Article

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Myeloid Neoplasms Post Cytotoxic Therapy in Chinese Patients: A Comprehensive Analysis

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Background: Therapy-related myeloid neoplasms (MN-pCT) are serious long-term complications affecting cancer survivors. This study aimed to determine the incidence, characterize the clinical and genetic features, and assess outcomes along with prognostic factors in a cohort of Chinese patients with MN-pCT.

Methods: We conducted a retrospective analysis of 460 patients diagnosed with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) at our institution between 2008 and 2022. Among them, 31 patients met the diagnostic criteria for MN-pCT. The clinical parameters, prior treatment history, cytogenetic profiles, and mutational status were reviewed. Overall survival (OS) and disease-free survival (DFS) were calculated, and prognostic factors were identified using univariate and multivariate analyses.

Results: The incidence of MN-pCT was 6.7%, with significantly poorer median OS than primary myeloid neoplasms (15 months for AML-pCT vs. 30 months for primary AML; 7 months for MDS-pCT vs. 47.5 months for primary MDS). Breast cancer was the most common prior malignancy. Univariate analysis identified advanced age ($p < 0.018$), elevated lactate dehydrogenase (LDH) levels ($p < 0.006$), higher bone marrow blast percentage ($p < 0.042$), presence of TP53 mutations ($p < 0.018$), and complex karyotype($p < 0.015$) as significant adverse prognostic factors. A novel prognostic scoring model incorporating age, TP53 mutation status, and complex karyotype effectively stratified patients into low- and high-risk groups with markedly different OS ($p < 0.0305$) and DFS ($p < 0.0453$) outcomes. Additionally, allogeneic stem cell transplantation (allo-SCT) was associated with improved survival, including in patients with high-risk features such as TP53 mutations.

Conclusions: MN-pCT is associated with poor prognosis and a high frequency of adverse genetic abnormalities. The newly developed prognostic scoring system offers a practical tool for risk stratification. Allo-SCT represents a critical and potentially curative treatment option, highlighting the need for innovative approaches to expand transplant accessibility for more affected patients.

Keywords: myeloid neoplasms post cytotoxic therapy; diagnosis; prognosis; treatment

Introduction

Advances in diagnostic and therapeutic technologies have improved survival rates for cancer patients, yet this progress has also been associated with an elevated risk of developing myeloid neoplasms following cytotoxic therapy (MN-pCT) [1,2]. According to the 2022 World Health Organization (WHO) classification, MN-pCT encompasses myeloid malignancies that emerge after exposure to cytotoxic agents. Recent evidence indicates a growing incidence of MN-pCT, which now constitutes approximately 15–20% of all cases of acute myeloid leukemia (AML) and myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN) [3,4]. Patients with MN-pCT generally experience poorer outcomes compared to those with de novo AML or MDS/MPN [5]. Conventional treatments for MN-pCT are associated with uniformly dismal prognosis, with median survival reported at 8.6 months for therapy-related MDS and 6.9 months for therapy-related AML [6]. Given these challenges, current research efforts are increasingly directed at elucidating the underlying mechanisms of MN-pCT and developing strategies for risk prediction and mitigation. This study aims to determine the incidence of therapy-related myeloid neoplasms (t-MN) at a tertiary hematology-oncology referral center, identify their clinical characteristics and prognostic factors, and evaluate survival outcomes under currently available treatment modalities.

Patients and Methods

Study Design and Patient Selection

This retrospective, single-center cohort study involved the analysis of existing, de-identified clinical data

without prospective interventions. We screened the electronic medical records database of Tianjin Cancer Hospital Airport Hospital to identify all adult patients (≥18 years old) diagnosed with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) between January 2008 and December 2022 (n = 460). From this cohort, patients who developed MDS, AML, or chronic myelomonocytic leukemia (CMML) following cytotoxic therapy and/or radiotherapy for a prior malignancy were identified as having myeloid neoplasms post cytotoxic therapy (MN-pCT). The diagnosis of MN-pCT was based on the 2022 World Health Organization (WHO) classification criteria. Patients with incomplete clinical data or unclear prior therapy histories were excluded. Finally, 31 patients met the criteria and comprised the study cohort. This study was approved by the Medical Ethics Committee of Tianjin Cancer Hospital Airport Hospital (IREC number: LWK-2024-0009) and conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

For the identified MN-pCT patients, the following data were extracted from medical records: demographics, details of the primary malignancy (type, treatment modalities, agents used), clinical and laboratory parameters at MN-pCT diagnosis (complete blood count, lactate dehydrogenase (LDH) level, bone marrow blast percentage), cytogenetic reports, treatment details for MN-pCT, and survival outcomes. The latency period was calculated as the time (in months) from the initiation of therapy for the primary malignancy to the diagnosis of MN-pCT.

Molecular Genetic Analysis

Genetic mutation profiling was performed using next-generation sequencing (NGS) on DNA extracted from diagnostic bone marrow aspirates or peripheral blood samples. Targeted sequencing was conducted using a customized panel (Myeloid Neoplasms Panel, Burning Rock Biotech, Guangzhou, China) encompassing full exons or critical hotspots of 68 genes recurrently mutated in myeloid malignancies. These genes included *TP53*, *FLT3*, *NPM1*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *ASXL1*, *RUNX1*, *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *EZH2*, *CBL*, *NRAS*, *KRAS*, *PTPN11*, *KIT*, *JAK2*, *MPL*, *CALR*, among others. Sequencing was performed on an Illumina NextSeq 550 platform (Illumina, San Diego, CA, USA). The mean coverage depth exceeded 500×, with more than 95% of the target regions achieving at least 100×. Sequence data were analyzed using a standard bioinformatic pipeline: Burrows-Wheeler Aligner (BWA, version 0.7.17, developed by Heng Li and maintained by the Genome Institute, Broad Institute, Cambridge, MA, USA) for alignment, Genome Analysis Toolkit (GATK, version 4.5.0.0, developed and maintained by the Broad Institute, Cambridge, MA, USA) for variant calling, and ANNOVAR (version 2023-03-13, developed by Dr. Kai Wang at the University of Pennsylvania, Philadelphia, PA, USA) for annotation. Single nucleotide variants (SNVs) and insertions/deletions (Indels) with a variant allele frequency (VAF) ≥3% were retained for analysis. Variants were interpreted with reference to public databases (COSMIC, dbSNP, ClinVar).

Treatment and Response Assessment

Treatment for MN-pCT was determined at the discretion of the treating physician and included intensive chemotherapy, hypomethylating agents (e.g., azacitidine), venetoclax-based combination regimens, allogeneic stem cell transplantation (allo-SCT), or supportive care. Response to treatment was assessed according to the 2017 European LeukemiaNet (ELN) recommendations for AML and the International Working Group (IWG) 2006 criteria for MDS. Overall survival (OS) was defined as the interval from the date of MN-pCT diagnosis to death from any cause or last follow-up. Disease-free survival (DFS) was defined as the time from achieving complete remission (CR) to disease relapse or death, whichever occurred first.

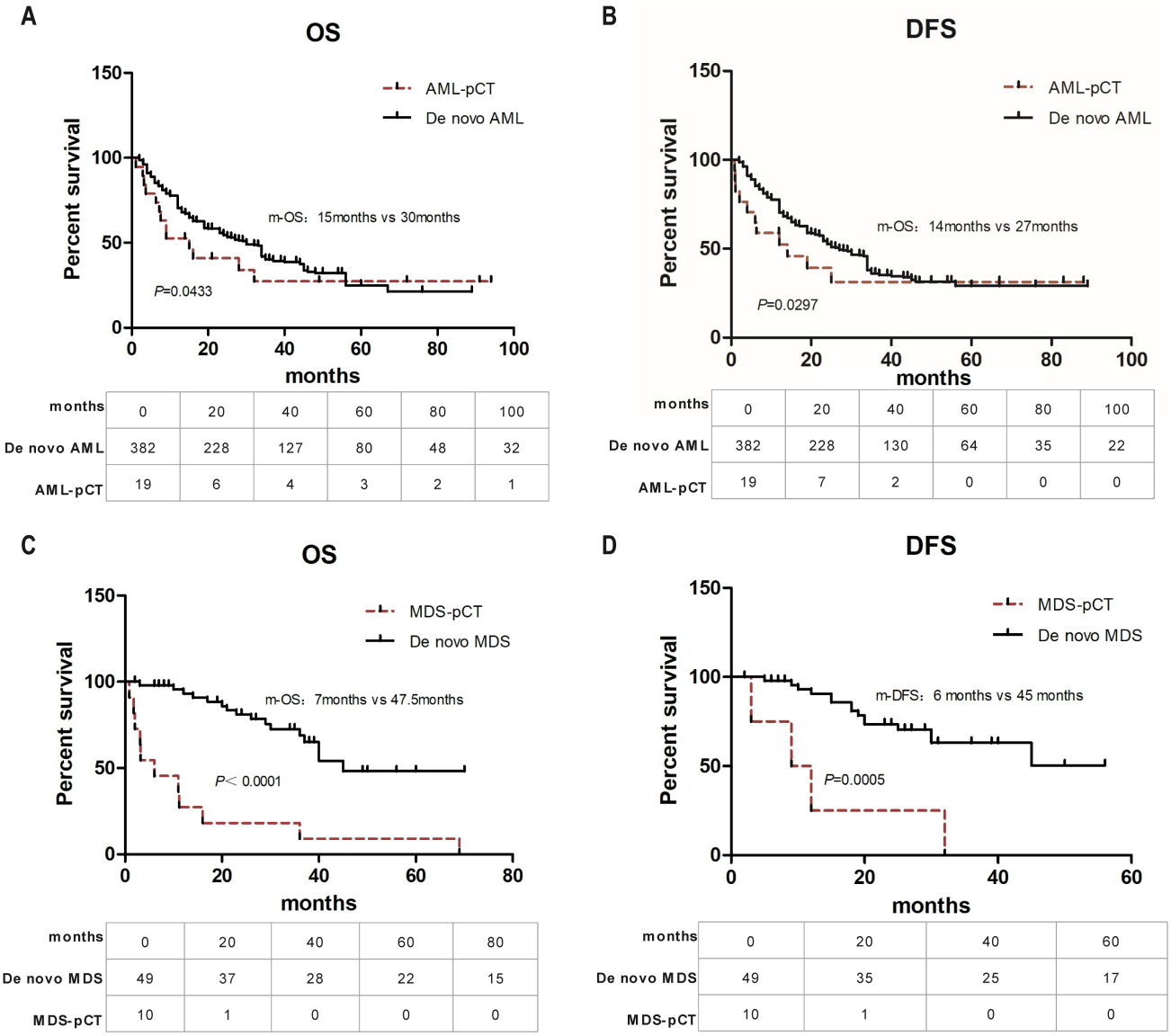
Statistical Analysis

All analyses were performed using SPSS (version 21.0, IBM Inc., Armonk, NY, USA) and GraphPad Prism (version 5.0, GraphPad Software, LLC, Boston, MA, USA). Baseline characteristics were summarized using descriptive statistics. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test. Prognostic factors for OS were analyzed using univariate and multivariate Cox proportional hazards regression models. Given the limited number of events, only variables with a p-value < 0.05 in the univariate analysis were considered for inclusion in the multivariate Cox model to avoid overfitting. The correlation between latency and survival time was analyzed using Spearman's rank correlation. A two-sided p-value < 0.05 was considered statistically significant.

Results

Incidence and Survival of MN-pCT

During the study period, 31 out of 460 patients diagnosed with MDS or AML at our institution were identified as having MN-pCT, accounting for 6.7% of the total cohort. These cases comprised 10 MDS-pCT, 19 AML-pCT, and 2 CMML-pCT patients. For the purpose of comparing survival outcomes between therapy-related and primary disease subgroups, the total cohort was further stratified by primary diagnosis: 401 patients had AML (including 19 AML-pCT and 382 primary AML), and 59 patients had MDS (including 10 MDS-pCT and 49 primary MDS). Within specific primary disease subgroups, the incidence was 16.9% (10/59) for MDS-pCT (among all MDS patients) and 4.7% (19/401) for AML-pCT (among all AML patients). Sur-



months	0	20	40	60	80	100
De novo AML	382	228	127	80	48	32
AML-pCT	19	6	4	3	2	1

months	0	20	40	60	80	100
De novo AML	382	228	130	64	35	22
AML-pCT	19	7	2	0	0	0

months	0	20	40	60	80
De novo MDS	49	37	28	22	15
MDS-pCT	10	1	0	0	0

months	0	20	40	60
De novo MDS	49	35	25	17
MDS-pCT	10	1	0	0

Fig. 1. OS (A) and DFS (B) of AML-pCT patients and De novo AML, OS (C) and DFS (D) of MDS-pCT patients and De novo MDS. Number at risk for each group is shown below the corresponding survival curve. OS, overall survival; DFS, disease-free survival; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

vival outcomes were compared between patients with MN-pCT and those with primary myeloid neoplasms, as summarized in Fig. 1. The analysis revealed significantly poorer prognosis in MN-pCT patients across both disease types. Specifically, the median OS for AML-pCT was 15 months compared to 30 months for primary AML (p = 0.0433). Likewise, patients with MDS-pCT had a median OS of 7 months versus 47.5 months for those with primary MDS ($p < 0.0001$). These findings consistently underscore the adverse impact of prior cytotoxic therapy on survival outcomes in myeloid neoplasms.

Clinical Characteristics of Patients With MN-pCT

The main clinical characteristics of the 31 enrolled patients are summarized in Table 1. A total of 31 patients with MDS-pCT (n = 10), AML-pCT (n = 19), or CMML-pCT (n = 2) were included in our study. Median age at diagnosis was 61 years (range: 32–88 years), with a female predominance (64.5%). Among the patients, 20 patients (64.5%) were under 65 years old. The distribution across age decades was as follows: 31–40 years (n = 2), 41–50 (n = 4), 51–60 (n = 9), 61–70 (n = 10), 71–80 (n = 4), and >80 (n = 2). Regarding morphological subtypes, AML-M5 was the most common subtype among AML-pCT cases (n = 8), while MDS with excess blasts (MDS-EB) accounted for the majority of MDS-pCT cases (n = 4). According to the French-American-British (FAB) classification, MDS-pCT cases included 3 patients with refractory anemia (MDS-RA) and 4 with excess blasts (MDS-EB). Among AML-pCT cases, the subtypes were as follows: AML-M2 (n = 2),

Table 1. Baseline characteristics of the study cohort (n = 31).

Characteristic	Median (range)/Count (%)
Sex	
Male	11 (35.5%)
Female	20 (64.5%)
Age at diagnosis (years)	61 (32–88)
WHO subtypes	
MDS	10 (32.3%)
AML	19 (61.3%)
CMML	2 (6.4%)
CBC	
Hemoglobin (g/dL)	10.1 (2.9–31.7)
Platelet counts (/L)	65 (1–620)
ANC (/L)	1.06 (0.01–59.2)
Bone marrow blasts (%)	12 (0–90)
Central nervous system involvement	2 (6.4%)
LDH (U/L)	360 (240–980)
Treatment	
Hypomethylating agents	14 (45.2%)
Intensive chemotherapy	12 (38.7%)
Allogeneic stem cell transplant	3 (9.7%)
Supportive treatment	5 (16.1%)
Outcome	
CR1	3 (9.7%)
CR2	4 (12.9%)
Death	24 (77.4%)
Follow up (months)	56 (36–94)

CBC, complete blood count; CR1, first complete remission; CR2, second complete remission; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count. Duration of follow-up was calculated from the date of diagnosis.

AML-M3 (n = 2), AML-M4 (n = 1), AML-M5 (n = 8), and AML-M6 (n = 2), as detailed in Table 2.

Based on the classification of prior malignancies, 28 patients (90.3%) had a history of solid tumors, while 3 patients (9.7%) had previous hematologic malignancies. Among the primary tumors, breast cancer (9 cases), lung cancer (3 cases), and gastrointestinal cancer (3 cases) were the most common. In terms of prior anticancer therapy, 25 patients (80.6%) received chemotherapy alone, 2 patients (6.5%) received radiotherapy alone, and 4 patients (12.9%) received combined chemotherapy and radiotherapy (Table 2). The chemotherapy regimens used for the primary tumors included EC (epirubicin+cyclophosphamide), TH (docetaxel+trastuzumab), TEC (docetaxel+epirubicin+cyclophosphamide), AC (doxorubicin+cyclophosphamide), TAC (docetaxel+pirarubicin+cyclophosphamide), R-CHOP (rituximab+cyclophosphamide+doxorubicin+vincristine+prednisone), EP (etoposide+cisplatin), BI (bleomycin+ifosfamide+cisplatin), and erlotinib. A comprehensive listing of the specific treatment modalities (surgery, chemotherapy, radiotherapy), agents, and regimens for each patient is provided in Table 2. Alkylating agents were administered to 17 patients, anthracyclines to 11 patients, and topoisomerase II inhibitors to 2 patients. All radiotherapy courses were delivered to local lesions with fractional doses of 2 Gy/time and 2.5 Gy/time, for total treatment courses of 20, 25, or 30 fractions, respectively.

Among the 19 patients with AML-pCT, treatment information was available for 18 patients, while 1 patient discontinued pharmacologic therapy. Of these 18 patients, 3 patients underwent allo-SCT, and 15 received standard chemotherapy. The chemotherapy regimens were as follows: IA (idarubicin, cytarabine; n = 5), DA (daunorubicin, cytarabine; n = 3), CAG (clarithromycin, cytarabine, granulocyte colony-stimulating factor; n = 3), azacitidine (n = 1), azacitidine + CAG (n = 1), DA + ATRA (n = 1), and ATRA + arsenic trioxide (n = 1). The complete remission rate after induction therapy was 75% among all AML-pCT patients. Overall, patients with AML-pCT had poor clinical outcomes, with a median overall survival (OS) of 15 months (Fig. 1A), and the major cause of death was secondary malignancy. However, AML-pCT patients who underwent allo-SCT had significantly improved outcomes, with a median OS that was not reached.

Among the 10 patients with MDS-pCT, treatment modalities were as follows: 3 patients discontinued active treatment shortly after diagnosis (Patients 4, 6, and 20), 1 received only symptomatic supportive care (Amifostine+EPO+Testosterone; Patient 26), 4 were treated with azacitidine (Patients 3, 5, 7, and 15), and 2 received a CAG regimen (Patients 22 and 27). No patient underwent allo-SCT (Table 3).

Cytogenetic Alterations of Patients With MN-pCT

Among the 19 AML-pCT patients, abnormal karyotypes were detected in 8 patients, predominantly complex karyotypes; normal karyotypes were observed in 7 patients, and karyotype analysis was not performed in 4 patients. When stratified by karyotype status, significant survival differences were observed. The median OS was 7.6 months in the abnormal karyotype group compared to not reached in the normal karyotype group (p = 0.0247), and median DFS was 6.55 months versus not reached (p = 0.0240), as illustrated in Fig. 2. Among the 10 patients with MDS-pCT, 3 exhibited abnormal karyotypes, most of which were complex karyotypes, and 2 had normal karyotypes (Table 3).

Gene mutations were detected in 11 patients, including 7 patients with *TP53* mutations and 2 patients with FLT3 mutations. Other detected mutations included *KIT*, *KRAS*, *TET2*, and *ASXL2*. The 31 patients were divided into two groups according to their mutation state. The median OS was 9 months versus 14 months (p = 0.0882), and the median DFS was 13 months versus undefined (p = 0.360), as illustrated in Fig. 2.

Table 2. Type and treatment of primary tumor.

Patient number	Gender	Age (year)	FAB classification	Protopathy	Treatment for protopathy	Latency (months)
1	Male	84	AML	Carcinoma of urinary bladder	Intravesical therapy with Anthracyclines	9.0
2	Female	51	AML-M3	Endometrial cancer	Surgery+Chemotherapy (EP)	24.0
3	Female	78	MDS-EB2	Cervical cancer	Surgery+Chemotherapy (Platinum-based)	3.0
4	Female	74	MDS	Diffuse large B-cell lymphoma	CHOP+Radiotherapy	50.0
5	Male	66	MDS-EB2	Prostate cancer	Surgery+Chemotherapy (Docetaxel-based)	5.0
6	Male	72	MDS	Laryngocarcinoma	Surgery+Chemotherapy (Platinum-based)	69.0
7	Male	88	MDS-EB1	Carcinoma of urinary bladder	Intravesical therapy with Anthracyclines	36.0
8	Female	54	AML-M5	Breast cancer	Surgery+Chemotherapy (EC)	7.0
9	Female	45	AML-M2b	Breast cancer	Surgery+Chemotherapy (AC)	47.0
10	Female	56	AML-M3	Carcinoma of the rectum	Surgery+Chemotherapy (FOLFOX)	16.0
11	Female	69	AML-M5	Endometrial cancer	Surgery+Chemotherapy (Carboplatin + Paclitaxel)	33.0
12	Female	65	AML	Breast cancer	Surgery+Chemotherapy (TAC)	144.0
13	Female	50	AML-M5	Breast cancer	Chemotherapy (EC)	69.0
14	Female	65	AML-M4EO	Colon cancer	Surgery+Chemotherapy (FOLFOX)	23.0
15	Female	32	MDS	Cutaneous squamous cell carcinoma	Chemotherapy (Platinum-based)	10.0
16	Female	50	AML	Ovarian cancer	Chemotherapy (Carboplatin + Paclitaxel)	17.0
17	Female	33	AML	Breast cancer	Chemotherapy (AC)	13.0
18	Female	66	CMML	Thyroid cancer	Chemotherapy (AC)	121.0
19	Female	51	AML-M5	Breast cancer	Surgery+chemotherapy (EC)+endocrine therapy+Radiotherapy	29.0
20	Female	49	MDS-EB1	Breast cancer	Surgery+chemotherapy (AC)+endocrine therapy	94.0
21	Female	57	AML-M5b	Diffuse large B-cell lymphoma	R-CHOP	26.0
22	Male	65	MDS-RA	Esophagus cancer	DDP+Radiotherapy	22.0
23	Male	61	AML-M5	Squamous carcinoma	Radiotherapy	10.0
24	Female	56	AML-M5	Breast cancer	Paclitaxel+Anthracyclines	42.0
25	Female	64	CMML	Breast cancer	CTX+MTX+5-FU	152.0
26	Female	58	MDS-RA	Lung cancer	CBP+VP-16+VM-26	48.0
27	Male	68	MDS-RA	Colon cancer	LOHP+CF+FT-207	14.0
28	Male	66	AML-M6	Lung cancer	Paclitaxel	162.0
29	Male	55	AML-M2b	Lung cancer	CBP+VM-26+CPT-11+ DDP+Radiotherapy	34.0
30	Male	52	AML-M5	Follicular lymphoma	CTX+VDS+Anthracyclines+5-FU+MIT	12.0
31	Male	78	AML-M6	Cutaneous squamous cell carcinoma	Radiotherapy	84.0

Latency is from the diagnosis of the original disease to the diagnosis of t-AML/t-MDS. CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, rituximab plus CHOP; EC, epirubicin, cyclophosphamide; AC, doxorubicin, cyclophosphamide; TAC, docetaxel, pirarubicin, cyclophosphamide; EP, etoposide, cisplatin; ifosfamide, cisplatin; DDP, cisplatin; LOHP, oxaliplatin; CF, calcium folinate; FT-207, tegafur; CBP, carboplatin; VP-16, etoposide; VM-26, teniposide; CPT-11, irinotecan; CTX, cyclophosphamide; MTX, methotrexate; 5-FU, 5-fluorouracil; VDS, vindesine; MIT, mitoxantrone; FOLFOX, 5-FU, leucovorin, oxaliplatin.

Table 3. Therapies and prognostics of the 31 patients.

Patient number	AML/MDS	Cytogenetic stratification	Chromosome	Cytogenetics (gene mutation)	Inductive treatment	Transplant	Current state
1	AML	moderate	46,XY[20]	Not done	DA	-	Died
2	AML-M3	favourable	t(15;17)	Not done	DA+ATRA	-	Survival
3	MDS-EB2	unfavourable	46,XX[20]	*TP53*, *SET*, *KMT2D*	Azacitidine	-	Died
4	MDS	high-risk	46,XX[20]	*TP53*, *TBOR*	Treatment abandoning	-	Died
5	MDS-EB2	low-risk	45,XY,–15[1]	Not done	Azacitidine	-	Died
6	MDS	-	Not done	Not done	Treatment abandoning	-	Died
7	MDS-EB1	high-risk	Not done	*FLT3-ITD*	Azacitidine	-	Died
8	AML-M5	moderate	46,XX[20]	Not done	IA	-	Died
9	AML-M2b	unfavourable	der(7),t(6;7)	*TP53*, *RUNX1*	DA	Allo-SCT	Survival
10	AML-M3	-	Not done	Not done	ATRA+arsenic trioxide	-	Survival
11	AML-M5	-	Not done	Not done	Azacitidine	-	Died
12	AML	unfavourable	der(3)der5, der11; 17, add21p+mar	*TP53*, *TET2*, *NF-1*, *PPMID*, *SF3B1*	Azacitidine+CAG	-	Died
13	AML-M5	moderate	46,XX[20]	Not done	DA	-	Died
14	AML-M4EO	moderate	46,XX inv16	*KMT2C*, *KRAS*, *FLT3ITD*, *KIT*	IA	-	Survival
15	MDS	-	Not done	Not done	Azacitidine	-	Died
16	AML	-	Not done	Not done	IA	-	Died
17	AML	unfavourable	t(8;21),t(9;10),del(11q)	*ASXL2*, *KIT*, *BRCA2*, *SMC-3*, *POT1*, *CSMD1*, *CHD8*, *SPEN*, *TP53*	DA	Allo-SCT	Survival
18	CMML	high-risk	46,XX[20]	*SRSF2*, *ABCB1*, *JAK3*, *SETD2*, *PTPN11*, *FLT3-ITD*, *ASXL1*	Azacitidine	-	Survival
19	AML-M5	unfavourable	46,XX,der(6)t(6;9)(p23;q34),der(9)[20]	*TP53*	Venetoclax+Azacitidine	Allo-SCT	Survival
20	MDS-EB1	high-risk	der(x;17),–5,–12,add(12p),+14,+14	*TP53*	Treatment abandoning	-	Died
21	AML-M5b	unfavourable	46,XX[20]	*TP53*	DA	-	Died
22	MDS-RA	-	Not done	Not done	CAG	-	Died
23	AML-M5	moderate	–21	Not done	CAG	-	Died
24	AML-M5	moderate	46,XX[20]	Not done	IA	-	Died
25	CMML	high-risk	46,XX[20]	Not done	CAG	-	Died
26	MDS-RA	-	Not done	Not done	Amifostine+EPO+Testosterone	-	Died
27	MDS-RA	low-risk	+8	Not done	CAG	-	Died
28	AML-M6	moderate	46,XY[20]	Not done	CAG	-	Died
29	AML-M2b	unfavourable	t(8;21),-Y	*TP53*	IA	-	Died
30	AML-M5	moderate	46,XY[20]	Not done	CAG	-	Died
31	AML-M6	-	Not done	Not done	Treatment abandoning	-	Died

Allo-SCT, allogeneic stem cell transplantation; DA, daunorubicin+cytarabine; IA, idarubicin+cytarabine; CAG, clarithromycin+cytarabine+granulocyte colony-stimulating factor; ATRA, all-trans retinoic acid.

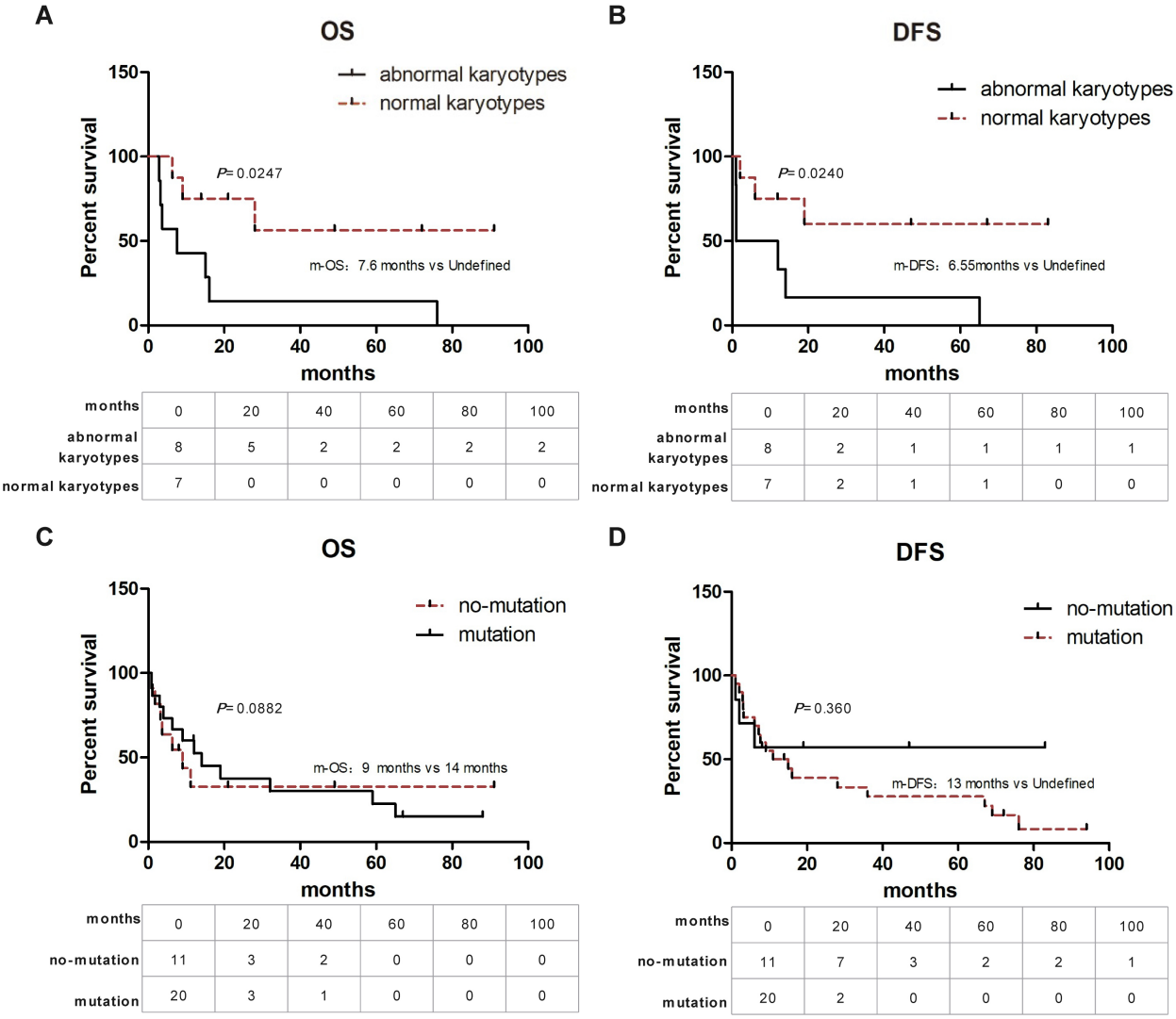


Fig. 2. OS (A) and DFS (B) of AML-pCT patients based on karyotype, OS (C) and DFS (D) of AML-pCT patients based on mutation status. Number at risk for each group is shown below the corresponding survival curve.

Survival and Prognosis of Patients With MN-pCT

In general, patients with MDS-pCT demonstrated a poorer prognosis compared to those with AML-pCT, exhibiting a median OS of 7 months (Fig. 1). Univariate Cox regression analysis identified several factors significantly associated with worse OS, including patient age >65 years (*HR* = 2.58, 95% *CI*: 1.18–5.64, $p = 0.018$), elevated lactate dehydrogenase (LDH) level (*HR* = 1.18, 95% *CI*: 1.05–1.33, $p = 0.006$), higher bone marrow blast percentage (*HR* = 1.65, 95% *CI*: 1.02–2.67, $p = 0.042$), presence of TP53 mutation (*HR* = 3.02, 95% *CI*: 1.21–7.55, $p = 0.018$), and complex karyotype (*HR* = 3.45, 95% *CI*: 1.28–9.32, $p = 0.015$). In the multivariate Cox regression model, patient age more than 65 years (*HR* = 2.21, 95% *CI*: 1.09–4.48, $p = 0.028$), *TP53* mutation (*HR* = 2.85, 95% *CI*: 1.15–7.05, $p = 0.024$), and complex karyotype (*HR* = 3.78, 95% *CI*: 1.20–11.85, $p = 0.023$) remained independently associated with inferior OS (Table 4).

31 patients were stratified according to the prognostic factors (age, TP53 mutation, complex karyotype), assigning one point for each factor. The 31 patients were then stratified into two risk groups: low-risk (total score <2) and high-risk (total score ≥2). The low-risk group had a significantly longer median OS compared to the high-risk group (16 months vs. 6.5 months, $p = 0.0305$; Fig. 3A). Similarly, low-risk patients had a significantly higher DFS than those in the high-risk group (8.5 months vs. 6 months, $p = 0.0453$; Fig. 3B).

Relationship Between Latency and Prognosis

The median latency from initial cytotoxic therapy and/or radiation exposure to the development of MN-pCT was 29 months (range: 3–162), as summarized in Table 2. Analysis by treatment modality revealed that patients who received combined chemotherapy and radiotherapy ($n = 4$) had a median latency of 34 months. In the radiotherapy-

Table 4. Univariate and Multivariate Cox regression analysis of OS in 31 patients with MN-pCT.

Characteristics	OS					
	Univariate			Multivariate		
	HR	95% *CI*	*p*	*HR*	95% *CI*	*p*
Age (>65 years)	2.58	1.18–5.64	0.018	2.21	1.09–4.48	0.028
ECOG score (≥2 points)	0.94	0.56–1.68	0.697			
Albumin	1.34	0.78–1.72	0.913			
High WBC (>10 × 10^9/L)	1.48	0.79–2.80	0.090			
LDH	1.18	1.05–1.33	0.006	1.03	1.00–1.06	0.064
BM Blast Percentage	1.65	1.02–2.67	0.042	1.58	0.89–2.78	0.123
TP53 Mutation	3.02	1.21–7.55	0.018	2.85	1.15–7.05	0.024
Complex Karyotype	3.45	1.28–9.32	0.015	3.78	1.20–11.85	0.023

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell count; LDH, lactate dehydrogenase; BM, bone marrow. The multivariate model included only variables significant in univariate analysis ($p < 0.05$) to mitigate overfitting, given the sample size.

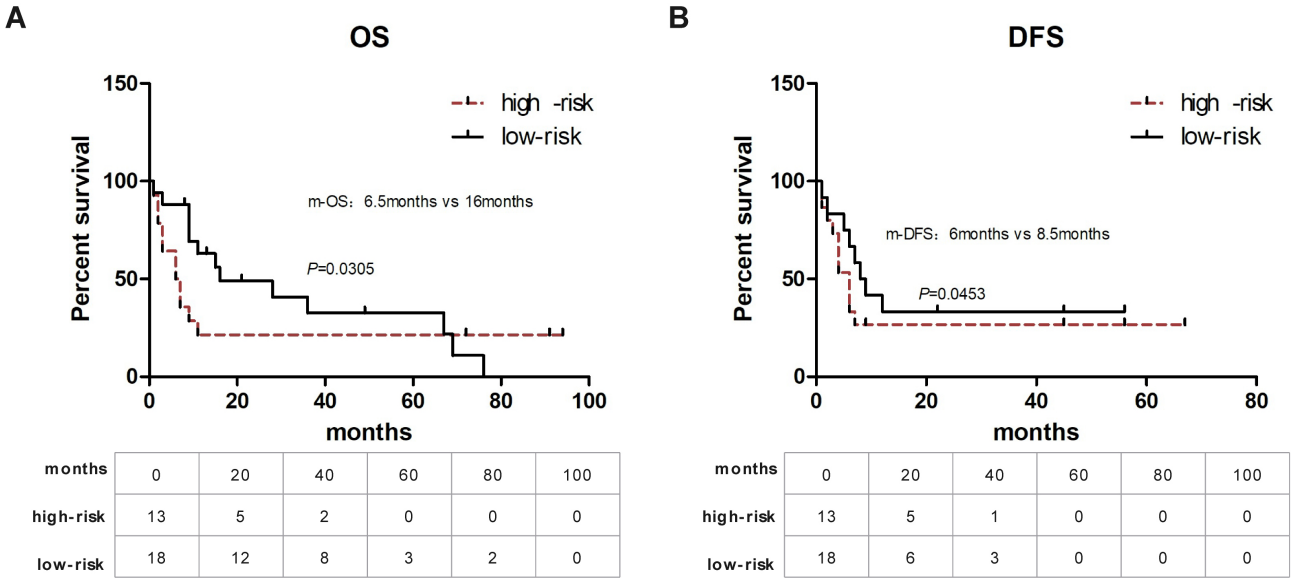


Fig. 3. Thirty-one patients were stratified according to the prognostic factors (age, TP53, complex Karyotype), assigning one point for each factor. Integral <2 points were divided into the low-risk group, integral ≥2 points were divided into the high-risk group. OS (A) and DFS (B) of the low-risk and high-risk groups. The number at risk for each group is shown below the corresponding survival curve.

alone subgroup (n = 2), latency periods were 10 and 84 months, while the chemotherapy-alone group (n = 25) exhibited a median latency of 26 months. When stratified by prior malignancy type, patients with previous hematologic malignancies (n = 3) presented latencies of 50, 26, and 12 months, whereas those with prior solid tumors (n = 28) showed a median latency of 31 months. Notably, Spearman's rank correlation analysis revealed no significant correlation between latency duration and OS (R^2 = 0.001776, p = 0.8219) or DFS (R^2 = 0.0006869, p = 0.8887) in this cohort (Fig. 4).

Discussion

Our single-center retrospective analysis corroborates the established understanding that AML/MDS-pCT constitutes a distinct and highly aggressive disease entity with a dismal prognosis. The clinical and molecular profiles of our cohort—characterized by a high frequency of adverse-risk genetic features, particularly *TP53* mutations and complex karyotype, alongside a low response rate to conventional intensive chemotherapy—align with the findings reported in the literature [3,7–10]. Nevertheless, our study also reveals certain differences compared to previous reports: the incidence of MN-pCT in our study was lower than that described in the literature, which may be attributed to the fact

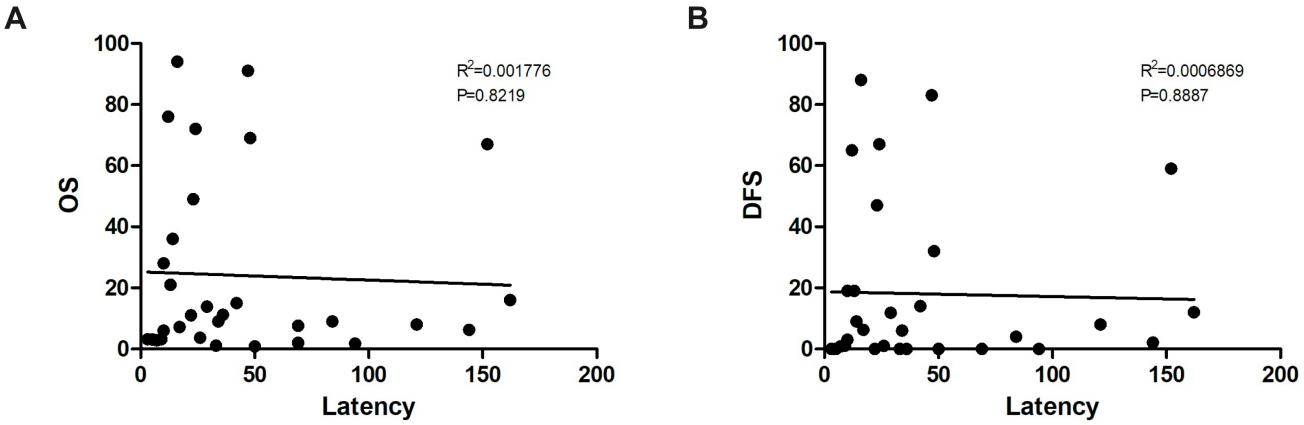


Fig. 4. Relationships between latency and OS (A) and DFS (B). Spearman's correlation coefficient (R^2) and the corresponding *p*-value are indicated on each plot, demonstrating no significant linear association.

that our hospital is a specialized cancer center rather than a dedicated hematology hospital. Furthermore, the poorer prognosis observed in MDS-pCT patients might be related to the treatment discontinuation after diagnosis.

According to existing literature, breast cancer and lymphoma represent the most common primary tumors preceding therapy-related myeloid neoplasms (t-MN/MN-pCT) [11]. Malignant tumors of the female reproductive system, such as cervical cancer and ovarian cancer, are more common than those of the male reproductive system, such as prostate cancer and testicular cancer. Some malignant tumor types, such as lung cancer and prostate cancer, are less likely to produce MN-pCT in elderly patients. In our study, the incidence of MN-pCT was the highest in patients with breast cancer (9 patients), which was consistent with the previous literature [10]. The incidence of lymphoma was low (3 patients), which may be related to the fact that the overall incidence of lymphoma in China was significantly lower compared with Europe, the United States, and Japan.

A particularly noteworthy finding in our study involves the three patients with *TP53*-mutated breast cancer who underwent allo-SCT and have subsequently maintained sustained remission. Given that *TP53* mutations are universally recognized as a marker of aggressive disease biology, conferring resistance to conventional chemotherapy and predicting dismal OS, the durable remission observed in these patients is highly remarkable. This clinical outcome suggests that the potent graft-versus-tumor (GVT) effect induced by allo-SCT may potentially overcome the adverse prognostic impact of *TP53* dysfunction [12]. Our findings underscore the critical inadequacy of conventional treatment paradigms for this patient population. The superior outcomes observed in the small subset of patients who successfully underwent allogeneic stem cell transplantation highlight its role as the only potentially curative therapy, while also emphasizing the challenge of achieving sufficiently deep remission to bridge to transplant [13,14].

Most importantly, our study, apparently the first to establish a prognostic stratification system for the MN-PCT population, discovered that these patients can be stratified using specific indicators. We demonstrated that a scoring system incorporating age, *TP53* mutation status, and complex karyotype can effectively and simply identify high-risk patients within the MN-pCT population. However, our study has several limitations that must be acknowledged. First, the sample size ($n = 31$) is relatively small, which limits the statistical power and generalizability of our findings. This is particularly relevant for subgroup analyses, such as the evaluation of allo-SCT outcomes, which included only 3 patients. While the association between allo-SCT and improved survival is promising and consistent with established literature, our data are insufficient to robustly establish its independent benefit or generalize it across all MN-pCT subgroups. Therefore, the prognostic scoring model we propose, though intuitive, requires validation in larger, multi-center cohorts to confirm its reproducibility and clinical utility across diverse settings. Second, from a methodological standpoint, we did not formally test the proportional hazards assumption for the Cox regression models or assess multicollinearity among covariates, which may affect the stability and interpretation of the hazard ratios. Furthermore, due to the exploratory nature of the analysis and small cohort size, *p*-values in univariate analyses were not adjusted for multiple testing. These statistical limitations should be considered when interpreting our results. Third, cytogenetic data were incomplete, with karyotype analysis "not done" for a notable proportion of patients (as seen in Table 3). This missing data could introduce bias, as patients with more aggressive disease might have been prioritized for testing, whereas frailer patients might not have undergone full assessment. No statistical imputation was performed for missing karyotype data; conclusions regarding complex karyotypes are drawn from the subset with available results. This limitation underscores the challenge of retrospective studies and suggests that the reported fre-

quency and impact of complex karyotype might be an estimate. Future prospective studies should mandate comprehensive genetic profiling at diagnosis to minimize missing data and accurately define the prognostic landscape.

Moving forward, the future management of sAML/t-MN lies in the rapid integration of molecular profiling into initial diagnostic workups. This approach enables risk-adapted strategies that avoid futile intensive chemotherapy in favor of novel agents and mechanisms [15]. The incorporation of venetoclax-based regimens, hypomethylating agents, and emerging targeted therapies (e.g., *TP53* stabilizers, menin inhibitors for *KMT2A*-rearranged cases, or immunotherapies) into clinical practice offers a beacon of hope. Improving outcomes will depend on early detection, the development of effective novel combinatorial therapies to achieve better responses, and timely consolidation with transplantation. Our center's experience adds to the growing body of evidence that calls for a paradigm shift from one-size-fits-all chemotherapy towards a precision medicine approach for these challenging diseases. To overcome the limitations of this single-center, retrospective analysis, we strongly advocate for collaborative, multi-center, prospective studies. Such efforts are essential to validate our prognostic model, clarify the role of allo-SCT in various genetic subgroups—especially *TP53*-mutated cases—and establish optimal treatment pathways incorporating novel agents.

Conclusions

MN-pCT, a complication of tumor radiotherapy and chemotherapy, has a poor prognosis. Clinicians should remain vigilant about the risk of MN-pCT during cancer treatment and minimize the dosage of leukemogenic agents where possible. For patients who have already developed MN-pCT, timely and active therapeutic intervention is essential, as it may improve survival outcomes.

Availability of Data and Materials

Anonymized data are available from the corresponding authors upon reasonable request.

Author Contributions

JM and ZGZ created the study protocol; JM, SG, and LL were involved in data collection and critical manuscript revision. JM, ZYZ, SL, and LC performed statistical analysis and data interpretation and also critically reviewed the manuscript. JM, QL, ZC, and ZGZ were involved in preliminary data design and assessment, and literature review. JM and QL drafted the manuscript. ZC and ZGZ provided a critical revision and regular feedback on the manuscript. All authors contributed to the refinement of the study protocol. All authors have read and approved the final manuscript to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This retrospective analysis of de-identified patient data was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol, involving the review of medical records from patients diagnosed between 2008 and 2022, was submitted for ethical review. Formal approval (IREC number: LWK-2024-0009) was granted by the Medical Ethics Committee of Tianjin Cancer Hospital Airport Hospital on 14 November 2024, prior to the commencement of the research data analysis. The Ethics Committee waived the requirement for individual informed consent for this retrospective study due to the use of anonymized data and the minimal risk posed to participants.

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Conflict of Interest

The authors declare no conflict of interest.

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