Am J Cancer Res 2023;13(10):4803-4810
www.ajcr.us /ISSN:2156-6976/ajcr0145314

Original Article

Characterization and prognostic features of secondary acute myeloid leukemia in survivors of multiple myeloma

Jing Jia, Wenming Chen

Department of Hematology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China

Received July 13, 2022; Accepted September 8, 2023; Epub October 15, 2023; Published October 30, 2023

Abstract: This large population-based study determined the epidemiology and outcomes of secondary acute myeloid leukemia (sAML) in multiple myeloma (MM) survivors using the Surveillance Epidemiology and End Results (SEER) Research Plus 9 database. To identify 64,753 cases of MM which included 136 cases with sAML; these patients were juxtaposed with patients with *de novo* AML from the same database. Younger MM patients who received chemotherapy (ChT) had a higher sAML risk. The novel agent era saw a decreased sAML incidence (0.15% vs. 0.26%) and shorter latency period (median: 56 vs. 66 months, P=0.031). Compared to *de novo* AML, sAML patients were older (median age 69 vs. 68 years, P=0.027), less likely to receive ChT (51.9% vs. 67.4%, P<0.001), and had inferior overall survival (OS) (median OS: 2 vs. 5 months, P<0.001). Multivariate Cox regression revealed that younger diagnosis age, diagnosis after 2003, and ChT were associated with prolonged OS in sAML patients. Clinicians should be aware of the sAML risk in younger, intensively-treated MM patients. Given the poor sAML prognosis compared to *de novo* AML, clinical trials of novel therapies based on age, geriatric assessment, and cytogenetic features are warranted.

Keywords: Multiple myeloma, secondary acute myeloid leukemia, SEER, survival

Introduction

Multiple myeloma (MM) is a malignancy characterized by neoplastic plasma cell proliferation and monoclonal immunoglobulin production, leading to a wide spectrum of target-organ damage. It accounts for an estimated 1.2% of new cancer cases and 2% of cancer deaths in the United States [1], predominantly affecting older and male patients. Over the past several decades, conventional MM chemotherapy (ChT) includes melphalan, prednisone, cyclophosphamide, vinca alkaloids and anthracyclines. Radiation therapy (RT) is potentially curative for localized disease (solitary plasmacytoma) but is typically reserved for palliative bone disease therapy. The incorporation of novel agents (immunomodulatory agents, proteasome inhibitors, monoclonal antibodies) and increased autologous hematopoietic stem cell transplantation (HSCT) use since 2003 have significantly improved MM patient survival, with median survival times now ranging from 5 to 8 years [2, 3].

As improved survival leads to an extended MM patient lifespan, second primary malignancies (SPMs) have emerged as a long-term risk. Leukemias, particularly secondary acute myeloid leukemia (sAML), account for the most significant cancer excesses following MM diagnosis, with sAML rates 8.19 times higher than in the general population [4]. Incidence rates of sAML depend on follow-up duration and therapy type. sAML risks start to increase 12 months post-MM diagnosis and elevate significantly 5-10 years post-initial diagnosis. This increased sAML risk likely reflects more intensive MM treatment regimens, often administered for 6 to 12 months or longer [5-7].

The pathogenesis of sAML post-MM is complex, involving multiple proposed pathogenic pathways [8]. A combination of intrinsic (biolog-

ic-related, disease-related) and extrinsic (treatment regimens, duration, environmental factors) risk factors contribute to MM patient molecular heterogeneities [7]. Various cytogenetic abnormalities can lead to aberrant gene transcription, resulting in dysfunctional proteins. These abnormal proteins eventually drive deregulated cellular proliferation and apoptosis, ultimately resulting in aberrant cell growth and leukemogenesis [9].

While the incidence of sAML after MM diagnosis is highlighted in numerous literature sources, there is a distinct lack of data regarding outcomes of MM survivors who develop sAML, warranting future research focus [7]. The aim of this study was to discuss the characteristics, risk factors, and survival of sAML developing after MM juxtaposed with *de novo* AML.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a mandatory national registry that provides data on cancer cases throughout the United States. The SEER Research Plus 9 database (1975-2018) was used to identify cases diagnosed with MM using the International Classification of Disease for Oncology, third edition (ICD-0-3) code 9732/3. Following prior studies, inclusion criteria were age 18 or older and a defined diagnosis of sAML with a latency of at least 12 months between MM and AML occurrences according to the Warren and Gates criteria [5, 10]. Exclusion criteria included sAML cases with more than two primary malignancies or missing survival data. The SEER Research Plus 9 database was also utilized to identify *de novo* AML cases aged 18 years or older using ICD-0-3 histology code 9861/3. Acute promyelocytic leukemia cases (ICD-0-3 code 9866/3) were excluded from our analysis due to their favorable prognosis.

Patient characteristics included age at diagnosis, year of diagnosis, sex, race, survival time, and marital status. Marital status was classified as married (including common law) and other. Period analysis was used to account for various treatments, relying on agent approval to infer exposure. Patients were analyzed in the pre- (1975-2002) and post- (2003-2018) novel agent era groups, respectively.

Statistical analysis

Statistical analysis was performed using SPSS version 25. Categorical variables were analyzed using Chi-square tests or Fisher's exact test, whereas continuous variables were analyzed using Student's t-tests. To adjust for potential confounders that might cause bias, propensity score matching (PSM) accounting for all covariates was performed using SPSS to create a matched dataset based on AML type (*de novo* AML vs. sAML following MM). A 1:1 ratio (one *de novo* AML case for each sAML) with the propensity score radius difference of 0.02 was used. Survival curves for both unmatched and matched datasets were generated with the Kaplan-Meier method and compared using the log-rank test. Cox multivariate regressions were performed to study the impact of various covariates on the overall survival (OS) of patients with sAML.

Results

The SEER query identified a total of 64,753 adults actively followed up who were diagnosed with MM between 1975 and 2018, of whom 136 developed sAML. We excluded three sAML cases with more than two primary malignancies, resulting in a total of 133 sAML cases and 64,617 MM without AML cases selected for final analysis. A total of 36,184 *de novo* AML cases were extracted from the database. We excluded 9,890 with more than one primary malignancy to avoid its impact on survival, and 385 with missing survival data, resulting in a total of 25,909 *de novo* AML cases selected for final analysis.

Clinical characteristics of MM patients with and without sAML

As depicted in **Table 1**, MM patients with sAML tended to have a younger age of diagnosis (median age: 63 vs. 69 years, $P<0.001$) and received more ChT (78.9% vs. 62.2%, $P<0.001$) than those without sAML. sAML incidence significantly decreased from 0.26% (84/32,068) before novel agent era to 0.15% (49/32,682) in novel agent era ($P=0.002$). The median latency period between MM diagnosis and sAML development significantly decreased from 66 (19-351) months among MM cases diagnosed prior to the novel agent era to 56 (12-142) months in the novel agent era ($P=0.031$).

Table 1. Characteristics of MM patients with and without sAML

Characteristics	MM without sAML N (%)	MM with sAML N (%)	*P*-value
Total number	64617	133	
Age of MM, median (range); years	69 (18-85)	63 (40-84)	<0.001
Gender			0.125
Male	35071 (54.3)	81 (60.9)	
Female	29546 (45.7)	52 (39.1)	
Race			0.673
White	49122 (76.3)	105 (78.9)	
Blake	11296 (17.5)	22 (16.5)	
Other	3975 (6.2)	6 (4.5)	
Marital status			0.041
Married	36890 (60.7)	91 (69.5)	
Other	23845 (39.3)	40 (30.5)	
Year of MM diagnosis			0.002
1975-2002	31984 (49.5)	84 (63.2)	
2003-2018	32633 (50.5)	49 (36.8)	
Chemotherapy for MM			<0.001
Yes	40203 (62.2)	105 (78.9)	
No	24414 (37.8)	28 (21.1)	

MM, multiple myeloma; sAML, secondary acute myeloid leukemia.

Table 2. Characteristics of patients with *de novo* AML and sAML

Characteristics	In raw data			After propensity score matching		
	De novo AML N (%)	sAML N (%)	*P*-value	*De novo* AML N (%)	sAML N (%)	*P*-value
Total number	25909	133		133	133	
Age, median (range); years	68 (18-85)	69 (51-85)	0.027	18 (18-19)	69 (51-85)	<0.001
Gender			0.139			0.533
Male	14119 (54.5)	81 (60.9)		76 (57.1)	81 (60.9)	
Female	11790 (45.5)	52 (39.1)		57 (42.9)	52 (39.1)	
Race			0.001			0.137
White	21643 (83.8)	106 (79.7)		106 (79.7)	106 (79.7)	
Black	1946 (7.5)	21 (15.8)		14 (10.5)	21 (15.8)	
Other	2247 (8.7)	6 (4.5)		13 (9.8)	6 (4.5)	
Marital status			0.080			<0.001
Married	14987 (57.8)	91 (68.4)		6 (4.5)	91 (68.4)	
Other	9961 (38.5)	40 (30.1)		126 (94.7)	40 (30.1)	
Unknown	961 (3.7)	2 (1.5)		1 (0.8)	2 (1.5)	
Chemotherapy for AML			<0.001			<0.001
Yes	17454 (67.4)	69 (51.9)		126 (94.7)	69 (51.9)	
No	8455 (32.6)	64 (48.1)		7 (5.3)	64 (48.1)	

Clinical characteristics of patients with de novo AML and sAML

Patients with sAML, compared with *de novo* AML, were more likely to be older (median age 69 vs. 68, *P*=0.027) and from the black race group (15.8% vs. 7.5%, *P*=0.001); sAML patients were less likely to receive ChT (51.9% vs. 67.4%, *P*<0.001). After PSM in a 1:1 ratio, a total of 133 cases of sAML and 133 cases of

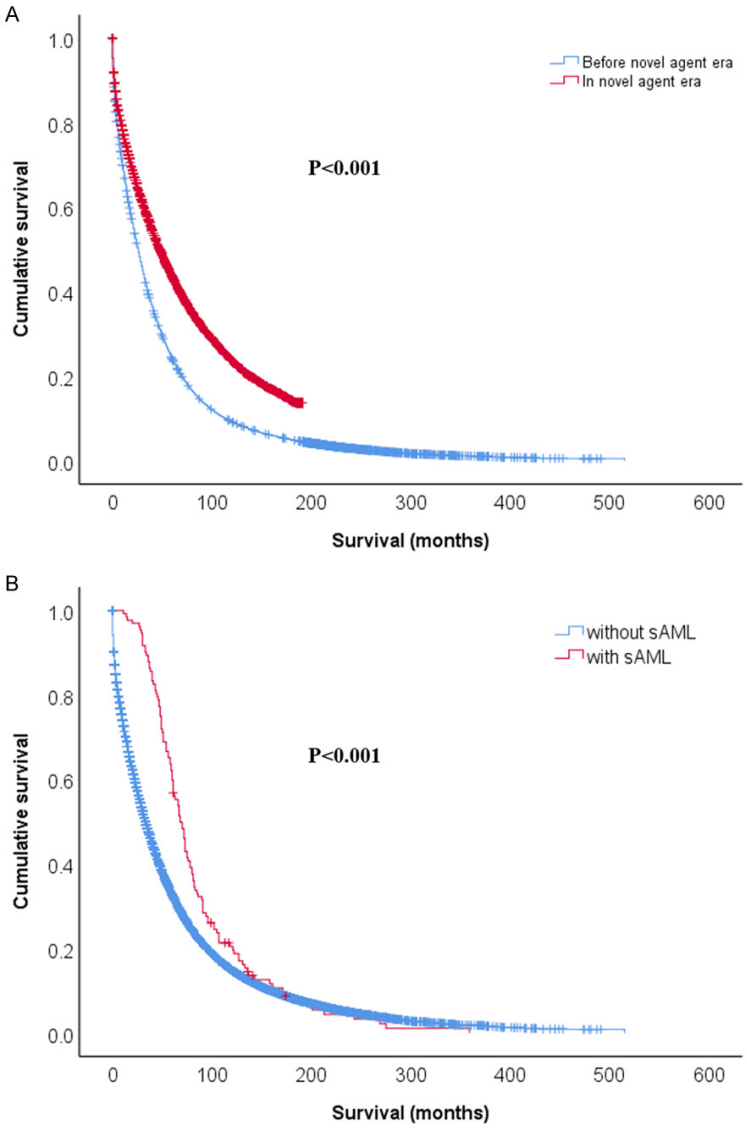

Figure 1. A. Kaplan-Meier survival Curves in MM patients before and after novel agent era; B. Kaplan-Meier survival Curves for MM patients with and without sAML. MM, multiple myeloma; sAML, secondary acute myeloid leukemia.

de novo AML were included. Except for the distribution of age, marital status, and ChT application, the two groups did not differ in any other demographic characteristics (**Table 2**).

Survival and prognostic factors

As was shown in **Figure 1**, the median OS increased significantly from 26 (range 25.498-26.502) months among MM cases diagnosed prior to novel agent era to 48 (46.937-49.063) months in the novel agent era (P<0.001). Patients with sAML had a more favorable survival time following MM diagnosis, with a median OS of 68 months (range 61.045-74.955) vs. 34 months (range 33.516-34.484) in those without sAML (P<0.001).

Patients since sAML diagnosis had a worse median OS (2 months, range 1.263-2.737) compared with those with *de novo* AML (5 months, range 4.828-5.172, P<0.001). The survival difference between sAML and *de novo* AML was confirmed after PSM (2 months, range 1.263-2.737) vs. 12 months (range 8.776-15.224, P<0.001, **Figure 2**).

In a multivariate Cox proportional hazard regression model, younger age of diagnosis, diagnosis after 2003, and ChT were significantly associated with prolonged OS in patients with sAML (**Table 3**).

Discussion

This study is, to our knowledge, the most extensive population-based analysis of AML secondary to MM, accounting for treatment-related effects; it aims to elucidate the characteristics and survival of sAML, and juxtapose sAML and *de novo* AML using PSM tools. The findings highlight three critical points: first, sAML risk is higher in patients diagnosed with MM at a younger age and who underwent more ChT. The latency period between MM diagnosis and sAML development significantly decreased in the novel agent era. Second, compared to *de novo* AML, sAML patients were older, less likely to receive ChT, and had worse survival. Third, multivariate Cox regression revealed that a younger age of diagnosis, diagnosis after 2003, and ChT were significantly associated with prolonged OS in patients with sAML.

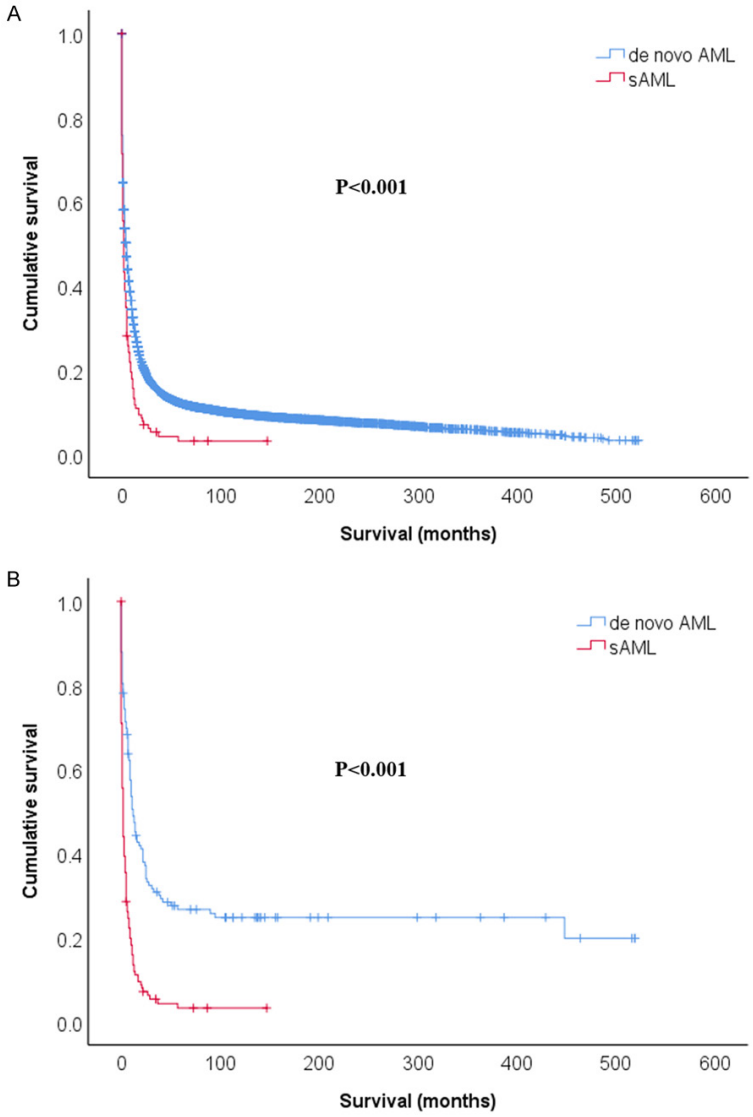

Figure 2. A. Kaplan-Meier survival Curves in patients with *de novo* AML or sAML; B. Kaplan-Meier survival Curves for patients with *de novo* AML or sAML after propensity score matching. sAML, secondary acute myeloid leukemia.

As MM patient survival time improves, the development of potentially fatal sAML has become a clinical reality [4, 11-13]. Overall, the risk is multifactorial [14]. Ashwin et al. demonstrated mutant hematopoietic stem cell clones, mainly harboring TP53 mutations, can act as leukemia-initiating cells many years before the sAML onset [15]. The MM-015 trial showed that 3 of 11 MM patients with plasma cell complex cytogenetics eventually developed myelodysplastic syndromes (MDS)/AML [16], supporting a role for disease-related factors in AML secondary to plasma cell dyscrasias. Among potential host-related factors, older age has been mostly associated with increased SPMs incidence after MM [17]. However, recent results indicate that sAML risk in MM was significantly increased in patients aged <65 years, consistent with our findings [12]. Govindarajan et al. observed that extended rather than limited preceding treatments before autologous HSCT increased secondary MDS/AML incidence [18]. Our study also highlighted the role of ChT in sAML development. Patients with sAML did not fare worse than those without sAML in the analysis, possibly because the long disease latency due to indolent myeloma may have allowed for sAML manifestation.

Ola Landgren *et al.* reported that the excess risk for AML/MDS following MM was the same before and after the introduction of autologous HSCT. The combination of melphalan and prednisone was the mainstay of MM therapy before autologous HSCT introduction. This potentially reflects that lower doses of extended oral melphalan and melphalan concentrated to 1 or 2 high-dose courses could have a similar impact on AML/MDS risk due to direct mutagenic effects inducing DNA damage [11]. Randomized clinical studies have reported an increased sAML incidence in MM patients treated with lenalidomide maintenance, especially in combination with melphalan [14, 19, 20]. However, the mechanism remains undefined. The immunosuppressive activity and effect on tumor microenvironment of lenalidomide might favor abnormal clone escape. A possible damaging stem-cell effect of lenalidomide may also facilitate the development of sAML [14]. Lenalidomide-induced cereblon/DDB1 complex inhibition impairs nucleotide excision

Table 3. Overall survival of patients with sAML

Characteristics	OS	*P*
	HR (95% CI)	
Sex		0.669
Male	0.922 (0.635-1.339)	
Female	Reference	
Race		0.243
White	1.205 (0.476-3.049)	
Black	1.824 (0.665-5.004)	
Other	Reference	
Age at diagnosis, y		0.037
18-39		
40-64	0.628 (0.406-0.972)	
65+	Reference	
Year of diagnosis		0.01
1975-2002	1.692 (1.135-2.523)	
2003-2018	Reference	
Chemotherapy		0.01
No	1.632 (1.127-2.363)	
Yes	Reference	

repair of melphalan-induced DNA damage, which might be associated with sAML development [14, 21].

In our study, we conducted period analyses to study sAML in relation to the introduction of MM novel agents (year of 2003). Specifically, we estimated sAML risk before and after 2003 and found different risk patterns. Although the novel agent era witnessed a lower sAML risk among MM patients, the latency period to sAML diagnosis decreased significantly in the novel agent era. Another study reported a similar result, with a significant decreasing trend for sAML in the novel agent era, particularly for patients ≥65 [12]. This may be partly attributable to the less frequent use of melphalan in the novel agent era, especially for patients ≥65, who are ineligible for autologous HSCT. In a Swedish study, the median time to AML/MDS diagnosis following MM was 45.3 months [11]. The shorter latency period compared with our result may be due to the inclusion of MDS in the study, which preludes AML development. In the novel agent era, consolidation therapy with autologous HSCT followed by lenalidomide maintenance has been the choice for some MM patients. Co-exposure of melphalan and lenalidomide may lead to earlier evolution of leukemia-initiating cells, presenting as shorter latency in the novel agent era [14, 21].

AML is a disease affecting all ages but mainly occurs in elderly patients with a median age of 69-72 years [22]. Age significantly impacts the management and outcome of AML patients. In our study, sAML patients were slightly older than those with *de novo* AML. Furthermore, these patients mostly underwent extensive therapy for MM, resulting in poor hematopoietic reserves. Consequently, a considerable number of sAML patients are judged unfit for standard ChT. The median survival of *de novo* AML for the total population in the United States was 4-11 months during 1980 through 2017 [23]. This was consistent with our result (median OS: 5 months). Survival of sAML is even poorer than that of *de novo* AML. In a Finnish Leukemia Group study, the majority of 14 MM patients died within 2 months of secondary acute leukemia diagnosis [24]. Our study verified this result with a median OS of 2 months after sAML diagnosis.

The poor prognostic value of age in sAML has been confirmed in a population-based study. This real-world data also revealed that standard intensive ChT improves early death rates and long-term survival compared with palliation among sAML patients [25]. However, MM patients with sAML, often with poor performance status and profound cytopenia, may be less tolerable to intensified ChT and often need dose modification. Geriatric assessment has been shown to predict toxicities as well as OS following the use of intensive therapy in AML [26]. The spectrum of cytogenetic abnormalities in therapy-related AML is similar to *de novo* AML, but the incidence of high-risk cytogenetics, including a complex karyotype or deletion or loss of chromosomes 5 and/or 7, is considerably higher in therapy-related AML [8]. Patients with unfavorable cytogenetics may have poor outcomes despite the use of allogeneic HSCT [27]. Therefore, patients with a favorable karyotype, particularly with good performance status, should receive modified induction and consolidation ChT (allogeneic HSCT often ineligible) recommended for other *de novo* AML patients with similar characteristics. Patients with high-risk cytogenetics and frail, older patients may be better served with clinical trials rather than intensive therapy. In recent years, this patient population seemed to have achieved slight benefit from novel therapeutic options such as Venetoclax/Azacitidine, Venetoclax/Decitabine, and Enasidenib [28].

This study provides insight into the risk of sAML development at the population level. Large population studies are more generalizable to MM patients. However, limitations include a lack of records about clinical and pathological information, chemotherapy regimens, and radiation doses. We used period analysis in the above study to account for treatment-related factors; this was based on the approval of various agents to infer exposure. However, misclassification may be present.

In conclusion, this study reinforces the risk of sAML in younger and intensively-treated MM patients, especially with melphalan and lenalidomide. Patients with sAML have more poor prognoses compared with *de novo* AML and should enroll in clinical trials investigating novel therapeutic options.

Disclosure of conflict of interest

None.

Address correspondence to: Wenming Chen, Department of Hematology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China. Tel: +86-010-85231572; E-mail: 13910107759@163.com

References

[1] Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ and Thun MJ. Cancer statistics, 2005. CA Cancer J Clin 2005; 55: 10-30.

[2] Bladé J and Rosiñol L. Changing paradigms in the treatment of multiple myeloma. Haematologica 2009; 94: 163-166.

[3] Pulte D, Gondos A and Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. Oncologist 2011; 16: 1600-1603.

[4] Dong C and Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer 2001; 85: 997-1005.

[5] Curtis RE FD, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA and Fraumeni JF Jr (eds). New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute. NIH Publ; 2006.

[6] Costa LJ, Godby KN, Chhabra S, Cornell RF, Hari P and Bhatia S. Second primary malignancy after multiple myeloma-population trends and cause-specific mortality. Br J Haematol 2018; 182: 513-520.

[7] Poh C, Keegan T and Rosenberg AS. Second primary malignancies in multiple myeloma: a review. Blood Rev 2021; 46: 100757.

[8] Godley LA and Larson RA. Therapy-related myeloid leukemia. Semin Oncol 2008; 35: 418-429.

[9] Qian Z, Joslin JM, Tennant TR, Reshmi SC, Young DJ, Stoddart A, Larson RA and Le Beau MM. Cytogenetic and genetic pathways in therapy-related acute myeloid leukemia. Chem Biol Interact 2010; 184: 50-57.

[10] Warren S and Gates O. Multiple primary malignant tumors: a survey of the literature and a stastical study. Am J Cancer 1932; 16: 1358-1414.

[11] Mailankody S, Pfeiffer RM, Kristinsson SY, Korde N, Bjorkholm M, Goldin LR, Turesson I and Landgren O. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). Blood 2011; 118: 4086-4092.

[12] Razavi P, Rand KA, Cozen W, Chanan-Khan A, Usmani S and Ailawadhi S. Patterns of second primary malignancy risk in multiple myeloma patients before and after the introduction of novel therapeutics. Blood Cancer J 2013; 3: e121.

[13] Ailawadhi S, Swaika A, Razavi P, Yang D and Chanan-Khan A. Variable risk of second primary malignancy in multiple myeloma patients of different ethnic subgroups. Blood Cancer J 2014; 4: e243.

[14] Musto P, Anderson KC, Attal M, Richardson PG, Badros A, Hou J, Comenzo R, Du J, Durie BGM, San Miguel J, Einsele H, Chen WM, Garderet L, Pietrantuono G, Hillengass J, Kyle RA, Moreau P, Lahuerta JJ, Landgren O, Ludwig H, Larocca A, Mahindra A, Cavo M, Mazumder A, McCarthy PL, Nouel A, Rajkumar SV, Reiman A, Riva E, Sezer O, Terpos E, Turesson I, Usmani S, Weiss BM and Palumbo A; International Myeloma Working Group. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol 2017; 28: 228-245.

[15] Sridharan A, Schinke CD, Georgiev G, Da Silva Ferreira M, Thiruthuvanathan V, MacArthur I, Bhagat TD, Choudhary GS, Aluri S, Chen J, Pradhan K, Xia Y, Panjikaran M, Sims G, Bhagat CK, Bender R, Keeler L, Graber A, Heuck C, Fletcher FA, Alapat D, Weinhold N, Johnson SK, Wickrema A, Barlogie B, Morgan GJ, Shastri A, Steidl U, Will B and Verma A. Stem cell mutations can be detected in myeloma patients years before onset of secondary leukemias. Blood Adv 2019; 3: 3962-3967.

[16] Palumbo AP, Delforge M, Catalano J, Hajek R, Kropff M, Petrucci MT, Yu Z, Mei JM and Dimopoulos MA. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older. J Clin Oncol 2011; 29 Suppl: abstr 8007.
[17] Chakraborty S, Hauke RJ, Bonthu N and Tarantolo SR. Increased incidence of a second lymphoproliferative malignancy in patients with multiple myeloma--a SEER based study. Anticancer Res 2012; 32: 4507-4515.
[18] Govindarajan R, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B and Tricot G. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. Br J Haematol 1996; 95: 349-353.
[19] Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, Gisslinger H, Wiktor-Jędrzejczak W, Zodelava M, Weisel K, Cascavilla N, Iosava G, Cavo M, Kloczko J, Bladé J, Beksac M, Spicka I, Plesner T, Radke J, Langer C, Ben Yehuda D, Corso A, Herbein L, Yu Z, Mei J, Jacques C and Dimopoulos MA; MM-015 Investigators. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012; 366: 1759-1769.
[20] Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, Stoppa AM, Hulin C, Benboubker L, Garderet L, Decaux O, Leyvraz S, Vekemans MC, Voillat L, Michallet M, Pegourie B, Dumontet C, Roussel M, Leleu X, Mathiot C, Payen C, Avet-Loiseau H and Harousseau JL; IFM Investigators. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1782-1791.
[21] Zhu YX, Braggio E, Shi CX, Kortuem KM, Bruins LA, Schmidt JE, Chang XB, Langlais P, Luo M, Jedlowski P, LaPlant B, Laumann K, Fonseca R, Bergsagel PL, Mikhael J, Lacy M, Champion MD and Stewart AK. Identification of cereblon-binding proteins and relationship with response and survival after IMiDs in multiple myeloma. Blood 2014; 124: 536-545.
[22] Juliusson G, Antunovic P, Derolf A, Lehmann S, Möllgård L, Stockelberg D, Tidefelt U, Wahlin A and Höglund M. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. Blood 2009; 113: 4179-4187.
[23] Sasaki K, Ravandi F, Kadia TM, DiNardo CD, Short NJ, Borthakur G, Jabbour E and Kantarjian HM. De novo acute myeloid leukemia: a population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980 to 2017. Cancer 2021; 127: 2049-2061.
[24] Acute leukaemia and other secondary neoplasms in patients treated with conventional chemotherapy for multiple myeloma: a Finnish leukaemia group study. Eur J Haematol 2000; 65: 123-127.
[25] Hulegårdh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Rangert Derolf Å, Möllgård L, Uggla B, Wennström L, Wahlin A, Höglund M, Juliusson G, Stockelberg D and Lehmann S. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish acute leukemia registry. Am J Hematol 2015; 90: 208-214.
[26] Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, Ellis LR and Powell BL. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood 2013; 121: 4287-4294.
[27] 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 and 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; 18: 963-971.
[28] Richardson DR, Green SD, Foster MC and Zeidner JF. Secondary AML emerging after therapy with hypomethylating agents: outcomes, prognostic factors, and treatment options. Curr Hematol Malig Rep 2021; 16: 97-111.