Am J Hematol. 2007 Nov;82(11):976-80. https://doi.org/10.1002/ajh.20939 PMid:17636473
30. Larson RA, Le Beau MM. Prognosis and therapy when acute promyelocytic leukemia and other "good risk" acute myeloid leukemias occur as a therapy-related myeloid neoplasm. Mediterr J Hematol Infect Dis. 2011;3(1):e2011032. doi: 10.4084/MJHID.2011.032. Epub 2011 Jul 8. https://doi.org/10.4084/mjhid.2011.032
31. Klimek VM. Recent advances in the management of therapy-related myelodysplastic syndromes and acute myeloid leukemia. Curr Opin Hematol. 2013 Mar;20(2):137-43. doi: 10.1097/MOH.0b013e32835d82e6. Review. https://doi.org/10.1097/MOH.0b013e32835d82e6
32. Kantarjian HM, Estey EH, Keating MJ. Treatment of therapy-related leukemia and myelodysplastic syndrome. Hematol Oncol Clin North Am. 1993;7:81-107. PMid:7680643
33. Hake CR, Graubert TA, Fenske TS. Does autologous transplantation directly increase the risk of secondary leukemia in lymphoma patients? Bone Marrow Transplant. 2007 Jan;39(2):59-70. Epub 2006 Dec 4. ht.tps://doi.org/10.1038/sj.bmt.1705547 PMid:17143301
34. Takeyama K, Seto M, Uike N, Hamajima N, Ino T, Mikuni C, Kobayashi T, Maruta A, Muto Y, Maseki N, Sakamaki H, Saitoh H, Shimoyama M, Ueda R. Therapy-related leukemia and myelodysplastic syndrome: a large-scale Japanese study of clinical and cytogenetic features as well as prognostic factors. Int J Hematol. 2000 Feb;71(2):144-52. PMid:10745624
35. Klimek VM, Tray NJ. Therapy-related myeloid neoplasms: what's in a name?. Curr Opin Hematol. 2016 Mar;23(2):161-6. doi: 10.1097/MOH.0000000000000222. https://doi.org/10.1097/MOH.0000000000000222
36. Quesnel B, Kantarjian H, Bjergaard JP, Brault P, Estey E, Lai JL, Tilly H, Stoppa AM, Archimbaud E, Harousseau JL, Bauters F, Fenaux P. Therapy-related acute myeloid leukemia with t(8;21), inv(16), and t(8;16): a report on 25 cases and review of the literature. J Clin Oncol. 1993 Dec;11(12):2370-9. https://doi.org/10.1200/JCO.1993.11.12.2370 PMid:8246025
37. Fianchi L, Criscuolo M, Lunghi M, Gaidano G, Breccia M, Levis A, Finelli C, Santini V, Musto P, Oliva EN, Leoni P, Aloe Spiriti A, D'Alò F, Hohaus S, Pagano L, Leone G, Voso MT. Outcome of therapy-related myeloid neoplasms treated with azacitidine. J Hematol Oncol. 2012 Aug 1;5:44. doi: 10.1186/1756-8722-5-44. https://doi.org/10.1186/1756-8722-5-44
38. Chang C, Storer BE, Scott BL, Bryant EM, Shulman HM, Flowers ME, Sandmaier BM, Witherspoon RP, Nash RA, Sanders JE, Bedalov A, Hansen JA, Clurman BE, Storb R, Appelbaum FR, Deeg HJ. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders. Blood. 2007 Aug 15;110(4):1379-87. https://doi.org/10.1182/blood-2007-02-076307 PMid:17488876 PMCid:PMC1939908
39. Garcia-Manero G, Huang X, Cabrero M, Di Nardo CD, Pemmaraju N, Daver NG, Borthakur G, Wierda WG, Kadia T, Alvarado Y, Cortes JE. A bayesian phase II randomized trial of azacitidine versus Azacitidine Vorinostat in patients with newly diagnosed AML or high risk MDS with poor performance status, organ dysfunction, or other comorbidities. Blood. 2014;124:3277.
40. Bally C, Thépot S, Quesnel B, Vey N, Dreyfus F, Fadlallah J, Turlure P, de Botton S, Dartigeas C, de Renzis B, Itzykson R, Fenaux P, Adès L. Azacitidine in the treatment of therapy related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML): a report on 54 patients by the Groupe Francophone Des Myelodysplasies (GFM). Leuk Res. 2013;37:637-40. doi:10.1016/j.leukres.2013.02.014. https://doi.org/10.1016/j.leukres.2013.02.014
41. Duong VH, Lancet JE, Alrawi E, AlAli NH, Perkins J, Field T, Epling Burnette PK, Zhang L, List AF, Komrokji RS. Outcome of azacitidine treatment in patients with therapy-related myeloid neoplasms with assessment of prognostic risk stratification models. Leuk Res. 2013;37: 510-5. doi:10.1016/j.leukres.2012.12.012. https://doi.org/10.1016/j.leukres.2012.12.012
42. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, Di Persio J, Klimek V, Slack J, de Castro C, Ravandi F, Helmer R, Shen L, Nimer SD, Leavitt R, Raza A, Saba H. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006;106:1794-803. doi:10.1002/cncr.21792. https://doi.org/10.1002/cncr.21792
43. Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, Albitar M, Larsen JS, Arora S, Cullen MT, Kantarjian H. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009;27:3842-8. doi:10.1200/JCO.2008.19.6550. https://doi.org/10.1200/JCO.2008.19.6550
44. Klimek VM, Dolezal EK, Tees MT, Devlin SM, Stein K, Romero A, Nimer SD. Efficacy of hypomethylating agents in therapy-related myelodysplastic syndromes. Leuk Res. 2012;36:1093-7. doi:10.1016/j.leukres.2012.04.025. https://doi.org/10.1016/j.leukres.2012.04.025
45. Fianchi L, Pagano L, Piciocchi A, Candoni A, Gaidano G, Breccia M, Criscuolo M, Specchia G, Maria Pogliani E, Maurillo L, Aloe-Spiriti MA, Mecucci C, Niscola P, Rossetti E, Mansueto G, Rondoni M, Fozza C, Invernizzi R, Spadea A, Fenu S, Buda G, Gobbi M, Fabiani E, Sica S, Hohaus S, Leone G, Voso MT. Characteristics and outcome of therapy-related myeloid neoplasms: Report from the Italian network on secondary leukemias. Am J Hematol. 2015 May;90(5):E80-5. doi: 10.1002/ajh.23966. Epub 2015 Mar 3. https://doi.org/10.1002/ajh.23966
46. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005 Oct 15;106(8):2912-9. https://doi.org/10.1182/blood-2005-05-2004 PMid:15994282 PMCid:PMC1895304
47. ElSawy M, Storer BE, Pulsipher MA, Maziarz RT, Bhatia S, Maris MB, Syrjala KL, Martin PJ, Maloney DG, Sandmaier BM, Storb R, Sorror ML. Multi-centre validation of the prognostic value of the haematopoietic cell transplantation- specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. Br J Haematol. 2015;170:574–583. doi: 10.1111/bjh.13476. https://doi.org/10.1111/bjh.13476
48. Armand P, Deeg HJ, Kim HT, Lee H, Armistead P, de Lima M, Gupta V, Soiffer RJ. Multicentre validation study of a transplantation-specific cytogenetics grouping scheme for patients with myelodysplastic syndromes. Bone Marrow Transplant. 2010 May;45(5):877-85. doi: 10.1038/bmt.2009.253. Epub 2009 Sep 28. https://doi.org/10.1038/bmt.2009.253
49. Poiré X, Labopin M, Cornelissen JJ, Volin L, Richard Espiga C, Veelken JH, Milpied N, Cahn JY, Yacoub-Agha I, van Imhoff GW, Michallet M, Michaux L, Nagler A, Mohty M. Outcome of conditioning intensity in acute myeloid leukemia with monosomal karyotype in patients over 45 year-old: A study from the acute leukemia working party (ALWP) of the European group of blood and

marrow transplantation (EBMT). Am J Hematol. 2015 Aug;90(8):719-24. doi: 10.1002/ajh.24069. Erratum in: Am J Hematol. 2016 May;91(5):E301. https://doi.org/10.1002/ajh.24069
50. Koenecke C, Göhring G, de Wreede LC, van Biezen A, Scheid C, Volin L, Maertens J, Finke J, Schaap N, Robin M, Passweg J, Cornelissen J, Beelen D, Heuser M, de Witte T, Kröger N; MDS subcommittee of the Chronic Malignancies Working Party of the EBMT. Impact of the revised International Prognostic Scoring System, cytogenetics and monosomal karyotype on outcome after allogeneic stem cell transplantation for myelodysplastic syndromes and secondary acute myeloid leukemia evolving from myelodysplastic syndromes: a retrospective multicenter study of the European Society of Blood and Marrow Transplantation. Haematologica. 2015 Mar;100(3):400-8. doi: 10.3324/haematol.2014.116715. Epub 2014 Dec 31. https://doi.org/10.3324/haematol.2014.116715
51. Finke J, Schmoor C, Bertz H, Marks R, Wäsch R, Zeiser R, Hackanson B. Long-term follow-up of therapy-related myelodysplasia and AML patients treated with allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2016 Jun;51(6):771-7. doi: 10.1038/bmt.2015.338. Epub 2016 Jan 11. https://doi.org/10.1038/bmt.2015.338
52. Tang FF, Huang XJ, Zhang XH, Chen H, Chen YH, Han W, Chen Y, Wang FR, Wang Y, Wang JZ, Yan CH, Sun YQ, Mo XD, Liu KY, Xu LP. Allogeneic hematopoietic cell transplantation for adult patients with treatment-related acute myeloid leukemia during first remission: Comparable to de novo acute myeloid leukemia. Leuk Res. 2016 Aug;47:8-15. doi: 10.1016/j.leukres.2016.05.005. Epub 2016 May 12. https://doi.org/10.1016/j.leukres.2016.05.005
53. Liu N, Ning HM, Hu LD, Jiang M, Xu C, Hu JW, Wang J, Li YH, Li BT, Lou X, Yang F, Chen JL, Su YF, Li M, Wang HY, Ren J, Feng YQ, Zhang B, Wang DH, Chen H. Outcome of myeloablative allogeneic peripheral blood hematopoietic stem cell transplantation for refractory/relapsed AML patients in NR status. Leuk Res. 2015 Dec;39(12):1375-81. doi: 10.1016/j.leukres.2015.10.011. Epub 2015 Oct 19. https://doi.org/10.1016/j.leukres.2015.10.011
54. Spina F, Alessandrino PE, Milani R, Bonifazi F, Bernardi M, Luksch R, Fagioli F, Formica C, Farina L. Allogeneic stem cell transplantation in therapy-related acute myeloid leukemia and myelodysplastic syndromes: impact of patient characteristics and timing of transplant. Leuk Lymphoma. 2012 Jan;53(1):96–102. doi:10.3109/10428194.2011.603445. https://doi.org/10.3109/10428194.2011.603445
55. Zinke-Cerwenka W, Valentin A, Posch U, Beham-Schmid C, Groselj-Strele A, Linkesch W, Wölfler A, Sill H. Reduced-intensity allografting in patients with therapy-related myeloid neoplasms and active primary malignancies. Bone Marrow Transplant. 2011 Dec;46(12):1540-4. doi:10.1038/bmt.2011.165. Epub 2011 Aug 22. https://doi.org/10.1038/bmt.2011.165
56. Armand P, Kim HT, Mayer E, Cutler CS, Ho VT, Koreth J, Alyea EP, Antin JH, and Soiffer RJ. Outcome of allo-SCT for women with MDS or AML occurring after breast cancer therapy. Bone Marrow Transplant. 2010 November;45(11):1611–7. doi:10.1038/bmt.2010.20. https://doi.org/10.1038/bmt.2010.20
57. Nevill TJ, Hogge DE, Toze CL, Nantel SH, Power MM, Abou Mourad YR, Song KW, Lavoie JC, Forrest DL, Barnett MJ, Shepherd JD, Nitta JY, Wong S, Sutherland HJ, Smith CA. Predictors of outcome following myeloablative allo-SCT for therapy-related myelodysplastic syndrome and AML. Bone Marrow Transplant. 2008 Nov;42(10):659-66. doi: 10.1038/bmt.2008.226. Epub 2008 Aug 4. https://doi.org/10.1038/bmt.2008.226
58. Witherspoon RP, Deeg HJ, Storer B, Anasetti C, Storb R, Appelbaum FR. Hematopoietic stem-cell transplantation for treatment-related leukemia or myelodysplasia. J Clin Oncol. 2001 Apr 15;19(8):2134-41. https://doi.org/10.1200/JCO.2001.19.8.2134 PMid:11304765
59. de Witte T, Hermans J, Vossen J, Bacigalupo A, Meloni G, Jacobsen N, Ruutu T, Ljungman P, Gratwohl A, Runde V, Niederwieser D, van Biezen A, Devergie A, Cornelissen J, Jouet JP, Arnold R, Apperley J. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol. 2000 Sep;110(3):620-30. https://doi.org/10.1046/j.1365-2141.2000.02200.x PMid:10997974
60. Yakoub-Agha I, de La Salmonière P, Ribaud P, Sutton L, Wattel E, Kuentz M, Jouet JP, Marit G, Milpied N, Deconinck E, Gratecos N, Leporrier M, Chabbert I, Caillot D, Damaj G, Dauriac C, Dreyfus F, François S, Molina L, Tanguy ML, Chevret S, Gluckman E. Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: a long-term study of 70 patients-report of the French society of bone marrow transplantation. J Clin Oncol. 2000 Mar;18(5):963-71. https://doi.org/10.1200/JCO.2000.18.5.963 PMid:10694545
61. Anderson JE, Gooley TA, Schoch G, Anasetti C, Bensinger WI, Clift RA, Hansen JA, Sanders JE, Storb R, Appelbaum FR. Stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy. Blood. 1997 Apr 1;89(7):2578-85. Review. PMid:9116305
62. Ballen KK, Gilliland DG, Guinan EC, Hsieh CC, Parsons SK, Rimm IJ, Ferrara JL, Bierer BE, Weinstein HJ, Antin JH. Bone marrow transplantation for therapy-related myelodysplasia: comparison with primary myelodysplasia. Bone Marrow Transplant. 1997 Nov;20(9):737-43. https://doi.org/10.1038/sj.bmt.1700971 PMid:9384475
63. Scharz J, Tuchler H, Sole F, Mallo M, Lu-o E, Cervera J, Granada I, Hildebrandt B, Slovak ML, Ohyashiki K, Steidl C, Fonatsch C, Pfeilstöcker M, Nösslinger T, Valent P, Giagounidis A, Aul C, Lübbert M, Stauder R, Krieger O, Garcia-Manero G, Faderl S, Pierce S, Le Beau MM, Bennett JM, Greenberg P, Germing U, Haase D. New comprehensive cytogenetic scoring system for primarymyelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30(8):820–829. https://doi.org/10.1200/JCO.2011.35.6394 PMid:22331955 PMCid:PMC4874200
64. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017 Jan 26;129(4):424-447. doi: 10.1182/blood-2016-08-733196. Review. https://doi.org/10.1182/blood-2016-08-733196
65. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. 1974 Oct; 18(4):295-304. https://doi.org/10.1097/00007890-197410000-00001 PMid:4153799
66. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015 March; 21(3): 389–401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001 PMid:25529383 PMCid:PMC4329079
67. Fang M, Storer B, Estey E, Othus M, Zhang L, Sandmaier BM, Appelbaum FR. Outcome of patients with acute myeloid leukemia with monosomal karyotype who undergo hematopoietic cell transplantation. Blood. 2011 Aug 11;118(6):1490-4. doi: 10.1182/blood-2011-02-339721. Epub 2011 Jun 16. https://doi.org/10.1182/blood-2011-02-339721
68. Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group (SWOG) experience. Blood. 2010 Sep 30;116(13):2224-8. doi: 10.1182/blood-2010-02-270330. Epub 2010 Jun 18. https://doi.org/10.1182/blood-2010-02-270330
69. Sierra J, Pérez WS, Rozman C, Carreras E, Klein JP, Rizzo JD, Davies SM, Lazarus HM, Bredeson CN, Marks DI, Canals C, Boogaerts MA, Goldman J, Champlin RE, Keating A, Weisdorf DJ, de Witte TM, Horowitz MM. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. Blood. 2002 Sep 15;100(6):1997-2004. PMid:12200358
70. Gupta V, Tallman MS, He W, Logan BR, Copelan E, Gale RP, Khoury HJ, Klumpp T, Koreth J, Lazarus HM, Marks DI, Martino R, Rizzieri DA, Rowe JM, Sabloff M, Waller EK, DiPersio JF, Bunjes DW, Weisdorf DJ. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. Blood. 2010 Sep 16;116(11):1839-48. doi: 10.1182/blood-2010-04-278317. Epub 2010 Jun 10. https://doi.org/10.1182/blood-2010-04-278317

71. Cornelissen JJ, Breems D, van Putten WL, Gratwohl AA, Passweg JR, Pabst T, Maertens J, Beverloo HB, van Marwijk Kooy M, Wijermans PW, Biemond BJ, Vellenga E, Verdonck LF, Ossenkoppele GJ, Löwenberg B. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. J Clin Oncol. 2012 Jun 10;30(17):2140-6. doi: 10.1200/JCO.2011.39.6499. Epub 2012 May 7 https://doi.org/10.1200/JCO.2011.39.6499
72. Zahid MF, Parnes A, Savani BN, Litzow MR, Hashmi SK. Therapy-related myeloid neoplasms - what have we learned so far? World J Stem Cells. 2016 Aug 26;8(8):231-42. doi: 10.4252/wjsc.v8.i8.231. https://doi.org/10.4252/wjsc.v8.i8.231