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Therapy-related myeloid neoplasms after treatment for plasma-cell disorders

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ABSTRACT

Therapy-related myeloid neoplasms (t-MN), including therapy-related acute myeloid leukaemia and myelodysplastic syndrome, are second primary malignancies (SPM) that are of growing importance as patients with plasma cell disorders (PCD) such as multiple myeloma (MM) are living longer with more effective therapies. Both patient-specific and treatment-specific factors likely impact the risk of t-MN development after diagnosis and treatment of PCD. Alkylating chemotherapy, especially melphalan, has been strongly tied to the risk of t-MN. More recently, there has been a shift away from long-term alkylating therapies to immunomodulatory agents and high-dose therapy with autologous stem cell transplant (HD-ASCT). This shift has led to improved survival and long-term outcomes for most MM patients. However, the risks of t-MN remain despite the improved efficacy of these treatments, and patients who develop t-MN have a poor prognosis. Understanding the risk factors predisposing MM patients to t-MN can thus help to tailor individualized therapy to maximize anti-myeloma efficacy and minimize the risks of t-MN.

1. Introduction

The association between plasma cell disorders (PCD) and myeloid malignancies was first identified in the 1970s, when Rosner et al. reported a case series of patients with multiple myeloma (MM) developing acute myeloid leukaemia (AML) [1]. Chemotherapy used in the treatment of MM, particularly alkylating agents, were postulated to be potential contributors [1–3], after previous studies had demonstrated the association of cytotoxic agents and development of therapy-related myeloid neoplasm (t-MN) in various malignancies [4,5]. Further supporting this, Cuzick et al. demonstrated an increased incidence of myelodysplastic syndrome (MDS) and AML with the use of melphalan for treatment of MM, with a 5-year cumulative incidence of 3% and 8-year cumulative incidence of 10% [6].

Cytotoxic chemotherapy consisting of vincristine, adriamycin and dexamethasone as well as melphalan remained the backbone of myeloma treatment until the late 1990s, when the use of high-dose therapy with autologous stem cell transplant (HD-ASCT) and the development of immunomodulatory agents became treatment options for MM. As these options have changed the landscape of MM treatment, patients are now living longer, and the long-term toxicities of therapies are becoming more important. Second primary malignancies (SPM) have been an area of focus, with the first large registry studies conducted by the Finnish Leukaemia Group and the Swedish Family-Cancer Database showing a significantly increased incidence of AML in MM patients compared to the general population, with risk of up to 9.8% at 9 years from first chemotherapy [7,8]. Further studies have shown an SPM rate of about 5–7%, which is slightly above the baseline population rate. However, the majority of these studies demonstrated a higher than expected rate

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of haematological SPM, particularly AML and MDS, at around 1–2% (1.5–2 times the expected rate), and for AML, more than 5 times the expected rate, suggesting a true increase in t-MN after MM treatment [7–16]. Patients who developed SPM and t-MN had a worse survival [17–20], as highlighted by Jonsdottir et al., where MM patients with AML/MDS had a 8.5-fold increase risk of death compared to matched MM patients without a SPM and a 1.7-fold increased risk of death compared to matched patients with de novo AML/MDS [18].

Given this, there has been increased interest in understanding the factors that predispose MM patients to developing SPM and t-MN. Host-susceptibility factors as well as treatment-related factors appear to be important contributors [10,21]. As MM treatment has evolved, the role of immunomodulatory treatments and HD-ASCT in the development of SPM and t-MN have become a centre of focus. The importance of this became evident after several landmark phase III trials demonstrated an increased risk of SPM in patients with myeloma treated with maintenance lenalidomide in both elderly/transplant-ineligible patients [22] and patients post HD-ASCT [23,24]. Nevertheless, these studies demonstrated a significant improvement of progression free survival (PFS) by 17 months for elderly/transplant-ineligible patients on lenalidomide maintenance [22] and by 18–19 months in patients treated with maintenance lenalidomide post-HD-ASCT [23,24], and thus have led to the widespread use of lenalidomide in the treatment of MM.

The impact of the increasing use of immunomodulatory therapy and the decreasing use of cytotoxic chemotherapy over time was explored in the US SEER 13 Registries by Costa et al. [25]. This study analysed three cohorts of MM patients: those diagnosed during 1995–99 (pre-thalidomide, limited use of HD-ASCT), 2000–04 (post-thalidomide, pre-lenalidomide and bortezomib, increased use of HD-ASCT), and 2005–09 (post-lenalidomide and bortezomib, highest use of HD-ASCT). As expected, all-cause mortality improved over time, suggesting that new treatments and supportive care are improving survival. However, cumulative incidence of SPM at 90 months significantly increased over the different eras, from 4.7% in 1995-99 to 6.3% in 2005–09. This was driven by an increase in haematological malignancies, with standardised incidence ratio (SIR) for haematological malignancies in years 1–5 after diagnosis rising from 1.28 in 1995–99 to 2.17 in 2005–2009 and similarly, rising from 3.02 to 4.45 in years 6–10 when comparing the 1995–99 to the 2000–2004 cohort. Table 1 summarizes several notable observational studies conducted over time focusing on SPM and t-MN in MM patients.

These findings emphasize the need to better understand the risk factors and therapy implications associated with the development of t-MN in patients with MM, especially given the extremely poor prognosis with t-MN. This review will discuss the current literature on risk factors associated with development of t-MN and highlight the association of different myeloma therapies with development of t-MN. Evidence-based management recommendations will also be proposed.

2. Patient/disease-specific risk factors

Only a small proportion of patients with MM will develop t-MN. There is likely a complex interplay between patient/disease-specific factors and treatment-induced changes that ultimately precipitate the development of t-MN, as illustrated in Fig. 1. Understanding these patient/disease-specific risk factors may help to identify patients who are at higher risk for development of t-MN.

Advanced age at diagnosis was correlated with increased risk of SPM in multiple studies [23,26–29]. The overall increase with age appears to be driven predominantly by secondary solid malignancies [27]. However, in a SEER analysis by Razavi et al., there was higher SIR for AML in patients diagnosed at age 65 or younger compared to those who were older across all 5-year intervals between 1973 and 2008 [30]. One possible hypothesis is that younger patients were treated more aggressively. In addition, older patients have been shown to have worse MM-related survival, and given the latency time before development of t-MN, older patients may have died before development of t-MN [16,17]. In contrast, for patients who underwent HD-ASCT, advanced age at transplantation was associated with increased risk of t-MN and SPM [26,31,32].

Polymorphisms and mutations in genes that affect DNA-repair and drug metabolism may also be important factors in the development of t-MN. Previous studies have demonstrated an enrichment in germline inherited cancer susceptibility genes involved in DNA repair, such as *BRCA1*, *BRCA2*, *TP53*, and *CHEK2*, in approximately 20% of patients with t-MN [33,34].

Prior malignancies may also have a role in the development of t-MN. Approximately 3–24% of MM patients were reported to have prior or synchronous malignancy at the time of MM diagnosis [9,16,17,29,35,36]. In addition to possible underlying genetic and environmental predispositions, patients with prior or synchronous malignancies may have previous exposures to chemotherapy and radiotherapy, which may further increase their risk for t-MN. Consistent with this, Jonsdottir et al. conducted a large population-based study which found that patients with prior malignancy had significant increased risk of developing a haematological SPM with a hazard ratio (HR) of 1.59 and 1.21-fold increase in death compared to MM patients without prior malignancy [36].

Factors intrinsic to PCD may impact the risk of developing subsequent t-MN as well. The reported increased risk of myeloid neoplasms in patients with monoclonal gammopathy of undetermined significance (MGUS) may suggest linkage between plasma cell and myeloid disorders independent of therapy-related factors. In a Swedish population-based study, Mailankody et al. reported an 8-fold increase in the risk of development of AML/MDS compared to age- and gender-matched controls in the general population. Higher risk was associated with IgG/IgA subtype compared to IgM and monoclonal protein > 1.5 g/dL. None of these MGUS patients developed MM following AML/MDS, which further supports the role for non-treatment-related factors in the subsequent development of AML/MDS after plasma cell dyscrasia [11]. Similarly, in a large Mayo Clinic cohort where patients were systemically screened for MGUS, Roeker et al. reported a 2-fold increase in the risk of developing AML/MDS in patients with MGUS compared to controls, primarily driven by increased risk of MDS [37]. Additionally, Korde et al. performed a prospective clinical study analysing the baseline bone marrow biopsies of 80 patients with untreated MGUS and SMM for early histopathological features and fluorescence in situ hybridization (FISH) abnormalities of myelodysplasia and found that 20% of these patients had abnormally high $CD34^+$ expression with increased dyspoietic morphologic features, which may suggest an increased susceptibility for clinical MDS

Table 1
Selected observational studies focusing on SPM and t-MN after MM.

Study	Study Type	Study Period	Patient Population	# of Patients	All SPM frequency (%)	Haematological SPM frequency (%)	Other key findings
Dong et al. [8]	Observational Registry Study	1958-1996	MM patients in Swedish Family-Cancer Database	8656	5.5	1	t-AML SIR: 8.19 (95% CI: 5.7-11.4) compared to general population.
Cuzick et al. [6]	Retrospective Study	1964-1975	MM patients treated with either cyclophosphamide or melphalan on clinial trial	648	Not assessed	1.9	t-MN: 5-year and 8-year actuarial rate of 3% and 10% respectively. Duration of melphalan use but not cyclophosphamide use associated with increased t-MN.
Finnish Leukemia Group [7]	Retrospective Study	1979-1985	MM patients treated on Finnish Leukaemia Group clinical trials	432	9.3	4	t-AML SIR: 45.6 ($p < 0.001$) compared to general population; actuarial rate of 9.8% at 9-years.
Jonsdottir et al. [18]	Observational Registry Study	1973-2010	MM patients in Swedish Family-Cancer Database	19791	7.4	1	Haematological SPM: HR 1.59 (95% CI: 1.04-2.42) for patients with prior malignancies compared to those without.
Razavi et al. [30]	Observational Registry Study	1973-2008	MM patients in the United States SEER 9 Database	36491	5.5	0.7	t-AML SIR: 6.51 (95% CI 5.42-7.83) compared to general population.
Mailankody et al. [11]	Observational Registry Study	1986-2005	MM patients in Swedish Family-Cancer Database;	8740	6.6	0.8	t-MN SIR: 11.51 (95% CI: 8.2 - 15.7) compared to general population.Median time to t-MN: 45.3 months.
Barlogie et al. [51]	Retrospective Study	1989-2007	MM patients treated with HD-ASCT at University of Arkansas	3077	Not assessed	0.8	10-year estimates for MDS-associated cytogenetic abnormaliteies observed transiently in 4% and persistently in 2%.
Krishnan et al. [28]	Retrospective Study	1989-2009	MM patient who underwent HD-ASCT at City of Hope Hospital	841	8.3	1.2	Cumulative incidence of t-MN: 1.0% at 5-years and 2.0% at 10-years.
Costa et al. [25]	Observational Registry Study	1995-2009	MM patients in the United States SEER 13 Database	9833	4.3	0.7	Haematological SPM 1995-99 year 1-5 SIR: 1.28 (95% CI: 0.47-2.7) compared to general population. Haemtological SPM 2005-09 year 1-5 SIR: 2.17 (95% CI: 1.27-3.48) compared to general population.
Engelhardt et al. [16]	Retrospective Study	1997-2011	MM patients treated at University of Freiburg	744	6.6	2.3	Cumulative t-MN rate: 1.6% Multivariate analysis: significant associations for IgG subtype (compared to non-IgG) with HR 2.55 (95% CI: 1.17-5.52) and bortezomib-use with HR 0.24 (95% CI: 0.07-0.81) for SPM development.
Hasskarl et al. [17]	Retrospective Study	1997-2008	MM patients treated at University of Freiburg	589	3.1	1.0	t-MN associated with worse survival with HR 3.4 (95% CI: 1.2-9.4) on multivariate analysis.
Usmani et al. [69]	Retrospective Study	1998-2009	MM patients treated in TT2, TT3A, and TT3B trials	1148	6.4	3.1	Age over 65 years and the presence of cytogenetic abnormalities associated with an increased incidence of

(*continued on next page*)

Table 1 (*continued*)

Study	Study Type	Study Period	Patient Population	# of Patients	All SPM frequency (%)	Haematological SPM frequency (%)	Other key findings
							SPM with HR 2.06 (p = 0.004) and HR 1.65 (p = 0.05) respectively.
Mahindra et al. [26]	Observational Registry Study	1990-2010	MM patients who underwent HD-ASCT in the CIBMTR registry	4161	3.9	1.1	Cumulative incidence of t-MN was 0.5% (95% CI: 0.28 -0.78%) at 3 years and 1.51% (95% CI: 0.97-2.16%) at 7 years. t-AML SIR: 5.19 (95% CI: 1.67-12.04) compared to general population.
Palumbo et al. [27]	Meta-analysis	2000-2012	MM patients treated on various phase 3 clinical trials	3218	3.3	1.1	Cumulative 5-year incidences of haematological SPM: 3.1% (95% CI: 1.9-4.3) in patients who received lenalidomide and 1.4% (0.0–3.6) in those that did not with HR 3.8 (95% CI: 1.15-12.62). Lenalidomide plus oral melphalan significantly increased haematological SPM versus melphalan alone with HR 4.86 (95% CI: 2.79-8.46). Lenalidomide plus cyclophosphamide and lenalidomide plus dexamethasone did not increase haematological SPM risk compared to melphalan alone.
Sahbei et al. [15]	Observational Registry Study	2008-2012	MM patients who underwent HD-ASCT and enrolled on CALM registry study	3204	4.2	0.9	Cumulative incidence of haematological SPM at 6-years: 1.4%.
Rifkin et al. [12]	Observational Registry Study	2009-2012	MM patients in the US-based Connect MM Registry	1450	4	1.2	Haematological SPM IR: 0.49 per 100 person-years. No difference in 3-year cumulative probability of haematological SPM between lenalidomide-treated (0.5%; 95% CI: 0.0-0.9%) and patients treated without lenalidomide (2.4%; 95% CI: 0.6-4.2%).

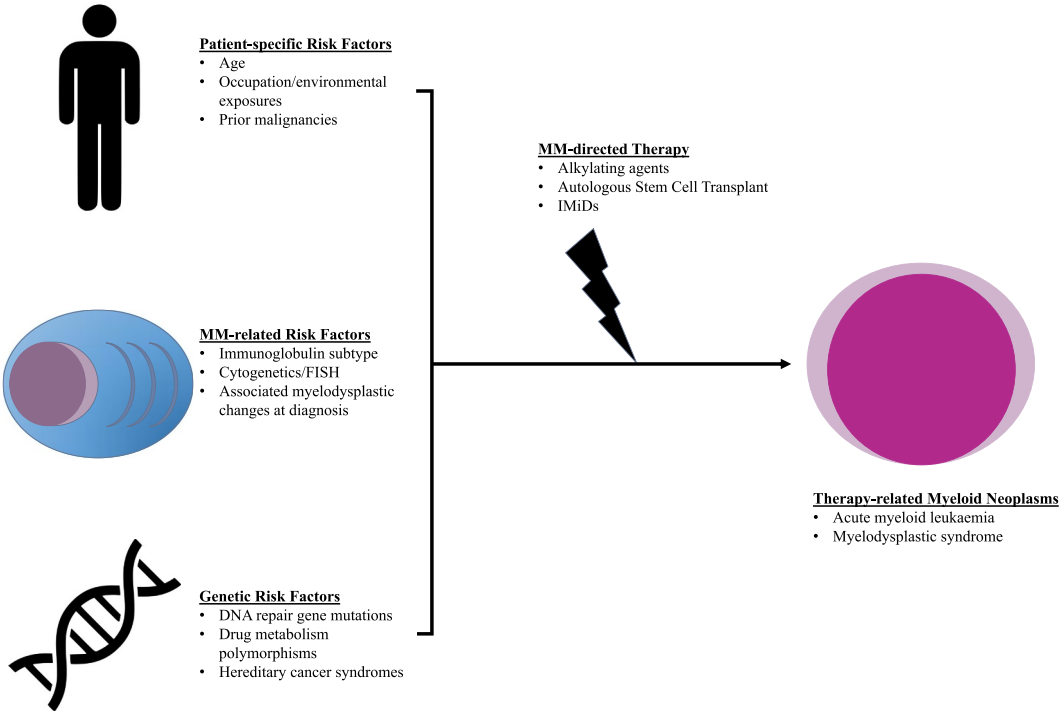

Fig. 1. Risk-factor schematic for the development of t-MN after MM.

[38]. Furthermore, Matarraz et al. reported on the presence of myelodysplasia-associated immunophenotypic alterations in the bone marrow of MM and smouldering MM patients by multi-parameter flow cytometry and found these present in approximately 47% of patients with symptomatic MM and 33% of smouldering MM patients [39]. Importantly, these immunophenotypic alterations at MM diagnosis also correlated with genetic/morphologic evidence of clonal haematopoiesis in myeloid lineage cells [40].

3. Alkylating agents

Despite the rise of novel immunomodulatory therapies, cytotoxic chemotherapy remains important for patients with PCD, especially in resource-limited settings. Much of our understanding regarding t-MN has been attained in the setting of alkylating agents and topoisomerase II inhibitors [34]. Melphalan and cyclophosphamide are two active and widely used agents for the treatment of PCD, and although they have similar mechanisms of action of disrupting DNA repair and replication via alkylation of DNA base pairs, they differ in their pharmacologic properties and as such may have different propensities for the development of t-MN.

3.1. Melphalan

Since the 1960s, melphalan has been utilized for the treatment of MM. Bergsagel et al. was first to report a significant increased risk of acute leukaemias of up to 17.4% after 50 months in patients treated with melphalan-based treatments [3]. Reddi et al. demonstrated that complex abnormalities and -5q/-7q cytogenetic abnormalities were present in 79% of their patients with MM and subsequent t-MN and this correlated directly with the use of melphalan-based chemotherapeutic regimens, with highest risk for combined melphalan-cyclophosphamide regimens. The median latency from myeloma treatment to t-MN was 60 months [41]. These findings are consistent with studies on t-MN in other malignancies after alkylator use [34].

Multiple studies have suggested that the duration of oral melphalan use may be associated with higher rates of t-MN. Prior to use of HD-ASCT and immunomodulatory agents, Cuzick et al. reported a significant relationship between length of melphalan treatment and development of t-MN with an additional 3% risk for development of t-MN at 10-years for every year of melphalan received [6]. Govindarajan et al. compared the rates of MDS after HD-ASCT in patients who were either treated with short courses of pre-transplant chemotherapy (median 7.6 months) versus longer courses of pre-transplant chemotherapy with alkylating agents (median 24 months) and found that all of the cases of post-transplant MDS were in the longer pre-transplant cohort [42]. Larger registry studies have had

differing results, with the Finnish Leukaemia Group showing similar cumulative doses of melphalan for MM patients who developed acute leukaemia compared to those who did not [7], whereas in the Swedish Cancer Registry, a higher mean cumulative dose of melphalan was associated with increased risk of developing t-MN [43].

The risk of SPM and t-MN also appears higher for patients treated with melphalan combination therapies, especially in combination with lenalidomide. The risk of melphalan combined with immunomodulatory therapies and in the setting of HD-ASCT will be discussed later.

3.2. Cyclophosphamide

Cyclophosphamide continues to be an important agent for myeloma therapy as both a direct cytotoxic agent against myeloma as well as a stem cell mobilizer for peripheral blood stem cell collection. Cyclophosphamide is thought to be a less stem cell-toxic alkylator compared to melphalan, with melphalan-use being associated with higher rates of inadequate stem cell collection for autologous transplant [44]. Cuzick et al. also suggested that cyclophosphamide may be less leukaemogenic than melphalan, as they observed no increased risk of t-MN in those treated with cyclophosphamide, whereas there was a duration-dependent increase in t-MN with melphalan [6]. In contrast to melphalan combinations, the risk of SPM and t-MN in patients treated with cyclophosphamide combinations for MM does not appear to be significantly increased. In a meta-analysis by Palumbo et al., the combination of lenalidomide plus cyclophosphamide did not appear to be associated with an increase in haematological SPM (HR 1.2 [95% CI 0.3–5.38]), whereas the combination of lenalidomide plus oral melphalan significantly increased the risk of haematological SPM (HR 4.86 [95% CI 2.79–8.46]) [27]. Several other trials have also not shown elevated SPM development in patients treated with cyclophosphamide [45,46].

4. High-dose therapy with autologous stem-cell transplant

For the past 20 years, HD-ASCT with intravenous melphalan conditioning has been a standard of care treatment option for younger patients with multiple myeloma after several large trials demonstrated significant improved PFS and overall survival (OS) when compared to chemotherapy alone [47,48]. However, observational studies and meta-analyses across haematological malignancies have shown an increased risk of SPM after autologous transplantation, particularly for the development of t-MN [31,32,49]. Further studies have been aimed at investigating this further in the MM population, but this has been challenging given the complex heterogeneity of treatments given prior to, at the time of, and after HD-ASCT. Although the exact mechanism of t-MN after HD-ASCT is unclear, there appears to be dynamic changes induced in the bone marrow after HD-ASCT with around 4–11% of patients developing either transient or persistent MDS associated cytogenetic abnormalities; patients with these changes had worse survival compared to those without, and up to 25% of these patients ultimately developed t-MN [50,51].

The five-year cumulative incidence of SPM after transplantation is estimated to be approximately 4–7% [14,15,25,26,28,45,52]. However, cumulative incidence regarding the development of t-MN appears to be changing over time with earlier studies demonstrating relatively high reported rates of t-MN of 3–12% [42,53] and more recent studies estimating a 5-year cumulative incidence closer to 0.5–2% [14,32,52,54], potentially due to the decreased utilization of oral melphalan prior to HD-ASCT. Although SPM rates in patients who underwent HD-ASCT were similar to the general population, several studies showed that for MM patients who underwent HD-ASCT, there was a 2–5-fold increase in the risk of haematological SPM when compared to the general population [25,26] and an approximately 2.6-fold increase when compared to MM patients who did not undergo HD-ASCT [14].

Given that melphalan is a key part of HD-ASCT and well-known contributor of t-MN, several studies attempted to identify whether there was an impact of melphalan given prior to HD-ASCT and/or as conditioning. Govindarajan et al. had reported increased rates of MDS in patients treated with longer courses of alkylating prior to HD-ASCT than shorter courses despite receiving the same HD-ASCT regimen, suggesting that pre-transplant therapy and not conditioning was a more important risk factor for t-MN [42]. Auner et al. compared the use of melphalan 140 mg/m^2 versus 200 mg/m^2 for HD-ASCT and found similar SPM rates of 4.8% at 5-years in both arms, again suggesting that conditioning may be less important in the risk of t-MN [55].

With the prolonged PFS achieved with maintenance lenalidomide after HD-ASCT, the role of maintenance therapy on t-MN may be even more important than the factors above given the extended duration on therapy and the cumulative risk of t-MN over time. The risk associated with maintenance lenalidomide will be further addressed in the next sections.

5. Lenalidomide

The exact mechanism by which lenalidomide and other IMiDs lead to SPM remains unclear. The anti-myeloma effects of IMiDs appear to be due to its interaction with cereblon, a protein that interacts with DDB1 and CUL4 to form an E3 ubiquitin-ligase. IMiDs bind to cereblon and stabilize E3 ubiquitin-ligase by preventing auto-ubiquitination. E3 ubiquitin-ligase is then able to help degrade IKZF1 and IKZF3, both important transcription factors involved in B- and T-cell development as well as plasma cell development and MM proliferation. DDB1 is a DNA damage binding protein that can also form a separate nucleotide excision repair complex involved in genome repair when bound with DDB2. Therefore, one hypothesis is that IMiDs may affect both ubiquitination, resulting in anti-myeloma efficacy, and DNA repair, potentially increasing susceptibility to alkylators in developing SPM [56].

5.1. Lenalidomide in transplant patients

Lenalidomide maintenance after HD-ASCT was shown to dramatically improve PFS to a median of 41–57 months compared to 23–29 months on placebo in two landmark trials: IFM2005-02 [23] and CALGB100104 [24,57]. A recent meta-analysis confirmed prolonged PFS (HR 0.48) and OS (HR 0.75) for lenalidomide maintenance over observation [58]. Based on these results, maintenance lenalidomide post-HD-ASCT has become a standard of care.

However, both the IFM2005-02 and CALGB100104 trials noted an increased SPM incidence in patients treated with lenalidomide relative to placebo. In IFM2005-02, the incidence of SPM was 3.1 per 100 patient-years in the lenalidomide arm versus 1.2 per 100 patient-years with placebo, and 13 of 306 patients in the lenalidomide arm versus 5 of 302 patients on the placebo arm developed haematological SPM with median follow-up of 45 months [23]. In CALGB100104, a cumulative incidence of 11.9% versus 3.1% was observed for SPM at 5-years, and 8 of 231 patients on lenalidomide versus 1 of 229 patients on placebo developed haematological SPM with median follow-up of 34 months [24,27]. At median follow-up of 91 months, 18 of 231 patients in the lenalidomide arm versus 3 of 229 patients in the placebo arm developed haematological SPM, although all 3 of these placebo arm patients had crossed-over to lenalidomide maintenance. The median time to development of haematologic SPM in the lenalidomide arm was 60.8 months [57].

Subsequently, Palumbo et al. conducted the largest meta-analysis to date focusing on the risks of SPM with lenalidomide use. Nine eligible trials were included with 3,218 patients analysed (2,620 received lenalidomide and 598 did not). The cumulative 5-year incidence of SPM was 6.9% for patients who received lenalidomide versus 4.8% for those who did not with HR 1.55. This was driven predominantly by haematological SPM with a 5-year cumulative incidence of 3.1% in lenalidomide-treated patients versus 1.4% for those that did not receive lenalidomide. On multivariate analysis, the combination of lenalidomide and oral melphalan was associated with statistically significant increase in risk of haematological SPM (HR 4.86) compared to melphalan alone, whereas exposure to lenalidomide plus cyclophosphamide and lenalidomide plus dexamethasone was not associated with increased risk compared to melphalan alone. Patients who underwent lenalidomide plus oral melphalan also had significantly higher risk of haematological SPM compared to those that received high-dose intravenous melphalan plus lenalidomide (HR 3.3). Multivariate analysis did demonstrate a slightly increased, but not statistically significant, risk of haematological SPM with exposure to lenalidomide plus intravenous melphalan compared to oral melphalan alone (HR 2.21). This may reflect the increased risk associated with HD-ASCT as patients exposed to intravenous melphalan presumably underwent HD-ASCT. These results suggest that risk of haematological SPM with lenalidomide may be significantly driven by prior or concurrent melphalan use, especially oral melphalan use and potentially from intravenous melphalan and HD-ASCT.

In the last two decades, melphalan-free immunomodulatory combinations with IMiDs and proteasome inhibitors have become a central part of induction regimens [24,59]. In recent trials that have excluded the use of oral melphalan, there appears to be a lower rate of SPM including the largest trial to date, the Myeloma XI trial, which showed a 3-year cumulative incidence of 2.7% for SPM and 0.7% for haematological SPM, although the trial did continue to show higher rates of SPM in the lenalidomide maintenance group compared to observation in HD-ASCT patients [54]. This persistent increase in risk with lenalidomide maintenance suggests that there is likely an intrinsic increased risk associated with lenalidomide and HD-ASCT, which is distinct from oral melphalan use.

Although the majority of clinical trials have reported an increase in SPM and t-MN with lenalidomide maintenance compared to without, other studies, particularly some registry and retrospective studies have not confirmed this. For example, Jagannath et al. reported a SPM rate of 1.38 versus 2.19 events per patient-years with lenalidomide maintenance versus no maintenance post-ASCT in the Connect MM Registry, the largest prospective non-interventional US-based newly-diagnosed MM registry. For haematological SPM, the event rate was slightly higher in the lenalidomide group versus no maintenance, but these numbers were small (0.82 versus 0.21 events per patient-years) [13]. Limitations of these observational studies include nonrandomised data and variability in collection and availability of data, but nevertheless, these results suggest that rates of SPM and t-MN are relatively low in the real-world setting.

5.2. Lenalidomide in transplant-ineligible and elderly patients

In the non-transplant setting, lenalidomide also has considerable efficacy and continues to be an important treatment for newly-diagnosed MM. This was first established in MM-015 trial, which found that patients treated with melphalan-prednisone-lenalidomide (MPR) with lenalidomide maintenance had significantly improved median PFS at 31 months compared to 14 months with MPR without lenalidomide maintenance and 13 months with melphalan and prednisone alone [22]. However, similar to IFM2005-02 and CALGB100104 for HD-ASCT, an increase in SPM was noted with 3-year SPM rates of 7% for patients treated with lenalidomide and 3% for those without, including haematological SPM of 5% versus 1% with most of these being t-MN [22,27]. The concurrent use of melphalan and lenalidomide was implicated as the cause of the higher SPM rates.

Subsequently, further trials have been conducted with lenalidomide in the absence of melphalan. The FIRST trial randomized transplant-ineligible newly diagnosed MM to either lenalidomide and dexamethasone (Rd) continuously until disease progression; Rd for 18 cycles; or melphalan, prednisone, and thalidomide (MPT) [60,61]. Rd continuously was shown to have superior PFS and OS, with median OS that was 10 months longer compared to MPT (59.1 vs 49.1 months). Five-year cumulative incidence of haematological SPM was higher with MPT compared to Rd with rates of 3% vs 1%, with overall SPM 9% versus 7% respectively, which was consistent with the meta-analysis by Palumbo et al. which found no increased risk of haematological SPM with lenalidomide plus dexamethasone compared to melphalan alone [27]. More recently, in the transplant-ineligible arms of the Myeloma XI trial, the risk of SPM with lenalidomide maintenance was noted to be higher than with observation (12.9% vs. 6.3%), but this was not statistically

significant, and older age appeared to confer greater risk. The 3-year haematological SPM incidence however, was very low at 0.2% [54]. Of note, all patients in Myeloma XI trial were exposed to cyclophosphamide, and although it has been previously shown that cyclophosphamide is less toxic to haematopoietic stem cells, there remains a possibility that it may have a synergistic role with lenalidomide in driving SPM and t-MN.

With regards to t-MN, maintenance lenalidomide in the non-transplant setting does not appear to substantially increase the risk of t-MN, especially when used without alkylator exposure and HD-ASCT. More recent combinations use lenalidomide in combination with proteasome inhibitors in lieu of alkylating agents, and these combinations will be discussed next.

6. Bortezomib

Bortezomib and other proteasome inhibitors have excellent anti-myeloma activity and are used as first-line agents throughout the world for both transplant-eligible and -ineligible patients. Several trials have assessed the efficacy of bortezomib and also reported on the risk of SPM and t-MN. The VISTA trial demonstrated a significant OS benefit with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) with median OS of 56.4 versus 43.1 months. The overall exposure-adjusted incidence rates for all SPM was 1.7 versus 1.3 per 100 patient-years and 0.26 versus 0.3 per 100 patient-years for haematological SPM for VMP and MP respectively, similar in both arms [62]. The SWOG S0777 trial similarly found that the addition of bortezomib to lenalidomide and dexamethasone (VRd) was superior to Rd alone, with median OS improving from 64 to 75 months. At median follow-up of 55 months, there were 4% SPM in both arms and 0.4% cumulative incidence of haematological SPM for VRd versus 0.8% for Rd [63].

In fact, several studies have suggested that bortezomib may actually be protective against SPM and t-MN. Brioli et al. reported in a phase III trial that the combination of bortezomib, thalidomide, and dexamethasone (VTD) was associated with a significant lower 6-year incidence rate of SPM (6% versus 13%) and haematological SPM rates (1% versus 4%) when compared to thalidomide and dexamethasone (TD) [64]. In a large registry analysis, Engelhardt et al. found a decreased SPM rate in patients treated with bortezomib with HR of 0.24 in a multivariate analysis [16].

These studies suggest that there is no clear increased risk of SPM or t-MN with the use of bortezomib. Studies in the post-transplant setting as maintenance also have not revealed evidence of increased SPM or t-MN [65–68].

7. Other agents

It has been suggested that thalidomide may also increase the risk of SPM and t-MN [28,50]. However, its risk compared to lenalidomide has been difficult to determine, but appears to be relatively similar or slightly less [69]. For other agents including pomalidomide, carfilzomib, ixazomib, elotuzumab, and daratumumab, long term SPM data is not yet available although in each of their landmark studies, there was no significant increase in SPM compared to the control arm [9].

8. Treatment strategies to minimize risk of therapy-related myeloid neoplasms

With the growing armamentarium of treatment options available for MM and other plasma cell neoplasms, the appropriate selection of treatments that maximize efficacy and minimize long-term toxicities for individual patients are of increasing importance. Fig. 2 outlines an algorithm that accounts for the risks of t-MN when making treatment decisions.

9. Summary

With patients living longer, therapy-related myeloid disorders are becoming more recognized as long-term complications of plasma cell neoplasms and their treatments. Multiple factors including both patient- and treatment-related factors appear to play an important role in the development of t-MN. Although t-MN remain quite rare, their development after plasma cell neoplasms, especially MM, have been shown to portend a poor prognosis. Patient risk factors including age, prior malignancies, and baseline bone marrow morphology and function should be taken into account when assessing for risk of t-MN and myeloma therapy should be aimed at minimizing these risks while maximizing treatment outcomes.

Certain treatment options have been found to be more myelotoxic and leukaemogenic. Alkylating chemotherapy, especially melphalan, has been associated with the development of t-MN and its use should be minimized if possible; cyclophosphamide appears to have a better safety profile with respect to t-MN when compared to melphalan. HD-ASCT also appears to be associated with a small increased risk of t-MN, but its benefits in terms of anti-myeloma therapy may outweigh the risks for transplant-eligible patients. Post-transplant maintenance with lenalidomide also appears to confer a small increased risk for t-MN and SPM, but similarly, the benefits of therapy appear to outweigh the risks for most patients. Patients at higher risk for t-MN could be considered for bortezomib-based maintenance strategies instead of lenalidomide. The risks of t-MN associated with lenalidomide is magnified by previous exposure to oral melphalan, but in the absence of prior melphalan use or HD-ASCT, lenalidomide does not appear to be associated with significant risk of t-MN and appears safe as a long-term maintenance strategy for transplant-ineligible MM patients.

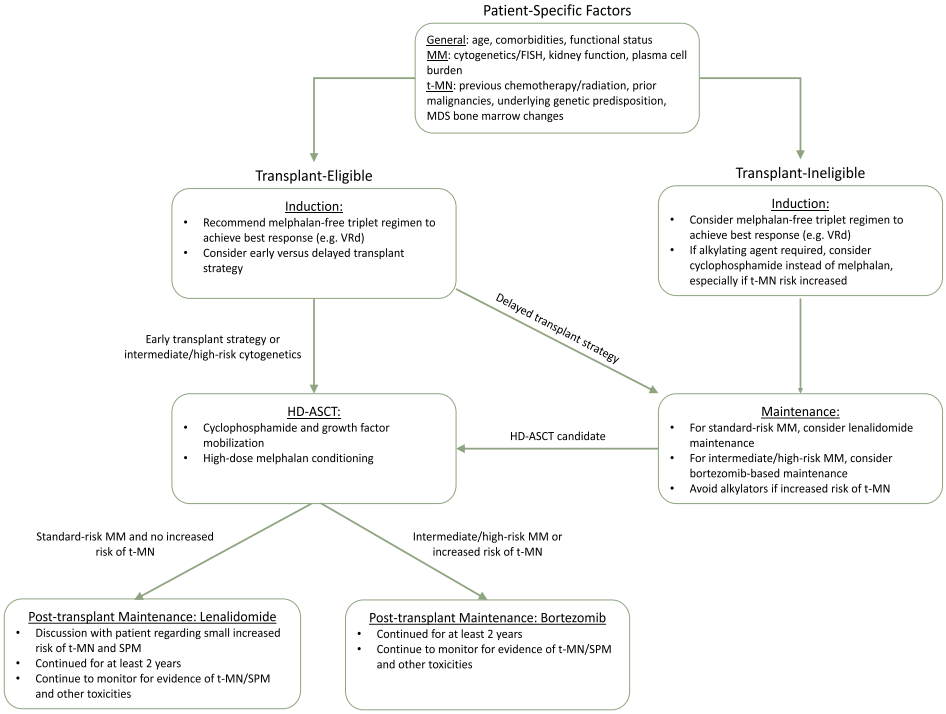

Fig. 2. Treatment algorithm for MM accounting for t-MN.

Practice Points

- Therapy-related myeloid neoplasms (t-MN) are an uncommon but clinically significant complication of plasma-cell directed therapies.
- Oral melphalan combinations and high-dose therapy with autologous stem-cell transplant (HD-ASCT) have been associated with an increased risk for t-MN.
- Lenalidomide maintenance after HD-ASCT is associated with a small increase in risk for t-MN after multiple myeloma, but in general, the benefits of improved survival outweigh the risks.
- For transplant-ineligible patients, lenalidomide use in the absence of concurrent melphalan use does not appear to be associated with an increased risk for development of t-MN.
- Treatment strategies for plasma-cell disorders should take into account an individual's risk for development of t-MN.

Research Agenda

- Longer-term follow-up data is needed to determine the contribution of more novel plasma-cell directed therapies to the development of t-MN after plasma-cell disorders.

Conflicts of interest

AC has no conflicts of interest. ML: *Amgen/Onyx:* Consultancy, Honoraria, Research Funding; *BlueBirdBio:* Research Funding; *Takeda:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Research Funding; *Caelum:* Membership on an entity's Board of Directors or advisory committees; *Prothena:* Honoraria, Membership on an entity's Board of Directors or advisory

committees, Research Funding; *Genentech/Roche:* Research Funding; *Gilead:* Membership on an entity'sBoard of Directors or advisory committees, Research Funding; *Janssen:* Research funding; *Adaptive*: Consultancy; *Agios*: Research Funding; *Celator*: Research Funding; *IQVIA/Jazz Pharmaceuticals*: Consultancy.

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