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REVIEW ARTICLE

VIA MEDICA

Therapy-related myeloid malignancies in patients with multiple myeloma

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Abstract

The significant advances in the efficacy of myeloma treatment in recent years have brought greater focus to the issues of long-term therapy complications. Therapy-related myeloid neoplasms are among the most severe secondary malignancies that can arise as a consequence of myeloma treatment. Although this complication is relatively rare, the prognosis for the small subset of patients who experience it is bleak. This review describes the incidence, pathogenesis, risk factors, and prognosis of acute myeloid leukemia and myelodysplastic neoplasms related to cytotoxic therapy in multiple myeloma patients.

Keywords: multiple myeloma, acute myeloid leukemia, myelodysplastic neoplasms, therapy-related neoplasms, lenalidomide

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Introduction

Emerging from terminally differentiated plasma cells, multiple myeloma (MM) is the second most common hematological malignancy worldwide, accounting for c.2% of all cancer deaths [1]. Each year in Poland, more than 2,000 people are diagnosed with MM. Recent advances in the field of myeloma therapy have led to unprecedented improvements in the prognosis for myeloma patients. Overall survival (OS) rates have doubled over the last two decades, with median OS exceeding 10 years for standard risk patients [2, 3]. These excellent results are expected to improve even further, with the widespread implementation of a 'quadruplet' induction regimen (containing an anti-CD38 antibody, a proteasome inhibitor, an immunomodulatory drug, and steroids) and the introduction of immunotherapy [chimeric antigen receptor T-cells (CAR-T) and bispecific antibodies] into earlier lines of treatment [4, 5]. The obvious consequence of these advances is the increased prevalence of myeloma patients in the general population. With longer survival, increasing attention is being paid to issues of survivorship, including quality of life and the long-term toxicities of anti-myeloma therapies [6, 7]. Among these late effects of treatment, second primary malignancies represent a group of serious complications, with therapy-related myeloid neoplasms being among the most serious. This review focuses on the incidence, risk factors, pathogenesis, and clinical implications of secondary myeloid malignancies in patients with multiple myeloma.

Myeloid neoplasms post cytotoxic therapy

Therapy-related acute myeloid leukemia (AML) represents a well-recognized hematopoietic stem cell malignant neoplasm which occurs as a late complication of DNA-damaging therapy administered for prior hematological malignancies, solid tumor or autoimmune disease [8, 9]. Together with myelodysplastic neoplasms post cytotoxic

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therapy (MDS-pCT) and MDS/ myeloproliferative neoplasms post cytotoxic therapy (MDS/MPN-pCT), AML post cytotoxic therapy (AML-pCT) constitutes a separate category of myeloid neoplasms post cytotoxic therapy (MN-pCT) according to the 2022 World Health Organization (WHO) classification [10]. The diagnostic criteria of MN-pCT are based on the criteria of AML, MDS and MDS/MPN with a previous history of treatment with chemotherapy and/or radiotherapy and/or poly-ADP-ribose polymerase 1 inhibitors (PARP1 inhibitors) [11]. Of note, methotrexate exposure has been excluded as a qualifying criterion of AML-pCT [10]. According to the International Consensus Classification guidelines (2022), AML after cytotoxic therapy should be described with the term "therapy-related" without forming a separate category [12]. In this review, we will use this latter nomenclature.

The increasing prevalence of therapy-related AML is a result of a growing number of patients surviving the primary malignancy [13–15]. Therapy-related AML accounts for up to 20% of all AML cases, and is generally considered as a subtype with an especially dismal prognosis, with estimated OS of 7–10 months [16–18], complete response rates of 30% [19], and shorter time of response after consolidation therapy than *de novo* AML [20]. Importantly, the median OS within therapy-related myeloid neoplasms patients after allogenic hematopoietic cell transplantation (alloHCT) has been estimated to be 14.6 months, with therapy-related MDS also associated with a dismal prognosis [21]. Breast cancer (among solid tumors) and non-Hodgkin's lymphoma (among hematological neoplasms) represent the most frequent primary malignancies preceding therapy-related AML [15].

Unique clinical and biological features distinguish therapy-related AML from *de novo* AML. Median age at diagnosis is 61 years [22]. Median time to develop AML after prior cytotoxic therapy is 63 months [23] and varies by cytotoxic agent. Prior radiotherapy and/or chemotherapy damage not only selectively the tumor cells, but also the DNA of normal cells, triggering mutagenic changes. Mutagenic damage is provoked by prior treatment with alkylating agents (e.g. melphalan, cyclophosphamide, chlorambucil, busulfan, carboplatin, cisplatin, nitrogen mustard, dacarbazine, procarbazine, carmustine, mitomycin, thiotepa, and lomustine), topoisomerase II inhibitors (e.g. etoposide, teniposide, doxorubicin, daunorubicine, amsacrine, mitoxantron, and actinomycin), radiation therapy, antimetabolites (e.g. mycophenolate mofetil, metothrexate, and fludarabine) or antitubuline agents (e.g. vinblastine, vincristine, vindesine, paclitaxel, and docetaxel).

A number of factors have been associated with the poorer prognosis of therapy-related AML: unfavorable karyotype, older age, low performance status, exposure to radiotherapy, alkylating agents and topoisomerase II inhibitors, the presence of certain mutations, and poor bone marrow reserve [24, 25]. It has been estimated that patients who receive chemotherapy are at a 4.7-fold increased risk for AML when to the general population [14]. Moreover, 10 years after chemotherapy exposure, the excess absolute risk of developing AML, when compared to the general population, is 5.8/1,000 for non-Hodgkin's lymphoma and 2.15/1,000 for breast cancer [14].

Therapy-related AML is driven by several complex mechanisms including: (a) genome instability; (b) pro-inflammatory and pro-leukemic bone marrow environment after exposure to cytotoxic agents; (c) direct induction of a fusion oncogene through chromosomal translocation; and (d) selection of pre-existing treatment-resistant hematopoietic cell clones [26, 27]. Therapy-related AML is characterized by the presence of unfavorable cytogenetic abnormalities, complex karyotype and high frequency of *TP53*, *DNMT3A*, *FLT3*, *NPM1* and *NRAS* mutations [28, 29].

Genes most frequently mutated and involved in the pathogenesis of this entity can be grouped into different functional classes: (a) transcription regulators (*RUNX1*, *TP53*), (b) signaling pathways regulators (*FLT3*), (c) RNA spliceosome machinery regulators (*SRSF2, SF3B1, U2AF1*), and (d) epigenetic regulators (*ASXL1, DNMT3A, EZH2, IDH1/IDH2, TET2*) [30–32]. Less frequent mutations involve DNA-damage response genes, requiring work-up for germline predisposition.

Management strategy in therapy-related AML should be adjusted to the patient's medical fitness and cumulative toxicity from prior cytotoxic therapy. Importantly, due to a distinct pathophysiology compared to *de novo* AML, therapy-related AML patients are often disqualified from clinical trials, making the treatment of this disease even more difficult [29, 33].

Conventional chemotherapy as an induction regimen in therapy-related AML patients has achieved a median OS of 6 months [25]. CPX-351 represents a liposomal drug combination of cytarabine and daunorubincin and has been recently approved by the US Food and Drug Administration for newly diagnosed therapy-related AML and AML myelodysplasia-related. In a randomized phase III trial, in which CPX-351 was compared to a standard chemotherapy with daunorubicine and cytarabine '3 + 7', median OS equaled 9.3 and 5.9 months, respectively [34]. AlloHCT represents the only curative approach in therapy-related AML. In a phase III study, 3-year OS within alloHCT recipients after CPX-351 vs. standard chemotherapy '3 + 7' was 56% vs. 23%, respectively [35].

Lower-intensity therapies can also be applied in therapy-related AML patients ineligible for intensive treatment. Many drugs have been evaluated in this setting, such as azacitidine, venetoclax in combination with azacytidine, decitabine, venetoclax on its own, low-dose cytarabine, nivolumab, dasatinib, aprenetapopt, eprenetapopt magrolimab, and flotetuzumab [36–44].

Incidence and risk factors of therapy-related myeloid neoplasms in patients with multiple myeloma

Firstly, it is worth noting that the risk of myeloproliferative neoplasms, MDS or AML is increased even in individuals with monoclonal gammopathy of undetermined significance (MGUS), irrespective of eventual progression to overt MM or subsequent treatment.

A Swedish register study reported an 8-fold increased risk of myeloid malignancies for people with MGUS compared to the general population [45]. This increased risk, although at a lower magnitude and predominantly for MDS, was also seen in a large MGUS screening study performed at the Mayo Clinic [46]. This suggests a possible role of intrinsic factors associated with immune alterations present even in premalignant plasma cell disorders [47]. Importantly, the risk of MDS/AML was higher in individuals with MGUS with a monoclonal protein concentration over 1.5 g/dl.

The first case report on the development of AML in four patients treated for myeloma was presented more than 50 years ago [48]. Since then, much has changed in the MM treatment paradigm, which is also reflected in the changing rates of therapy-related myeloid neoplasms. Population-based studies conducted prior to the introduction of immunomodulatory agents (IMiDs) documented standardized incident rates for therapy-related MDS/AML ranging from 6.5 to 8.5 [49, 50]. Notably, the risk of AML decreased from a 12-fold excess in patients diagnosed in 1973–77, to a 4-fold excess among those diagnosed in 2000–2008 [51]. A recent population-based study, utilizing the SEER (Surveillance, Epidemiology, and End Results) database, showed that median time from myeloma diagnosis to therapy-related AML equaled 56 months. The same study assessed the incidence of therapy-related AML in the novel agents era (2003–2018) to be 0.15%, compared to 0.26% in the previous period (1975–2002) [52]. This reduction is attributed to the decline in prolonged use of alkylating agents (i.e. melphalan) in first line therapy. Risks associated with exposure to particular anti-myeloma drugs are discussed in the next section.

It is hypothesized that a significant proportion of the therapy-related myeloid neoplasms emerge in the context of clonal hematopoiesis of indeterminate significance (CHIP) [53, 54]. CHIP refers to recurrent somatic mutations, present usually in a small fraction of cells detected in the peripheral blood of otherwise healthy individuals [55]. It is associated with a 0.5–1% risk of progression to AML or MDS and higher all-cause mortality, attributed mostly to the increased risk of cardiovascular events. CHIP incidence increases with age, and it is present in more than 10% of individuals older than 70 [56]. In the context of cytotoxic therapy, hematopoietic stem cells harboring clonal hematopoiesis (CH) mutations may gain a survival advantage that leads to expansion of these clones [57]. Those with particularly deleterious mutations such as *TP53* or *PPM1D* may further evolve into myeloid neoplasms with confirmed clonal relationship or help shape the genomic microenvironment to promote leukemogenesis [58]. That being said, the impact of CH on the risk of therapy-related myeloid neoplasms among patients with multiple myeloma is not yet fully understood.

As myeloma affects predominantly older patients, CH is very common, detected in 20–30% of patients in this population at diagnosis [59]. However, this high incidence is not only age-dependent, as MM can drive CH through interplay with the bone marrow microenvironment [60]. The biggest analysis published to date, by Mouhieddine et al. [59], evaluated CH among 629 patients treated with autologous hematopoietic stem cell transplantation (autoSCT). Hematopoiesis was detected in 21.6% of patients and was associated with impaired stem cell mobilization. Similarly to other studies, the most frequently mutated genes included *DNMT3A*, *TET2*, *TP53*, and *ASXL1*. Intriguingly, the presence of CH correlated with inferior OS and progression-free survival (PFS), but only in patients who had not received lenalidomide-based maintenance. Notably, rates of therapy-related MDS/AML did not differ between patients harboring CH clones and those without them. Similarly, there is contradictory data regarding the potential evolution of preleukemic clones after autoSCT. Some studies have confirmed the clonal relationship between CH and subsequent myeloid neoplasms, whereas others have not [61, 62]. Future studies are needed to establish the impact of CH, likely with a distinction between different mutated genes, on the risk of therapy-related myeloid neoplasms in multiple myeloma.

Impact of specific antimyeloma treatment on risk of therapy-related myeloid neoplasms

Two classes of drugs routinely used in myeloma therapy are associated with an increased risk of therapy-related myeloid neoplasms: alkylators (i.e. melphalan) and IMiDs (i.e. lenalidomide). Other widely used anti-myeloma drugs, such as proteasome inhibitors and anti-CD38 antibodies, do not appear to increase this risk. Rates of therapy-related MDS and AML in the key studies of modern agents are set out in Table I.

The alkylating action of melphalan, directly affecting not only malignant myeloma cells, but also hematopoietic stem cells, is responsible for the increased incidence of myeloid malignancies associated with the use of this drug [63]. A specific mutational signature, characteristic for melphalan exposure, has recently been described in myeloma patients [64]. Historical data clearly shows that prolonged use of melphalan is associated with

Table I. Summary of incidence of myeloid neoplasms reported in key studies of novel agents

	Phase	Design	Treatment arm	Group count	Median F-U	SPM Overall	Hematological SPM			Ref.
							AML	MDS	Other	
Determination NCT01208662	III	NDMM TE: RVd vs. RVd + ASCT with R maintenance in both arms	RVd	357	76 months	44	0	0	ALL – 7 CLL – 1 CML – 1	[71]
			RVd + ASCT	365		44	4	6	ALL – 3	
IFM2009 NCT01191060	III	NDMM TE: RVd vs. RVd + ASCT with one year of R maintenance in both arms	RVd	350	44 months	26	1	1	0	[70]
			RVd + ASCT	350		31	4	1	0	
CALBG 100104 NCT00114101	III	NDMM TE: R maintenance or placebo following ASCT	R	231	91 months	31	6	5	ALL – 6 HL – 1 WM – 1	[89]lenalidomide versus placebo after autologous stem-cell transplantation (ASCT)
			Placebo crossover to R	86		8	0	1	ALL – 2	
			Placebo no crossover	143		4	0	0	0	
IFM2005-02 NCT00430365	III	NDMM TE: R maintenance or placebo following ASCT	R	306	45 months	26	AML or MDS 5		ALL – 3 HL – 4 NHL – 1	[74]
			Placebo	302		11	AML or MDS 4		NHL – 1	
Myeloma XI NCT01554852	III	NDMM TE and TNE: R used at induction and maintenance	TE no R exposure	701	55 months for TE 46 months for TNE	11	0	1	DLBCL – 1	[76]
			TE single R exposure	1263		36	1	5	ALL – 1	
			TE double R exposure	568		47	4	6	DLBCL – 2 BL – 1 CML – 1 HL – 1	
			TNE no R exposure	677		18	1	0	0	
			TNE single R exposure	899		60	2	1	0	
			TNE double R exposure	260		47	1	1	Acute leukemia (mixed phenotype) – 1	

Table I (cont.). Summary of incidence of myeloid neoplasms reported in key studies of novel agents

	Phase	Design	Treatment arm	Group count	Median F-U	SPM Overall	Hematological SPM			Ref.
							AML	MDS	Other	
First NCT00689936	III	NDMM TNE: Rd vs. MPT	Rd until progression	532	67 months	36	1	2	ALL — 1	[66]
			Rd for 72 weeks	540		38	1	1	0	
			MPT for 72 weeks	541		46	5	5	MDS/AML — 4	
MAIA NCT02252172	III	NDMM TNE: DRd vs. Rd	DRd	364	56 months	74	1	N.R.	NHL — 2 DLBCL — 2 MCL — 1	[67]
			Rd	365		46	0	N.R.	DLBCL — 1 ALL — 1	
CARTITUDE-1 NCT03548207	I/IIb	RRMM: Cilta-cel	Cilta-cel	97	28 months	20	3	6	NHL — 1	[81]
CARTITUDE-4	III	RRMM: Cilta-cel vs. PVd or DPd	Cilta-cel	208	16 months	9	1	1	NHL — 1	[4]
			PVd/DPd	208		14	0	0	0	
KarMMa-3 NCT03651128	III	RRMM: Ide-cel vs. SOC	Ide-cel	225	19 months	13	1	3	0	[82]
			SOC	126		5	0	0	0	

ALL — acute lymphoblastic leukemia; AML — acute myeloid leukemia; ASCT — autologous stem cell transplantation; BL — Burkitt's lymphoma; Cilta-cel — ciltacabtagene autoleucel; CLL — chronic lymphocytic leukemia; CML — chronic myelogenous leukemia; DLBCL — diffuse large B-cell lymphoma; DPd — daratumumab, pomalidomide, dexamethasone; DRd — daratumumab, lenalidomide, dexamethasone; F-U — follow up; Ide-cel — idecabtagene vicleucel; MCL — mantle cell lymphoma; MDS — myelodysplastic neoplasms; MPT — melphalan, prednisone, thalidomide; NDMM — newly diagnosed multiple myeloma; NHL — non-Hodgkin's lymphoma; N.R. — not reported; pCT — post-cytotoxic therapy; PVd — pomalidomide, bortezomib, dexamethasone; R — lenalidomide; Rd — lenalidomide, dexamethasone; RRMM — relapsed/refractory multiple myeloma; RVd — lenalidomide, bortezomib, dexamethasone; sAML — secondary acute myeloid leukemia; sMDS — secondary myelodysplastic syndrome; SOC — standard of care; TE — transplant-eligible; TNE — transplant non-eligible; WM — Waldenström's macroglobulinemia

a high incidence of AML, reaching 17% at 50 months [65]. This has been further confirmed by recent data from phase III randomized clinical trials. In the FIRST trial, which enrolled transplant-ineligible patients with newly-diagnosed multiple myeloma, patients assigned to a control arm with melphalan-prednisone-thalidomide (MPT) experienced much higher rates of therapy-related myeloid neoplasms than did those randomized to lenalidomide-based, melphalan-free arms (14/541 vs. 3/532 vs. 2/540; [66]). Importantly, the incidence of therapy-related MDS and AML in this population remains low with the addition of daratumumab to the lenalidomide and dexamethasone backbone, as recently shown by the MAIA trial (1/364; [67]). Currently, melphalan use is mostly restricted to the high dose therapy preceding autoSCT. With such short exposure, the mutagenic impact of melphalan does not appear to be deleterious. In a Center for International Blood and Marrow Transplant Research registry analysis, which included 4,566 patients transplanted between 1995 and 2010 (who would not be expected to have received lenalidomide maintenance) the cumulative 10-year incidence of AML or MDS equaled 3% [68]. A study of the California Cancer Registry showed a 1.3% absolute increase in therapy-related myeloid malignancies for myeloma patients who had received autoSCT compared to those who had not, corresponding to a hazard ratio of 1.51 [69]. In the randomized phase III IFM-2009 study of lenalidomide, bortezomib, dexamethasone with or without autoSCT in newly diagnosed multiple myeloma, the incidence of therapy-related MDS/AML was numerically higher in the transplant group (5/350) than in the non-transplant group (2/350) [70]. The same observation was confirmed in the similarly designed DETERMINATION trial, where no myeloid malignancies were reported in the non-transplant group compared to 10/365 patients treated in the auto-SCT arm [71].

Lenalidomide maintenance after autoSCT is the current standard of care for eligible patients. In the pivotal phase III trials that established lenalidomide's role in the post-transplant setting, the rates of myeloid malignancies were higher in the treatment arms than in the placebo groups [72–74]. This was further confirmed in the meta-analysis of these trials, with a hazard ratio for secondary hematologic malignancies equaling 2.03 in the lenalidomide group [75]. Interesting data on therapy-related myeloid neoplasms after lenalidomide maintenance was recently published as a secondary analysis of the Myeloma XI study [76]. In this large, phase III randomized trial, lenalidomide was used as induction and maintenance in both transplant-eligible and transplant-ineligible patients with newly diagnosed MM. The study evaluated 2,532 patients in the transplant-eligible group and 1,825 in the transplant-ineligible group. Rates of therapy-related myeloid neoplasms after c.50 months of follow-up were relatively small. Sixteen cases of therapy-related MDS/AML were reported in transplant-eligible patients who received lenalidomide, compared to only one case among those patients who did not receive lenalidomide. In the transplant-ineligible group, the respective numbers of cases equaled five and one.

These observations add an important piece to the jigsaw of what is currently known about the risk of therapy-related myeloid neoplasms after autoSCT and lenalidomide maintenance. The risk is undoubtedly increased, but fortunately this complication remains very rare. Nevertheless, for patients on lenalidomide maintenance, International Myeloma Working Group experts recommend a low threshold for conducting a careful bone marrow examination in cases of unexplained cytopenias [77].

The mechanisms of leukemogenesis after lenalidomide exposure are probably multifactorial. The immunomodulatory effect of this drug may play an important role [78], but another interesting mechanism has recently been described [79]. Lenalidomide causes degradation of the essential transcription factors IKZF1 and IKZF3. Unlike pomalidomide, which has not been associated with an increased risk of myeloid malignancies, lenalidomide also promotes the degradation of CK1α. Suppression of CK1α induces p53-mediated apoptosis. Therefore, lenalidomide treatment may select *TP53* mutated clones which possess a survival advantage over normal hematopoietic stem cells in the setting of lenalidomide exposure. This explanation is in line with the hypothesis regarding the development of therapy-related myeloid neoplasms in the context of CH.

Among the most promising therapeutic agents recently approved for the treatment of multiple myeloma are CAR-T and bispecific antibodies [80]. Given the relatively short period of observation with these novel types of immunotherapies, it is difficult to assess their impact on the risk of developing therapy-related myeloid neoplasms. In the pivotal CARTITUDE-1 study of the anti-BCMA CAR-T cilta-cel, AML or MDS were reported in 9/97 evaluated patients, raising concerns about potential harm associated with this type of therapy [81]. Nevertheless, this was a heavily pretreated population, experiencing unprecedented survival. This is why, with a phase II single arm design, it was impossible to assess the direct impact of the CAR-T product on the observed incidence of therapy-related AML or MDS. Reassuringly, results from phase III studies of both approved anti-BCMA CAR-T products (cilta-cel and ide-cel) did not show any worrying sign of an increased incidence of myeloid malignancies among patients who received CAR-T compared to the standard of care [4, 82]. Phase II studies of the approved bispecific antibodies (elranatamab, teclistamab, talquetamab) did not report any cases of secondary malignancies [83–85]. Longer follow up is definitely needed to thoroughly assess the risk of therapy-related AML or MDS associated with these novel immunotherapies. However,

at the moment, it appears safe to say that the risk-to-benefit ratio is favorable.

Outcomes

It is very important to underscore that even considering the numerically higher incidence of therapy-related myeloid neoplasms after autoSCT or lenalidomide maintenance, the benefits of these treatment modalities clearly outweigh the risks.

In particular, the OS benefit associated with lenalidomide maintenance is not negated by the impact of secondary malignancies. Risk of death from myeloma progression is higher than any other competing risk, even among patients with long remission after autoSCT [86]. Yet that being said, unfortunately the prognosis of MM patients with therapy-related MDS/AML remains dismal. Therapy-related myeloid neoplasms in the course of multiple myeloma are not exempt from the general characteristics of this group of malignancies. Patients often present with the features of high risk disease, including *TP53* mutations and complex karyotype [87, 88]. Recent retrospective analyses from the Mayo Clinic and the MD Anderson Cancer Center have shown a median OS in these patients of only 12 months, with similar survival for AML and MDS [87, 88]. Slightly better results were seen in alloHCT recipients, although long-term remissions were achieved in only a small subset of patients.

Conclusions

Therapy-related myeloid malignancies are very rare complications of myeloma therapy. However, when individual cases occur, the diagnosis can be devastating, with very few effective treatment options. Currently, there is no justification to change treatment based solely on the risk of myeloid malignancies. Physicians should remain alert to the possibility of this complication, and thoroughly evaluate cytopenias in patients with multiple myeloma.

Hopefully, in the future, with an increasing understanding of the biology of therapy-related myeloid neoplasms, we will be able to better assess the individual risk of this complication and potentially tailor therapy to minimize it in selected cases.

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