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Short communication

Characteristics and outcomes of secondary acute lymphoblastic leukemia (sALL) after multiple myeloma (MM): SEER data analysis in a single-center institution

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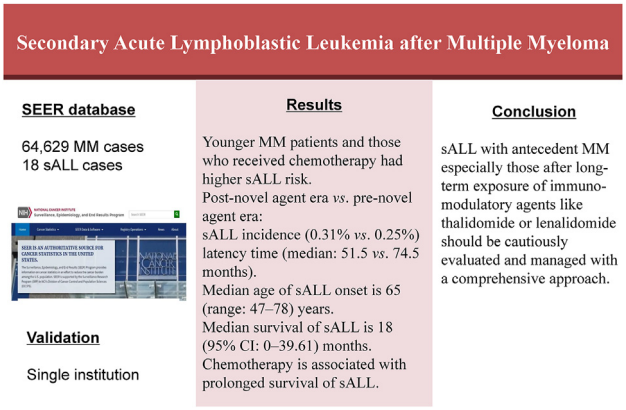
HIGHLIGHTS

- Risk factors, clinical characteristics, and outcomes of patients with secondary acute lymphoblastic leukemia (sALL) following multiple myeloma (MM).
- Data were analyzed using the Surveillance, Epidemiology, and End Results (SEER) database and validated in a single-institution cohort.
- Younger age and chemotherapy targeting MM are associated with a higher risk of sALL.
- Chemotherapy was significantly associated with sALL survival in multivariable analysis.

GRAPHICAL ABSTRACT



Characteristics and outcomes of sALL after MM. CI: Confidence interval; MM: Multiple myeloma; sALL: Secondary acute lymphoblastic leukemia; SEER: Surveillance, Epidemiology, and End Results.

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ABSTRACT

Background: Secondary acute lymphoblastic leukemia (sALL) is rare in patients diagnosed with antecedent multiple myeloma (MM). This study aimed to elucidate the clinical features and outcomes of patients with sALL after MM.
Methods: We conducted this population-based study using the Surveillance, Epidemiology, and End Results (SEER) database and retrospectively reviewed patients with sALL following MM treatment at our institution. Cox regression analysis was performed to investigate the prognostic factors for survival in patients with sALL.
Results: We identified 64,629 cases of MM (including 18 sALL from the SEER Plus 9 database, and three sALL from our institution). Younger patients with MM and those who received chemotherapy were at a higher risk of developing sALL. The novel agent era witnessed an increased incidence of sALL (post-novel agent era *vs.* pre-novel agent era: 0.31% [10/32,640] *vs.* 0.25% [8/31,989]) and shorter latency time (post-novel agent era *vs.* pre-novel agent era [median]: 51.5 *vs.* 74.5 months, $P = 0.516$), though the difference was not significant. The median age at sALL onset was 65 (range: 47–78) years. Significant cytopenia and absence of *BCR/ABL* fusion genes were common features in this patient population. The treatment of sALL is complicated by old age and poor performance status. The median survival of patients with sALL is 18 months, whereas those who received chemotherapy had significantly prolonged survival.

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Conclusions: Patients with sALL combined with an antecedent MM, especially those with long-term exposure to immunomodulatory agents such as thalidomide or lenalidomide, should be cautiously evaluated and managed with a comprehensive approach.

Introduction

Multiple myeloma (MM), the second most common hematological malignancy in the United States (US), has been associated with improved survival in recent years, largely because of the introduction of autologous stem cell transplantation (ASCT) and novel therapeutic agents.[1] The extended lifespan of patients with MM has led to renewed concerns about the long-term risk of secondary primary malignancies (SPMs). A Surveillance, Epidemiology, and End Results (SEER)-based study revealed that, while the age-adjusted rate of SPMs in MM was 0.22 per 100,000, the rate of secondary acute lymphoblastic leukemia (sALL) was 5.48 times higher than that in the general population.[2] B cell acute lymphoblastic leukemia (B-ALL) cases were identified as hematological SPMs in both the CALGB100104 and IFM 2005-02 trials mainly among MM survivors on lenalidomide maintenance.[3,4] In addition, sALL occurring after multiple chemotherapeutic and immunomodulatory treatments for MM has been described in several case reports and series.[5,6]

Given its rare incidence, the pathogenesis of SPMs in B-ALL remains to be fully elucidated. Its etiology is multifactorial, which may involve the host, MM disease, and treatment factors.[7] Certain genetic mutations may predispose patients to various malignancies. Given that MM and B cell ALL originate from post-germinal center B cells, it is unclear whether sALL following MM represents clonal dedifferentiation from indolent MM to aggressive ALL or is therapy-related leukemia triggered by MM treatment. The analysis of paired samples of MM and sALL demonstrated that the two diseases are not clonally related but potentially represent a therapy-related result.[8]

There is a paucity of literature regarding the clinical characteristics and outcomes of sALL after MM. Herein, we reviewed data of MM patients with sALL from the SEER database and summarized our experience with sALL following MM at our institution.

Methods

Surveillance, epidemiology, and End Results database analysis

The SEER Research Plus 9 database (1975–2018) was used to identify patients diagnosed with MM using the International Classification of Diseases for Oncology, third edition (ICD-O-3) code 9732/3. The inclusion criteria were as follows: age ≥18 years and a definite diagnosis of sALL with a latency of at least 12 months between MM and ALL occurrences according to the Warren and Gates criteria.[9] The exclusion criteria were sALL patients with more than two primary malignancies or missing survival data. The patient characteristics included sex, race, age at diagnosis, year of diagnosis, and survival.

Study design and patients

The data of patients diagnosed with MM at our institution between 2010 and 2021 were retrospectively reviewed. The diagnosis and treatment responses of MM were based on the International Myeloma Working Group (IMWG) criteria.[10,11] Patients with sALL fulfilled the diagnostic criteria for ALL according to the World Health Organization (WHO) classification. The patients were followed up until April 1, 2022.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM Corp.; Armonk, NY, USA). Categorical variables were compared using the chi-squared test or Fisher's exact test, whereas continuous variables were analyzed using Student's *t*-test. Survival estimates were calculated using the Kaplan–Meier method, and differences between survival rates were assessed using the log-rank test. Cox regression analysis was performed to investigate the impact of prognostic factors on the overall survival (OS) of patients with sALL. A two-tailed P value < 0.05 was deemed statistically significant.

Results

Surveillance, epidemiology, and End Results analyses

In total, 64,629 MM cases, including 18 sALL cases, were identified from the SEER database. As shown in Table 1, patients with sALL combined with MM tended to be younger at diagnosis (median age: 59 *vs.* 69 years, $P < 0.001$) and were more likely to receive chemotherapy (88.9% [16/18] *vs.* 62.2% [40,197/64,611]) than those without sALL. The median age at sALL onset was 65 (range: 47–78) years, and 55.6% (10/18) of the patients were male. The incidence rates of sALL before and during the novel agent era were 0.25% (8/31,989) and 0.31% (10/32,640), respectively. The median latency period between MM diagnosis and sALL development decreased from 74.5 (19–140) months before the novel agent era to 51.5 (21–150) months in the novel agent era, although the difference was not statistically significant ($P = 0.516$).

As was shown in Figure 1, the median survival following MM diagnosis was 34.0 (33.5–34.5) months *vs.* 125.0 (57.6–192.4) months for patients without and with sALL ($P = 0.006$). The median OS significantly increased from 26 (25.5–26.5) months among MM cases diagnosed prior to the novel agent era to 48 (46.9–49.1) months in the novel agent era ($P < 0.001$).

The median survival time following sALL diagnosis was 18 (95% confidence interval [CI]: 0–39.61) months. In the multivariate Cox proportional hazards regression model, chemotherapy was significantly associated with prolonged OS in patients with sALL [Table 2].

Clinical features and treatment of patients in our institution

A total of 1529 patients with MM were reviewed, and three (3/1529, 0.2%) patients with sALL were identified. The characteristics and

Table 1
Characteristics of patients with MM with and without sALL.

Characteristics	MM without sALL, *n* (%)	MM with sALL, *n* (%)	χ^2	*P* value
Total number	64,611	18	–	
Age of MM diagnosis (years), median (range)	69 (18–85)	59 (44–72)	–	<0.001
Gender			0.012	0.913
Male	35,067 (54.3)	10 (55.6)		
Female	29,544 (45.7)	8 (44.4)		
Race			1.303	0.521
White	49,117 (76.3)	12 (66.7)		
Black	11,296 (17.5)	5 (27.8)		
Other	3974 (6.2)	1 (5.5)		
Marital status			1.364	0.243
Married	36,886 (60.7)	12 (75.0)		
Other	23,843 (39.3)	4 (25.0)		
Year of MM diagnosis			0.184	0.668
1975–2002	31,981 (49.5)	8 (44.4)		
2003–2018	32,630 (50.5)	10 (55.6)		
Chemotherapy for MM			5.447	0.020
Yes	40,197 (62.2)	16 (88.9)		
No	24,414 (37.8)	2 (11.1)		

MM: Multiple myeloma; sALL: Secondary acute lymphoblastic leukemia; -: No data.

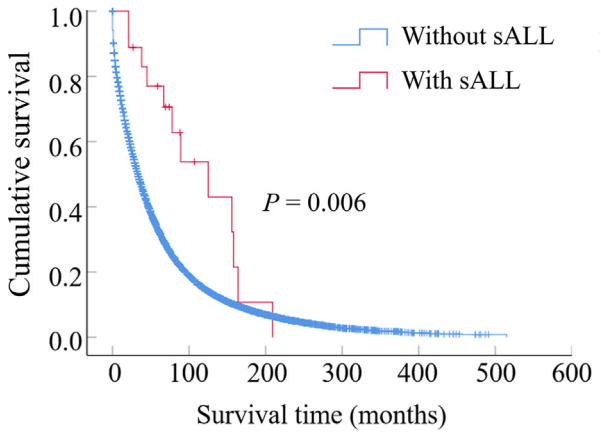

Figure 1. Survival curve of patients with MM with and without sALL. Median survival (MM patients with *vs.* without sALL): 125.0 (95% CI, 57.6–192.4) months *vs.* 34.0 (95% CI, 33.5–34.5, $P = 0.006$) months. CI: Confidence interval; MM: Multiple myeloma; sALL: Secondary acute lymphoblastic leukemia.

Table 2
Prognostic factors for the overall survival of patients with MM since sALL diagnosis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex		0.235		0.513
Male	0.47 (0.135–1.634)		0.602 (0.132–2.748)	
Female	Reference		Reference	
Race		0.375		0.379
White	0.628 (0.074–5.324)		3.467 (0.153–78.406)	
Black	0.160 (0.009–2.732)		0.835 (0.028–25.013)	
Other	Reference		Reference	
Age at diagnosis (years)		0.347		0.586
18–64	0.553 (0.161–1.897)		0.684 (0.174–2.680)	
≥65	Reference		Reference	
Year of diagnosis		0.722		0.535
1975–2002	1.263 (0.348–4.581)		0.616 (0.133–2.853)	
2003–2018	Reference		Reference	
Chemotherapy		0.017		0.011
No	6.366 (1.395–29.059)		13.840 (1.807–106.010)	
Yes	Reference		Reference	

CI: Confidence interval; HR: Hazard ratio; MM: Multiple myeloma; sALL: Secondary acute lymphoblastic leukemia.

treatments of the three patients with MM are summarized in Table 3. The median age at MM diagnosis was 62 (range: 58–67) years. All three patients received novel thalidomide-based induction therapy. Two patients received bortezomib as part of induction therapy. None of the patients underwent ASCT because of their age or individual preferences. All three patients received thalidomide as maintenance therapy for a median duration of 77 months. One patient experienced a MM relapse and received short-term lenalidomide treatment.

The characteristics and treatments of the three patients with sALL are depicted in Table 4. The median latency period from MM diagnosis was 87 (range: 65–91) months. All patients had B cell phenotypes. sALL genetics showed a normal karyotype and trisomy 14 in two cases. All three patients received reduced doses of chemotherapy for ALL. Two patients died 18 and 42 months after sALL diagnosis, respectively.

Table 3
Characteristics and treatment of patients with MM at our institution.

Parameters	Case 1	Case 2	Case 3
Age at MM diagnosis (years)	67	58	62
Sex	Female	Female	Male
MM subtype	IgG λ	IgG λ	IgG κ
Durie-Salmon stage	IIIA	IIIB	IIIA
ISS stage	II	III	III
FISH cytogenetics	NA	1q21 amplification	NA
Induction therapy/ response	CTD + M/CR	PADT, CTD/CR	PAD, TAD/CR
ASCT	No	No	No
Maintenance therapy/ duration (months)	Thalidomide/51	Thalidomide/85	Thalidomide/77
MM relapse	Yes	No	No
Treatment for relapsed MM/duration	Lenalidomide/ 2 weeks	No	No

ASCT: Autologous stem cell transplantation; CR: Complete remission; CTD + M: Cyclophosphamide, thalidomide, dexamethasone + melphalan; FISH: Fluorescence *in situ* hybridization; IgG κ: Immunoglobulin G kappa; IgG λ: Immunoglobulin G lambda; ISS: International Staging System; MLL: Mixed lineage leukemia; MM: Multiple myeloma; NA: Not available; PAD: Bortezomib, doxorubicin, dexamethasone; PADT: Bortezomib, doxorubicin, dexamethasone, thalidomide; TAD: Thalidomide, doxorubicin, dexamethasone.

Table 4
Characteristics and treatment of patients with sALL at our institution.

Parameters	Case 1	Case 2	Case 3
sALL onset from MM diagnosis (months)	65	91	87
Age at sALL diagnosis (years)	73	66	70
MM active when sALL onset	Yes	No	No
sALL phenotype	B cell (CD10+)	B cell (CD10-, c-IgM-)	B cell (CD10+, c-IgM-)
Cytogenetic analysis	NA	Normal karyotype	Trisomy 14
BCR/ABL fusion	Negative	Negative	Negative
MLL rearrangement	Negative	Negative	Negative
Induction therapy for sALL/response	VLP/CR	VDCP, MA/CR	VDCP, MA/CR
Survival time from sALL diagnosis (survival status)	18 months (dead)	37 months (alive)	42 months (dead)

c-IgM: Cytoplasmic Immunoglobulin M; CR: Complete remission; MA: Methotrexate-cytarabine; MLL: Mixed myeloid leukemia; MM: Multiple myeloma; NA: Not available; sALL: Secondary acute lymphoblastic leukemia; VLP: Vindesine, prednisone, pegaspargase; VDCP: Vindesine-daunorubicin-cyclophosphamide-prednisone.

Discussion

To the best of our knowledge, this may be the first population-based analysis to elucidate the characteristics and outcomes of sALL following MM. In the present study, three key points were highlighted. First, sALL risk was higher in MM patients diagnosed at a younger age and who underwent chemotherapy. Second, patients with sALL had a more favorable survival time after MM diagnosis than those without sALL. Third, the median survival after sALL diagnosis was 18 months, whereas patients receiving chemotherapy had significantly prolonged survival.

Krishnan et al.[8] analyzed 13 patients with sALL preceded by MM, all of whom received immunomodulatory drugs, with most undergoing ASCT. Further assessment indicated that the two malignancies were clonally unrelated. The authors postulated that sALL cases could be therapy-related because of MM treatment. Our study concluded that the risk of sALL was higher in patients diagnosed with MM at a younger age and who underwent chemotherapy. Younger patients with MM tend to receive more intensive chemotherapy. This also demonstrates that sALL may be a complication of exposure to MM therapeutics. Moreover, a nationwide study from Sweden found that the first-degree relatives of MM patients have a two-fold increased risk of developing ALL, indicating

that MM was genetically associated with ALL.[12] Experts from the European Leukemia Net (ELN) recommend that, for sALL patients with no prior cytotoxic therapy, inherited germline mutations in tumor suppressor genes or oncogenes such as *TP53* or mismatched repair genes (*MSH2*, *MLH1*, *MSH6,* and *PMS2*) should be suspected.[13] In our study, germline gene screening was necessary for 11.1% (2/18) of all sALL patients who did not receive MM-directed therapy.

Cases of sALL after thalidomide exposure have been reviewed.[14–16] Given that all three patients had extensive periods of thalidomide use, thalidomide treatment may have been responsible for the development of sALL. It remains unclear how thalidomide contributes to ALL pathogenesis. However, thalidomide and lenalidomide can enhance the Epstein–Barr virus lytic cycle in resting memory B cells and host immune suppression, increasing the possibility of various lymphoproliferative disorders.[17] In three randomized controlled trials of lenalidomide as maintenance therapy for patients with MM, ALL occurred in the lenalidomide arm.[4,18,19] Parrondo et al.[20] proposed that lenalidomide-induced alterations in IKZF1 are associated with leukemogenesis in sALL. García-Muñoz et al.[21] speculated that sALL development in patients receiving lenalidomide may result from the selection of refractory clones or neoplastic stem cells that evade lenalidomide's antineoplastic effects. The development of sALL after immunomodulatory drug therapy may indicate a specific biologic correlation.[22] This is likely to be more complex than the duration or cumulative dose usage.

Krishnan et al.[8] reported in their case series that the median white blood cell count at sALL presentation was 2000/μL. Lee et al.[23] reported two cases of therapy-related ALL in patients with MM, both of whom had notable cytopenia at diagnosis. Two patients in our study had neutropenia at the time of sALL diagnosis, indicating that there should be a low threshold for bone marrow biopsy in cases of unexplained cytopenia during MM follow-up. *Mixed myeloid leukemia* (*MLL*) gene rearrangements and t(9;22) (q34;q11) are the most common cytogenetic abnormalities associated with t-ALL.[24] Moreover, genetic features such as *TP53* mutation/deletion and monosomy 7 or 7q deletion have been reported in the sALL cohort following MM.[8] However, none of these cytogenetic features were described in our three patients. Further evaluation of genetic features in a larger sALL cohort is required.

Our study highlighted that patients with sALL did not have worse survival outcomes than those without sALL, suggesting that the long disease latency due to indolent myeloma may have allowed the occurrence of sALL. This also demonstrats that the therapeutic benefits of treating MM outweigh the risk of SPM, indicating that therapeutic decision-making should not be altered. For sALL after prior cytotoxic therapy, the US SEER registry data showed a median latency of 60 months following the diagnosis of the primary malignancy.[25] Other studies have reported a median latency of 36–51.1 months in patients with immunomodulatory agents related ALL[14,16] This was consistent with our finding that the latency time was shorter in the novel agent era.

Per ELN recommendation, the treatment strategy for sALL is similar to that for newly diagnosed ALL, although a higher risk of toxicity might be expected.[26] Krishnan et al.[8] reported a cohort of patients with sALL, 92% of whom used the hyperCVAD regimen for ALL induction and achieved a complete remission (CR) rate of 85%. Subsequently, 62% of patients underwent allogeneic hematopoietic stem cell transplantation (HSCT). The 1-year OS following sALL diagnosis is 70%. Tan et al.[27] reported two patients with sALL following MM who received chemotherapy and allogeneic HSCT. Both achieved CR and long-term survival. Charkraborty et al.[2] reported that the year of diagnosis was an independent predictor of survival in patients with MM and SPMs. Earlier age of onset indicates a greater possibility of tolerating allogeneic HSCT and intensive chemotherapy, resulting in longer survival. Our study showed that chemotherapy improved OS compared to standard-of-care therapies, which is consistent with the results of the above study. Based on current research, dose-adjusted induction therapies for *de novo* ALL are indicated for sALL patients following MM. Supportive therapy is reserved for frail patients, and allogeneic HSCT is feasible for younger patients who achieve remission.[28] A significantly inferior median 5-year survival for sALL has been noted compared to *de novo* ALL (6 *vs.* 15 months) in the literature.[25] Patients with sALL and antecedent MM tend to have better outcomes than those with non-MM sALL.[20] A domestic study reported a median survival of 11.9 months after sALL diagnosis, similar to the SEER results (18 months) in our study.[16] Advanced age and evolving cytopenia in our patients precluded the standard induction of *de novo* ALL. Instead, we chose reduced-intensity chemotherapy regimens for patients with sALL, which resulted in remission for 18–42 months. However, this finding should be validated in larger patient samples.

This study had some limitations. Owing to the retrospective nature of our study, details of the patients' clonal origins were not available. The relatively small number of patients with sALL resulted in lower power to detect statistical discrepancies.

In conclusion, patients with MM, especially those heavily pretreated with immunomodulatory agents like thalidomide or lenalidomide, should be carefully monitored for SPMs such as sALL. Patients with sALL had a more favorable survival time after MM diagnosis compared to those without sALL. However, survival after sALL diagnosis is generally poor. Regimens for *de novo* ALL are applicable to patients with sALL, with selected patients receiving allogeneic HSCT.

Authors contribution

Jing Jia: data collection and curation, formal analysis, writing of the original draft, and editing; Jiahui Yin: investigation; Aijun Liu: conceptualization and methodology; Chuanying Geng: supervision and review. All the authors have read and approved the final version of the manuscript.

Ethics statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital (No. 2022-1-12-1), Capital Medical University, Beijing, China, and performed in accordance with the *Declaration of Helsinki*. As this was a retrospective study and data analysis was performed anonymously, this study was exempt from obtaining informed consent from patients.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that generative artificial intelligence (AI) and AI assisted technologies were not used in the writing process or any other process during the preparation of this manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Data availability statement

The data is available on the Surveillance, Epidemiology, and End Results (SEER, http://seer.cancer.gov) database. The code used for the analysis of data in this study is available from the corresponding author on reasonable request.

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