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Allogeneic stem cell transplantation remains an effective therapeutic approach for patients with therapy-related acute myeloid leukemia

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Abstract

Introduction: Therapy-related acute myeloid leukemia (t-AML) remains a late consequence of exposure to cytotoxic chemo- and/or radiotherapy for prior malignant or non-malignant disorders. The prognosis of t-AML is extremely poor, and allogeneic stem cell transplantation (allo-SCT) seems to be the most effective therapeutic approach.We evaluated the efficacy and safety of allo-SCT for t-AML preceded by solid tumors and lymphomas.

Material and methods: Study patients were retrospectively identified using our institutional database. Nineteen patients (12 female, 7 male), median age 53 years, underwent allo-SCT for t-AML between 2006 and 2018.

Results: Prior malignancy was diagnosed at median age of 43.9 years. Among 19 patients included in the study, 6 (32%) had prior breast cancer, 2 (11%) were diagnosed with papillary thyroid cancer, and 2 (11%) were treated for lymphoma. A variety of other cancers were diagnosed in the remaining 9 patients. Median time from previous malignancy to development of t-AML was 4.9 years. Fourteen patients (74%) were transplanted in first complete remission (CR1), 4 patients (21%) were in CR2, and 1 patient received graft being in active disease. 10 patients (53%) are alive at last contact in CR. Patients died mainly from infectious complications. Median follow-up from prior malignancy and from transplantation was 9.5 years and 1.82 years, respectively. The 2-year overall survival (OS) was 57%. Median OS for survivors is 4.08 years. Grafts from unrelated donors and the presence of acute graft-versus-host disease affected OS.

Conclusions: Allo-SCT remains an effective therapy for t-AML.

Key words: therapy-related acute myeloid leukemia, solid tumor, lymphoma, allogeneic stem cell transplantation, survival

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Introduction

Therapy-related acute myeloid leukemia (t-AML) is a rare condition that accounts for 1–7% of all AML cases [1, 2]. It arises as a devastating consequence of prior exposure to radio- or chemotherapy for various solid cancers and/or hematologic malignant and non-malignant disorders. Direct genotoxic damage by prior radiation and chemotherapeutics, as well as the presence of a pre-existing clonal population that remained chemo-resistant, are postulated mechanisms responsible for the development of a new malignancy [3, 4]. It is estimated that adult patients after oncological treatment have an approximately quadrupled risk of developing AML compared to the general population [1].

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One may speculate that the incidence of t-AML is escalating along with the increasing cure rate of solid tumors and lymphomas [5].

According to the 2017 European LeukemiaNet (ELN) recommendations, t-AML should be categorized as a high-risk disease due to its often adverse cytogenetic profile [6]. It is estimated that approximately 50% of patients with t-AML present unfavorable cytogenetic abnormalities including deletions in chromosomes 5, 7 and 17, complex karyotype or translocations involving chromosome 11q23. All these are known to be associated with poor responses to therapy and shorter overall survival [7–9].

Other negative factors predisposing to the development of t-AML include: older age at diagnosis, frequent comorbidities (especially cardiac, renal and liver disfunction), type of prior malignancy, and exposure to specific cytotoxic drugs. Patients with t-AML are usually aged 40–66 [10]. The most common prior malignancy is breast cancer: up to 40% of cases in some published studies [7, 11, 12]. Among cytostatic agents, prior treatment with alkylating agents and topoisomerase II inhibitors (e.g. etoposide, anthracyclines) is considered to be the most leukemogenic [13]. All these factors may affect the disease outcome and make this patient population of great interest. Despite several novel agents that can be attempted in the treatment of high-risk AML (e.g. midostaurin, venetoclax), allogeneic stem cell transplantation (allo-SCT) still remains the only curative therapeutic approach.

Here, we present our retrospective data on 19 patients with t-AML who underwent allo-SCT.

Material and methods

Study patients were retrospectively identified through the use of our institutional database of medical records. Therapy-related AML was defined as AML arising at any time after exposure to chemo- and/or radiation therapy for previous solid tumor or lymphoma [9]. Oncological treatment before developing t-AML was considered intense if patients received chemotherapy as well as radiation and non-chemotherapy agents (e.g. monoclonal antibodies, hormonotherapy), moderate if they received chemotherapy and radiation, and mild if they were treated surgically with subsequent radiation [7].

The diagnosis of t-AML, genetic risk stratification and response criteria to therapy were based on the ELN recommendations [6].

Patients were treated according to the Polish Adult Leukemia Group (PALG) protocol with standard induction chemotherapy including DA ±C regimen (daunorubicin, cytarabine, cladribine). One patient received induction consisting of daunorubicin and etoposide. For those who achieved complete remission (CR), consolidative chemotherapy consisting of high-dose cytarabine was administered. For patients who did not respond to induction or who relapsed after achieving CR1, the following salvage regimens were given: CLAM (cladribine, cytarabine, mitoxantrone), DAC, DA and MEC (mitoxantrone, etoposide, cytarabine).

Response to treatment was assessed after each cycle of chemotherapy as well as before transplantation and at days +30, +60, +100, and then every 2–6 months after the procedure. The response was assessed using cyto-morphological evaluation of bone marrow and measurement of minimal residual disease (MRD) by flow cytometry. Additionally, donor chimerism was assessed by short tandem repeat polymerase chain reaction.

Acute and chronic graft-versus-host disease (GvHD) were graded according to the standard criteria [14, 15].

Not all data was available due to the retrospective nature of the study. All patients provided informed consent in accordance with the Declaration of Helsinki.

Statistics

Time to event was assessed from the day of transplantation. Nonparametric comparisons of group means were performed using the Mann-Whitney *U* test. Proportions were compared by Fisher exact test. The Kruskal-Wallis test was used to compare more than two independent groups of variables.

Overall survival (OS) was defined as time from day of transplant to death from any cause. The distribution for OS was estimated using Kaplan and Meier method and compared using the log-rank test. A $p < 0.1$ was considered significant. Proportional hazard models (Cox regression) were fitted to investigate effects of prognostic factors for OS. All computations were performed with StatSoft Poland analysis software (version 12.0).

Results

Patient characteristics

Nineteen patients (12 female, 7 male) with t-AML with a median age of 54 at diagnosis (range 18–70) underwent allo-SCT between 2006 and 2018.

Prior malignancy had been diagnosed at a median age of 43.9 (range 12.9–70.3). Of the 19 patients included in the study, 6 (32%) had a prior diagnosis of breast cancer, 2 (11%) were previously diagnosed with papillary thyroid cancer, and 2 (11%) were treated for lymphoma (1 patient with Hodgkin's disease and 1 with ocular B-cell lymphoma). Different solid cancers were diagnosed in the remaining 9 patients. All the patients were in complete remission (CR) after oncological treatment.

Median time from previous malignancy to development of t-AML was 4.9 years (range 0.93–17.56). Three patients had prior myelodysplastic syndrome. According to the ELN 2017, 6 patients were in the adverse risk category, 10 in the intermediate, and 3 in the favorable [6].

Induction regimen consisted of DAC (n =10), DA (n =8) or daunorubicin with etoposide (n =1). Sixteen patients (84%) achieved first CR, however 3 of them relapsed after consolidation and proceeded to salvage chemotherapy. Three patients remained resistant to induction treatment and required re-induction. In total, 14 patients (74%) had CR1 at transplant, 4 patients (21%) were in CR2, and 1 patient was transplanted in active disease. Minimal residual disease was negative in 9 patients (38%) before procedure and positive in 2 (11%). In 8 patients (43%), the results were missing or there was no immunophenotype to follow. Patient characteristics are set out in Table I.

Transplant data

Baseline characteristics of transplanted patients

Median recipient age was 53 (range 18–70). Median time from diagnosis of t-AML to transplantation was 7.1 months (range 4.9–20.5). Six patients were transplanted from an HLA-matched sibling and 13 patients received either 10/10 HLA-matched unrelated donor (n =11) or 9/10 HLA-mismatched grafts (n =2). Peripheral blood was a source of stem cell for 18 patients and one patient received stem cells from bone marrow. In total, myeloablative conditioning (MAC) was used in eight patients, whereas reduced intensity conditioning (RIC) was provided for 11 subjects. MAC consisted of busulfan and cyclophosphamide (BuCy) and fludarabine-based regimens were given as RIC. GvHD prophylaxis included cyclosporine (n =15), cyclosporine with mycophenolate mofetil (n =3), or mycophenolate mofetil alone (n =1).

Outcomes of transplanted patients

There were no primary graft failures (PGF). Median time to engraftment was 18 days (range 12–26).

Acute and chronic GvHD developed in seven (37%) and two (11%) patients, respectively. Acute GvHD grade III/IV occurred in one patient. One patient presented mild and one severe chronic GvHD [15].

Two patients developed life-threatening *Enterococci bacteremias* (*E. cloacae* and *faecium*) in early post-transplant period. One patient developed veno-occlusive disease (VOD). The other complications were mild and included mucositis (n =7), diarrhea (n =2) and fever (n =2).

None of the patients died within 30 days of transplantation, whereas one patient died before day +100 due to septic shock associated with *E. cloacae*. Post transplantation CR rate was achieved in 18 patients (95%). One patient relapsed 14 months after transplantation and finally died having failed to respond to salvage chemotherapy.

In total, nine (47%) patients have died. The main causes of death included pulmonary aspergillosis (n =2), recurrence of primary malignancy (n =2), ovarian and lung cancer fungal neuroinfection (n =1), AML relapse (n =1)

Table I. Patient characteristics

Variable	n =19
Gender (female/male)	12/7
Age at diagnosis of prior malignancy, years; median (range)	43.9 (12.9–70.3)
Prior malignancy, n [%]	
Breast cancer	6 (32)
Papillary thyroid cancer	2 (11)
Lymphoma	2 (11)
Colorectal cancer	1 (5)
Myxoid liposarcoma	1 (5)
Seminoma	1 (5)
Urothelial carcinoma	1 (5)
Pituitary microadenoma	1 (5)
Cervical cancer	1 (5)
Ovarian adenocarcinoma	1 (5)
Endometrial cancer	1 (5)
Non-small cell lung cancer	1 (5)
Treatment of primary malignancy	
Intense (hormonotherapy +chemotherapy +radiation)	4 (21)
Moderate (chemotherapy +radiation)	10 (53)
Mild (radiation)	5 (26)
Hemoglobin level [g/dL]; median (range)	9.3 (6.9–12.8)
Leukocyte count [$\times 10^9$/L]; median (range)	5.2 (1.14-45.8)
Platelet count [$\times 10^9$/L]; median (range)	49.5 (8–182)
Blasts in blood [%]; median (range)	9.5 (0–94)
Blasts in bone marrow (%); median (range)	57.5 (20–94)
Risk group according to ELN, n [%]	
Favorable	3 (15)
Intermediate	10 (53)
Adverse	6 (32)
Prior MDS, n [%]	3 (15)
Hematologic response at transplant, n [%]	
CR1	14 (74)
CR2	4 (21)
Active disease	1 (5)
MRD status before transplant, n [%]	
Positive	2 (11)
Negative	9 (46)
Missing	8 (43)
Time from t-AML to transplant, months; median (range)	7.1 (4.9–20.5)

ELN — European LeukemiaNet; MDS — myelodysplastic syndrome; CR1 — first complete remission; CR2 — second complete remission; MRD — minimal residual disease; t-AML — therapy-related acute myeloid leukemia

Table II. Transplant data

Variable	n =19
Age of recipient, median; years (range)	53 (19–71)
Age of donor, median; years (range)	34 (19–68)
Donor type, n [%]	
Related	6 (32)
10/10-HLA matched unrelated	11 (58)
9/10-HLA mismatched	2 (11)
Graft source	
Peripheral blood	18
Bone marrow	1
Myeloablative conditioning, n [%]	8 (42)
Conditioning regimen	
Busulfan/cyclophosphamide	8 (42)
Treosulfan/fludarabine	6 (32)
Busulfan/fludarabine	5 (26)
Number of transplanted CD34-positive cells [$\times 10^6$/kg]; median (range)	5.34 (2.7–9.67)
ANC >0.5 [$\times 10^9$/L]; median (range)	18 (12–26)
PLT >20 [$\times 10^9$/L]; median (range)	13 (7–25)
GvHD prophylaxis, n [%]	
CsA	15 (79)
CsA +MMF	3 (16)
MMF	1 (5)
Acute GvHD, n [%]	
Grades I–II	6 (32)
Grades III–IV	1 (5)
Chronic GvHD, n [%]	2 (11)
Hematologic relapse, n [%]	1 (5)
Death before day +100, n [%]	1 (5)
Alive at last contact, n [%]	10 (53)
Median follow-up from transplantation, years; median (range)	1.82 (0.25–13.3)
Median follow-up from t-AML diagnosis, years; median (range)	2.36 (0.8–13.9)
Median follow up from prior malignancy, years; median (range)	9.5 (2.56–20.8)

HLA — human leukocyte antigens; ANC — absolute neutrophil count; PLT — platelets; GvHD — graft-versus-host disease; CsA — cyclosporin A; MMF — mycophenolate mofetil; t-AML — therapy-related acute myeloid leukemia

and septic shock (n =1). Cause of death remains unknown in two patients.

Ten patients (53%) are alive at last contact and all remain in CR with full donor chimerism. Median follow-up from diagnosis of prior malignancy, t-AML and transplantation are 9.5 years, 2.36 years, and 1.82 years, respectively.

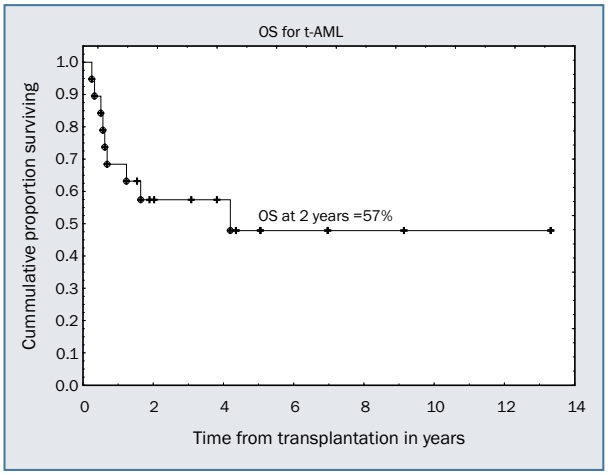

Figure 1. Overall survival (OS) for therapy-related acute myeloid leukemia (t-AML) after transplantation

Table III. Univariate and multivariate analysis of risk factors for overall survival

Univariate analysis (log rank)			Multivariate analysis (Cox regression)	
Risk factor	OS at 2 years	*p* value	HR (95%CI)	*p* value
Type of donor		0.06	3.85 (0.97–15.2)	0.05
Related =6	33%			
Unrelated =13	68%			
Acute GvHD		0.09	3.73 (0.9–15.3)	0.06
Yes, n =7	28%			
No, n =12	57%			

OS — overall survival; HR — hazard ratio; CI — confidence interval; GvHD — graft-versus-host disease

Transplant data is summarized in Table II. The 2-year OS was 57% (Figure 1). Median OS for survivors is 4.08 years (range 1.54–13.3).

Type of donor and presence of acute GvHD had statistically significant impacts on overall survival. Graft from unrelated donor was associated with a better outcome [hazard ratio (HR) 3.85, 95% confidence interval (CI): 0.97–15.2, p <0.1]. Presence of acute GvHD (aGvHD) negatively affected OS [HR 3.73, 95%CI: 0.9–15.3, p <0.1]. Details are shown in Table III.

Discussion

Therapy related-AML can refer to any leukemic process resulting from previous exposure to leukemogenic chemotherapeutic agents, and this term can be used interchangeably with secondary AML (sAML) [4, 16].

The pathophysiology of t-AML is very heterogenous. It has been proved that cytostatics have a direct mutagenic

impact on DNA, resulting in single- and double-strand breaks in repair processes and chromosomal breakage [17]. Among them, the role of alkylating agents and topoisomerase II inhibitors is well documented. Of note is that these drugs are widely used in the therapy of breast cancer, so it is unsurprising that this neoplasm was the commonest in our cohort, accounting for 32% of included patients [11, 17].

It has also been speculated that hematopoietic malignant clones can be already present at the time of cancer development, and reach their potential to transform into myeloid neoplasms after cytotoxic exposure [4].

It is still unclear whether the well-known poor outcome of t-AML is a result of previous malignancy, or can be explained by other factors such as unfavorable genetic profile or older age. Approximately 50% of patients with t-AML were found to have adverse karyotype abnormalities in a Danish study, but the long-term outcome remained independent of cytogenetics [2].

Interestingly, patients with core binding factor (CBF) factor t-AML were found to have a worse prognosis than those with *de novo* AML [18]. The European Bone Marrow Transplantation (EBMT) Group compared the post-transplant outcomes of patients with *de novo* AML to those transplanted for t-AML. In multivariate analysis, patients with t-AML had lower OS, lower leukemia-free survival (LFS), lower relapse-free survival (RFS), and higher non-relapse mortality (NRM) compared to newly diagnosed AML. There was no difference between the compared groups when *de novo* AML patients were transplanted in active disease, and the latter remained an independent risk factor for outcome after allo-SCT [19].

A large cohort study reported by the Center for International Bone Marrow Transplant Research (CIBMTR) analyzed 545 patients with t-AML who underwent allo-SCT in order to identify risk factors that negatively affected outcome [20]. The study patients received prior chemotherapy or radiation for solid tumors or hematological malignancies. Median age of the studied population was 40. Nearly half of the patients had a prior history of lymphoma and 16% had breast cancer. Only 30% of individuals had adverse cytogenetics. OS at 5 years was highly unsatisfactory at only 22% (*nota bene:* 57% at 2 years in our study). The following factors had an impact on OS: age >35 years, adverse cytogenetic profile, no remission at transplant, and graft from an unrelated donor. For patients without any of these factors, 5-year OS reached 50%. In contrast, OS was 4% in patients presenting all of the abovementioned factors. The incidence of aGvHD was comparable with our study: 39% versus 37%.

We have proved that OS is negatively affected by the occurrence of aGvHD and grafts from related donors. Disease status at transplantation and type of conditioning did not influence OS in our study. The impact of preparative regimen on the results of transplantation for t-AML with antecedent lymphoma was examined in a study by the EBMT Group. It was demonstrated that patients receiving RIC had a lower risk of NRM and improved LFS compared to those after MAC. OS at 2 years for the entire cohort was 37.4%. Moreover, patients transplanted in active disease, at older age, with adverse cytogenetics and prior autologous stem cell transplantation (auto-SCT) displayed worse outcomes [21]. If we consider the results of allo-SCT for patients with t-AML preceded by hematological neoplasms and solid tumors, OS and LFS at year 2 were 44.5% and 38.8% respectively. Patients receiving MAC regimen had decreased relapse rate, but higher NRM. No differences in terms of OS, LFS and RFS were demonstrated [22].

Another study reported on 65 patients with t-AML/MDS following allo-SCT [7]. Median follow-up for survivors was 72 months. OS at 2 years was noticeably lower than in our study (34% vs. 57%), however the study population was slightly different. AML relapse accounted for 41% of deaths, and this finding was in contrast with our observations, where there was only one fatal relapse among nine deceased patients. On the contrary, our patients died mainly from infectious complications. Unexpectedly, we noticed significantly better OS after transplantation from an unrelated donor. This latter finding is difficult to explain, although the study group was small. The EBMT Group demonstrated lower risk of relapse but higher NRM in patients transplanted from unrelated donors [23].

We demonstrated that the occurrence of acute GVHD negatively influenced survival (28% vs. 57% at 2 years), and this finding is with line with data presented by the EBMT Group [23].

The leukemogenic role of conditioning regimens used before auto-SCT for lymphoma has also been highlighted by others [24]: it was demonstrated that therapy with alkylating agents and total-body irradiation (TBI) in doses higher than 12 Grey (Gy) increases the risk of t-AML development. Cyclophosphamide-based regimens are proven to be less leukemogenic.

Regarding the lymphoma cases from our study, the outcome was as follows: one patient was primarily diagnosed with ocular B-cell lymphoma at the age of 12. He was successfully treated with a combination of chemo- and radiotherapy, and t-AML occurred six years later. He is alive 13 years after allo-SCT, being in CR. A second patient developed t-AML 17 years after therapy for Hodgkin's lymphoma. Due to his prior malignancy he received three lines of chemotherapy (ABVD — adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP — bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; and MOPP — mechlorethamine, vincristine, procarbazine, and prednisone) with subsequent radiotherapy. He relapsed within 14 months after allo-SCT and died of resistant leukemia.

An interesting dilemma is whether a patient with t-AML should be proceeded to auto-SCT. Surprisingly, 3-year OS was comparable between patients who received auto- and allo-SCT. Transplant-related mortality was only 12%, although the relapse incidence was 83% for patients not transplanted in CR. It has been suggested that only young patients transplanted in complete remission may benefit from this procedure [25].

However, it should be remembered that according to the current EBMT recommendations, auto-SCT cannot be considered as a standard of care in this indication, even in children [26]. This can be performed only within clinical trials for individual patients after careful assessment of the potential risks and benefits.

Conclusions

Despite the low number of included patients and the relatively short follow-up, our study has confirmed an unexpectedly high efficacy of allo-SCT for poor-prognosis patients with t-AML.

Authors' contributions

AS, GH — planned a study, wrote a manuscript, analyzed data; KW, AA, KM, AK, DK, AWK — collected data, ctitical review.

Conflict of interest

None

Financial support

None

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for Manuscripts submitted to Biomedical Journals.

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