HHS Public Access

Author manuscript

Best Pract Res Clin Haematol. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Best Pract Res Clin Haematol. 2020 March ; 33(1): 101144. doi:10.1016/j.beha.2020.101144.

Second malignancies in multiple myeloma; emerging patterns and future directions

Kylee Maclachlan[1], **Benjamin Diamond**[1], **Francesco Maura**[1], **Jens Hillengass**[2], **Ingemar Turesson**[3], **C. Ola Landgren**[1], **Dickran Kazandjian**[4]

[1]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[2]Division of Multiple Myeloma, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

[3]Department of Hematology, Skane University Hospital, Malmo, Sweden.

[4]Multiple Myeloma Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

The changing landscape of treatment options for multiple myeloma has led to a higher proportion of patients achieving deep, long-lasting responses to therapy. With the associated improvement in overall survival, the development of subsequent second malignancies has become of increased significance. The risk of second malignancy after multiple myeloma is affected by a combination of patient-, disease- and therapy-related risk factors. This review discusses recent data refining our knowledge of these contributing factors, including current treatment modalities which increase risk (i.e. high-dose melphalan with autologous stem cell transplant and lenalidomide maintenance therapy). We highlight emerging data towards individualized risk- and response-adapted treatment strategies and discuss key areas requiring future research.

Keywords

Multiple myeloma; Neoplasms; second primary; Risk factors; Melphalan; Transplantation; autologous; Lenalidomide

1. Introduction

The prognosis for patients with multiple myeloma (MM) has significantly improved over the past twenty years, which has been driven by the improved diagnostics, prognostication and efficacy of anti-MM treatment. The median overall survival (OS) for patients with favourable risk disease treated with modern therapies now exceeds 10 years, both in

Corresponding Author: Dr Kylee Maclachlan, maclachk@mskcc.org, 1 (212) 639-2000.

randomized clinical trials (1, 2), and in studies based on national cancer registries(3, 4). An improvement in survival has been observed in each of transplant-eligible(2) and -ineligible patients(5). Many recent studies have demonstrated that those patients achieving a very deep response to therapy, i.e. no detectable minimal residual disease (MRD(−)), may continue to enjoy a disease-free state for many years(6–11). Therefore, MM has an increased prevalence in the general population as patients are living longer before succumbing to myeloma or other disease(4). This extension of survival has reinvigorated debate on the significance of second malignancies following MM.

2. Defining Second Malignancy (SM) in MM patients

2a. Incidence of SM after MM

The incidence of SM in MM patients has been estimated from each of population-based registry studies, retrospective analyses and prospective clinical trials. These estimates vary due to the different populations studied and the change in treatment regimens over time. The overall rate of “any SM” are consistently low across studies, with 5–7% affected, and standardised incident rates (SIR; calculated from the ratio of the observed rate to the expected rate) of 0.98–1.26(12–14). However, variance is observed between sub-types of malignancy, with a significantly higher incidence of haematological cancer demonstrated compared with solid organ cancers(12–18). Population-based studies inclusive of patients treated prior to the wide-spread use of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) documented SIR for myelodysplastic syndromes (MDS) / acute myeloid leukaemia (AML) of 6.5–11.5(13, 14, 16, 17), with increased rates also observed in acute lymphoblastic leukaemia (ALL, SIR 5.5), chronic myeloid leukaemia (CML, SIR 2.3) and non-Hodgkin lymphoma (NHL, SIR 1.3–1.7)(13, 16, 17).

These patterns have been replicated in more recent registry studies(12, 15, 19) and retrospective reviews(20), with a reduction in incidence noted as the use of prolonged upfront alkylating agents declines. In addition, since reports of an increase in secondary malignancies following the use of lenalidomide(21, 22), phase III clinical trials have routinely included this as a secondary outcome measure. A summary of results from major population-based registries and retrospective analyses are presented in the International Myeloma Working Group overview published in 2016(23), while malignancy following particular therapies for MM are discussed in section 5 below.

The incidence of subsequent non-haematological cancer in patients diagnosed with MM is much lower than haematological cancers, but particular entities do have an increased rate. Registry studies report increased rates of gastrointestinal (SIR 1.3–2.03), kidney (SIR 1.3–1.51), bladder (SIR 1.22), melanoma (SIR 1.36–1.43) and non-melanotic skin cancers (SIR 2.22) and while reduced incidence rates have been observed in lung (SIR 0.28–0.88), breast (SIR 0.76–0.81) and prostate cancer (SIR 0.69–0.75) (12–14, 17, 18, 24). It has been reported that breast and prostate cancers are more commonly diagnosed at an early stage in patients with MM(13, 25), which may reflect closer attention to cancer-surveillance practice in patients already suffering a first malignancy.

2b. Features of therapy-related myeloid neoplasms; overall and after MM

Cancers of the myeloid lineage following chemo- or radiotherapy are defined as therapy-related myeloid neoplasms (t-MN) according to the World Health Organisation classification(26). Comprising therapy-related MDS (t-MDS), AML (t-AML) and myelodysplastic / myeloproliferative overlap syndrome (t-MDS/MPN), these entities have different clinical and pathological features compared with *de novo* myeloid neoplasms (dn-MN)(27–29). T-MN account for 6–7% of AML cases(29–31), and up to 10% all MDS cases(32), with multiple analyses including those using the United States (US) Surveillance, Epidemiology and End Results (SEER) database documenting an increase in incidence over time, both overall and specific to patients with MM(28, 33).

Patients with t-MN tend to be diagnosed at a younger age compared with dn-MN, at a median of 64–65 years(28, 34). Multiple studies have demonstrated a higher incidence of clonal cytogenetic aberrations, in particular complex karyotypes and adverse features including hypodiploidy in the MN cells(29–31). Molecular analyses define a higher rate of *TP53* mutations(35, 36) and a lower incidence of therapeutically targetable mutations (including *IDH1/2, EZH2* and *FLT3-ITD*(37, 38)). The concept of clonal haematopoiesis as it relates to t-MN after MM is discussed in section 4 below.

2c. Features of solid SM after MM

Solid malignancies occurring after MM have some differences from the primary cancers affecting the general population which largely reflect MM epidemiology, including an older age of diagnosis, a male predominance, and a higher percentage of black ethnicity(24). However, many of the prognostic features remain the same, including rates of hormone-receptor positivity in breast cancer, prostate-specific antigen levels in prostate cancer, lymph node involvement in colorectal cancer and proportion of adenocarcinoma amongst lung cancer cases(24, 25).

2d. Outcomes from SM after MM

Overall, outcomes from t-MN are less favourable than with dn-MN(28, 33, 38, 39). It has been demonstrated that the MDS prognostic scoring system remains discriminatory of risk with t-MDS, however the distribution of cases is not equivalent, with a shift toward high risk in t-MDS and a worse survival within each risk category compared with dn-MDS(40). Therefore, t-MN have a more aggressive clinical pattern compared with dn-MN and are less responsive to treatment, resulting in a median OS estimates between 8 and 14 months(28, 34, 41).

Outcomes from non-haematological cancers are less dismal than with t-MN, with some studies reporting a subset of patients showing a similar response to therapy as in *de novo* disease, particularly those able to tolerate intensive treatment(25, 42). There is obviously heterogeneity when considering outcomes from all solid organ malignancies, and the pattern of an earlier stage of diagnosis will likely affect outcomes. A SEER-based analysis detailed a significantly higher overall mortality (when compared with patients not having MM) with almost all cancers studied (HR 1.84–2.81, excepting lung cancer), however the mortality due

to the solid-organ malignancies were out-weighed by the MM-related death(25). The respective risk and effect on outcomes may change over time as MM survival improves.

3. Patient-related factors contributing to susceptibility to SM after MM

The development of SM after MM is multifactorial, which complicates the accurate estimation of risk for a particular patient or circumstance. However, several host-related factors appear to contribute to the risk of subsequent SM after MM, as detailed below, in Table 1 and in Figure 1.

3a. Age

Increasing age is associated with increased risk of t-MN, with a recent analysis using the US SEER database demonstrating a hazard ratio (HR) of 2.5 (1.5–3.9) in patients ≥55 years compared with those ≤55 years old(15). Previous estimates from earlier (alkylator-rich) treatment periods demonstrated an increased incidence of t-AML in patients <65, with the hypothesis that younger patients may have received more intensive up-front treatment(13). More recent studies in transplant-eligible patients detail an increased rate of t-MN specifically and SM overall in patients having an advanced age at transplantation(15, 20).

Regarding solid organ cancers; those with preceding MM are older on average than those with *de novo* disease, reflecting the demographics of MM patients overall(25). Increasing age is a known risk factor for many malignancies, and several multivariate analyses have confirmed advanced age to increase risk for SM in patients having MM(20, 22). As more efficacious therapies continue to improve outcomes for MM, survival bias may affect analyses of the effect of age in SM, with an increasingly prolonged opportunity for second malignancies to develop, unrelated in etiology to the history of MM.

3b. Sex

A recent analysis of SEER-database data detailed a HR of 2.3 (1.4–3.5) for male compared with female sex in MM patients treated with high-dose melphalan and autologous stem cell transplant (HDM-ASCT) (15). This confirmed previous reports(17), and has been demonstrated specifically in the post-transplant setting (HR for female 0.35–0.71)(20) and in meta-analyses assessing lenalidomide maintenance (HR for male 1.01–1.88)(22).

3c. Ethnicity

Ethnicity have been described in multiple studies to be a risk factor for the development of both monoclonal gammopathy of uncertain significance (MGUS) and subsequent MM(43–45). SEER-based analyses have highlighted the impact of ethnicity on the risk of subsequent SM, with varying effect according to the sub-type of SM. Reports include Non-Hispanic white patients having an increased risk of melanoma, AML and non-Hodgkin lymphoma, Hispanic white patients having a reduced risk of lung and prostate cancer, African Americans patients having an increased risk of renal cancer, and Asian- Pacific Islanders having a higher risk of AML(17, 46).

3d. Genetics

Genome-wide association studies have located multiple loci associated with susceptibility to MGUS and MM(47–49). Genes annotated by affected single nucleotide polymorphisms may also be relevant to subsequent development of SM, particularly those affecting DNA-damage repair (DDR) mechanisms and drug metabolism(50–52). It has been reported that nearly 10% of the population has a reduced capacity to respond to DNA-damage(51), with germline mutations (i.e. in *TP53*, *BRCA1*, *BRCA2*, *MSH6*, and *ATM*) detected in a higher proportion than expected when somatic screening was performed in malignancy (53), potentially contributing to the genetic instability observed in some MM patients(54), with subsequent t-MN containing a 20% incidence of germline DDR-gene mutations(38, 55). In addition, germline mutations in the *CDKN2A* gene have been reported to predispose to both MM and additional cancers(56), and a polymorphism affecting the erythropoietin gene promotor is associated with differing rates of MDS following MM(57).

3e. Environment / Behaviour

Smoking has not been associated with an increased risk of MM(58, 59), nor an increased risk of SM following MM beyond that associated with individual *de novo* cancers(20). Moderate alcohol intake has been reported to potentially reduce the incidence of MM(60, 61), and there is no strong data to suggest an increase in SM related to alcohol in MM. Obesity has been described as a risk factor for both the development of MGUS(62) and for progression from MGUS to MM(63, 64). In addition, obesity has been shown to be associated with an increased rate of SM following MM(20), which is postulated may relate to obesity-associated chronic inflammation(65, 66), with obesity also being associated with adverse cytogenetics in t-MN(67).

3f. Comorbidities- prior cancer / autoimmune disease

A large registry study demonstrated that MM patients with a history of prior malignancy had a higher risk of developing a subsequent cancer (HR 1.23–1.65), with an associated increased risk of death (HR 1.1–1.26), which was compounded if there had been more than 1 prior malignancy(68). The authors hypothesized that prior malignancy may reflect underlying genetic susceptibility to developing MM, though note chemo- and radiotherapy treating earlier cancers may contribute(69), just as pesticide exposure is reported to increase risk(70, 71).

Patients with autoimmune conditions are at an increased risk of developing several cancers including MM, which is due to both underlying immune dysregulation and to the use of immunosuppressive treatment regimens(72, 73). Pre-existing autoimmune disease predicts for an increased risk of death with MM, and for additional malignancy subsequent to MM(74–76). Dysregulation of the immune system can be viewed as affecting all 3 of patient-, disease- and treatment-specific risk of SM.

4. Disease-related factors contributing to susceptibility to SPM

The risk of MDS / AML is increased in those with MGUS, independent of whether or not MGUS progresses to MM, supporting a treatment-independent effect. The risk varies with

MGUS disease characteristics including immunoglobulin isotype, (increased risk only with IgG/IgA) and the size of the paraprotein, (increased risk with >1.5g/L, SIR 11.12), with MGUS patients assessed in a population-based registry having an 8-fold higher risk of AML/MDS (95% CI 5.40–11.43) (14).

In addition, there is increasing interest in the role of clonal haematopoiesis (CH) in the etiology of t-MN, with the hypothesis that treatment may induce the expansion of a pre-existing myeloid clone(36, 77). Retrospective examination of bone marrow in MGUS/MM patients obtained prior to the development of MDS/AML demonstrated that morphologic and immunophenotypic features typical for myelodysplastic syndromes are present in many patients prior to the receipt of treatment(78–80). Recent high-intensity sequencing of circulating cell-free DNA (cf-DNA) found that the majority of both patients with cancer and controls had cf-DNA mutations consistent with CH(81). The somatic genetic changes affect the subsequent risk of SM, with some reflecting CH (i.e. *DNMT3A*, *TET2*, *ASXL1*, *TP53*) while others are specific to the plasma cell genome(82, 83).

In addition, it has been shown that previously-treated cancer patients have a higher rate of CH in prior samples, with an enrichment demonstrated in DDR-gene mutations and data demonstrating that these mutations provided a selection advantage to the affected clones(84). In patients who progressed to t-MN, the clone present at diagnosis of CH defined that detected at diagnosis of t-MN. While we know that AML is preceded by CH, the exact impact of CH occurring concurrently with MM in defining the risk of SM is still unclear.

Immune dysregulation is a well-documented feature of MM, both as an integral part of untreated MM and as a result of therapy(85). MM cells have a symbiotic relationship with the tumour microenvironment (TME) and the hypothesis has been postulated that changes within the TME, (the immune components in particular), may predispose to subsequent SM(86, 87).

5. Treatment-related factors contributing to susceptibility to SPM

It is clear from historical studies that prolonged alkylator therapy significantly increases the risk of SM and should be avoided(88–90). Traditional anthracycline-containing combinations and prolonged oral melphalan are appropriately no longer in common use in the US due to toxicity concerns. Likewise, the relationship between high doses of ionizing radiation and SM has been clearly documented(15, 91), though data specific to MM is more limited. Here, we will focus on topical concerns related to therapies currently prescribed for MM.

5.1 High-dose melphalan- autologous stem cell transplant (HDM-ASCT)

Historical data examining the incidence of SM following HDM-ASCT was complicated by the prevalence of alkylator-containing induction regimens, with several studies finding that the effect of the induction contributed more to the risk of SM than the HDM-ASCT itself (90). However, recent multivariate analyses have shown an increase in t-MN specific to the use of HDM-ASCT(15, 92). Both the SEER database and the Center of International Blood and Marrow Transplant Research (CIBMTR) showed a higher relative risk of AML (10–50

times) and of MDS (100 times) than the background rate for patients with MM. However, the risk was higher in patients who received HDM-ASCT (CIBMTR data) compared to all MM patients (SEER data). The authors demonstrate that in the context of ASCT, the risk factors of age, male sex and number of prior lines of chemotherapy confer increased risk for subsequent MDS/AML, (HRs of 2.47 for age >55, 2.27 for male and 1.77 for >2 prior lines).

The mechanism for an increase in MDS/AML is likely directly related to the alkylating action of melphalan, (consistent with previous data following prolonged oral dosing), though the associated immunosuppression may also contribute. Historical data noted transient MDS-associated cytogenetic abnormalities following HDM-ASCT(93), with the time between melphalan-exposure and subsequent MDS/AML noted to be relatively short(14, 20), each of which support an etiological link. In addition, recent data on mutational signatures in MM, (whereby different processes contributing to cancer development are found to generate different combinations of mutation types(94)), defined a mutational signature in MM patients specific to melphalan exposure (95, 96). Further research is planned to define the clinical impact of these data.

In a measure of overall toxicity as assessed by patients themselves, patient-reported outcome studies show salvage ASCT in relapsed/refractory MM to have a greater deleterious impact on quality of life, with lower overall global health scores at day 100 post-ASCT, and higher side effects scores (both overall and pain-specific) persisting 6-months from ASCT (97). These findings are particularly important given that studies in the era of modern therapies have shown that upfront ASCT improves progression-free survival (PFS) but not necessarily OS(98). While undoubtedly a potent therapy, it may be that we are able to achieve equal measures of efficacy with a lower degree of toxicity, including incidence of SM(99).

5.2 Lenalidomide / other immunomodulatory agents (IMiDs)

A modest but statistically significant increase in SM with lenalidomide maintenance therapy has now been reported as a consistent finding across multiple large phase III trials, both when received after ASCT(100, 101), or continuing after induction therapy(102). Meta-analyses have demonstrated a HR of 2–4 for haematological SM when compared with placebo/observation, (95% CIs being 1.14–3.61 and 1.15–12.62 in 2 studies following ASCT), with HR of 1.1–1.7 for solid organ SM (95% CIs being 1.04–2.80 and 10.62–2.00) (22, 103). A significantly shorter time to development of SM was also demonstrated(103). Notably, when used as a component of upfront therapy, the increased risk of SM seen with lenalidomide was predominantly seen in those patients co-prescribed melphalan, but not in those receiving concomitant cyclophosphamide, nor those receiving just lenalidomide/dexamethasone since diagnosis(22). It appears that the wider treatment context (i.e. lenalidomide as one component of combination drug therapy, or ASCT followed by lenalidomide maintenance) may contribute to the overall risk of SM due to lenalidomide.

The mechanism/s by which lenalidomide increases the risk of SM are likely multifactorial. Lenalidomide efficacy requires the expression of cereblon, a component of the E3-ubiquitin ligase complex which is involved in DNA-damage repair(104). This may partially explain increased long-term toxicity observed with lenalidomide in combination with oral melphalan or HDM-ASCT. IMiDs also have effects on the TME and the immune system, including

inhibiting cell-surface adhesion, reducing osteoclastic activity, reducing cytokines (including IL-6 and TNF-α), changing T-cell subsets and NK-cell activity(105). A combination of these factors may promote subsequent SM and may contribute to the incidence of haematological SM being significantly higher than non-haematological cancers.

The data with other IMiDs is less clear than with lenalidomide; much of the data with thalidomide is confounded by concurrent alkylator therapy but the trend to increased incidence of SM has been published to occur at a lower rate than with lenalidomide(106). The data with pomalidomide is less mature, but there is no early signal for a significant increase in SM(107).

Considering all available data on lenalidomide in MM, outcomes are consistent regarding a statistically significant increase in SM. However, the meta-analyses are equally clear that the survival benefit provided by lenalidomide, both PFS and OS, outweigh the risk of death related to SM(22, 103). Therefore, the current risk-benefit analysis for the majority of patients remains in favour of lenalidomide.

5.3 Bortezomib

The available data on the risk of SM with the PI bortezomib is reassuring, with the addition of bortezomib to lenalidomide-dexamethasone induction not being associated with an increase in SM (0.4% with and 0.8% without)(108). In fact, some studies have reported a lower rate of SM; 1% vs 4% at 6 years with the addition of bortezomib to thalidomide and dexamethasone(109), with a registry analysis documenting a HR of 0.24 in MM patients treated with bortezomib(12).

Bortezomib is also in use in some centers as maintenance therapy, with data showing an improvement in PFS in the high-risk cytogenetic subgroup, a trend to a lower rate of SM compared with no maintenance and no cases of haematological SM(110, 111). The mechanism by which a potential improvement in SM may occur with bortezomib use is not known.

5.4 Other drugs

All drugs currently in use or under investigation for MM include the incidence of SM as a clinical trial outcome. There have been no concerning signals for an increased incidence of SM in any of the landmark trials for the PI's carfilzomib or ixazomib, nor the monoclonal antibodies daratumumab or elotuzumab. Monitoring is recommended to continue for agents following regulatory approval and commencement of off-trial routine treatment. Analysis of the data for chimeric antigen receptor T cells, bispecific antibodies, antibody drug conjugates and other novel therapies are currently limited by small numbers and short follow-up periods.

6. Future directions

Due to the growing population of patients living with MM, the rapidly evolving treatment options and the ever-increasing survival times, it is critical to carefully document the incidence, prevalence and risk factors for SM following MM. It is optimal to collect this data

with a standardized definition (rate per persons at risk per year), with routine incorporation into clinical trial design. Both non- and haematological cancers should be reported, as should both invasive and noninvasive cancers, which likely represent different modes by which MM disease biology and treatment are contributing to subsequent SM development.

6a. Patient-related factors

Considering recent reports regarding inherited DNA damage repair (DDR) deficits predisposing to both MM and to subsequent SM(54, 55), we require better definition of patients at risk, with increased testing of germline samples in parallel with the cancer genome. As treatment options widen, with increasing rates of deep MRD(−) response from potent induction regimens such as carfilzomib-lenalidomide-dexamethasone(11, 112, 113), this data may sway physicians away from DNA-damaging agents in some patients, including contributing to the decision to forgo upfront consolidative ASCT(99). This risk-benefit analysis may be further influenced by the addition of daratumumab which reportedly increases both rates of MRD-negativity and PFS(114). While, for the majority of patients, the use of HDM-ASCT appears efficacious in prolonging PFS with manageable toxicity, it seems likely that in the face of sustained MRD(−) responses, the risk-benefit ratio (which includes the risk of SM), may argue against HDM-ASCT in a subset of patients.

6b. Disease-related factors

MM is known to be genetically heterogenous, with a large number of mutations occurring at a low frequency(115–117). Limiting analysis to the exome results in an inadequate description of MM genomic development. Recent studies involving whole genome sequencing(118), investigation of the role of rare structural variants(119), defining the contribution of various mutational signatures(120) and examining the clonal evolutionary trajectory over time (96, 121) are better defining the genomic landscape of MM. These features, critical to the progression from precursor disease to MM, are no doubt also central to the risk of subsequent SM. Considering the differing cytogenetic and molecular features of t-MN compared with dn-MN(27, 38, 122), we suggest integrating into clinical trial design the collection of DNA for comprehensive genomic analysis, both at baseline and following treatment, to better define those at increased risk for progression in either the MM clone or in clonal haematopoeisis as it relates to t-MN.

It has been previously demonstrated that MM growth and progression involves complex interactions within the tumour microenvironment (TME). It would seem likely that examining this relationship further may give insight into the subsequent development of SM after MM. Advances in analytic techniques have enabled definition of tumours and their transcriptome at single cell level, which in MM has revealed information regarding intra-tumoural heterogeneity, subclonal architecture, genomic progression and the potential for defining drug sensitivity(123–125). Extending this single-cell analysis to examine the TME in concert with the tumour cells will likely elucidate further mechanisms related to both the progression of disease and to the development of SM. Though too expensive and computationally intensive at this point in time to be incorporated as routine in clinical trials, serial examination of tumour cells and the TME at a single cell level would elucidate how this relationship changes in response to therapy, including which changes precede and

predict subsequent SM. We anticipate research in this area to improve our understanding of SM following MM.

6c. Treatment-related factors

The data appear clear that particular MM treatments contribute to the risk of SM, with strong historical evidence linking prolonged oral alkylator therapy to increased risk, and lenalidomide use consistently associated with a modest but statistically significant increase in incidence. In the context of a demonstrated increase in PFS, (and in some studies, including a meta-analysis, OS), with lenalidomide, this risk has been accepted as the lesser evil compared with the ongoing potential for progressive disease and myeloma-associated death. This risk-benefit analysis needs continued evaluation, however, with rapid changes in clinical practice. IMWG guidelines broadened the definition of those requiring treatment initiation in 2014 and multiple groups are attempting to better define those patients with "smoldering" MM (SMM) but high risk of imminent progression, suggesting earlier initiation of therapy(126–128). A recent publication suggested lenalidomide now be considered standard-of-care for SMM, based on a study in which two-thirds of patients had intermediate or low risk SMM, with the potentially sub-optimal primary outcome of PFS(129). We now find ourselves faced with the prospect of otherwise healthy SMM patients being started on lenalidomide to delay disease progression without clear direction on the optimal duration of therapy, the effects of this single-agent therapy on subsequent genomic progression, or adequate information on the rate of SM expected from what may be very prolonged treatment. While the increased risk of SM from lenalidomide as a maintenance therapy appears modest, the same may not be true if this therapy is prescribed for a considerably longer duration.

HDM-ASCT is currently regarded as the standard-of-care (with caveats) based on trials demonstrating a prolongation of PFS compared with no HDM-ASCT (98). Again, this assertion requires ongoing evaluation in the context of more potent induction therapies. It has been demonstrated that the attainment of MRD-negativity is more important than the mode by which a patient achieves this state(6). In the context of induction regimens able to elicit sustained MRD-negativity(7, 11), which will likely be improved with quadruplet antibody-containing regimens(130), the subsequent role for both HDM-ASCT and prolonged maintenance therapy should be re-examined. It appears evident that the contribution of subsequent consolidation therapy to MM control, (with the associated risk of SM), may be reduced if the induction therapy alone is able to attain sustained MRD-negativity.

As a part of our ongoing examination of SM incidence and risk, it seems prudent to consider the potential for risk-adapted therapy, including monitored cessation of maintenance therapy. While lenalidomide until progression has been shown to have PFS (and in some studies OS) benefit(131, 132), this may not be required with more potent induction, and may not be adding to response in all patients. It is hypothesized that in patients achieving a sustained MRD-negative state for 2–3 years, continuing maintenance therapy may be adding financial and clinical toxicity, without providing additional efficacy. In order to test this hypothesis, ongoing and upcoming clinical trials are examining planned cessation of lenalidomide,

(guided by MRD-status in some trials), analogous to trials ceasing tyrosine kinase inhibitors in chronic myeloid leukaemia patients having achieved a prolonged major molecular remission (NCT01863550, ENDURANCE; NCT04071457, DRAMMATIC trials).

Finally, continued examination of SM rates following the diagnosis of and treatment for MM must consider the effect of novel therapies. Monoclonal antibodies, in particular daratumumab, are regarded as one of the most promising therapeutic classes to emerge for MM in recent years. The addition to triplet induction regimens appears to increase the depth of response(130), and daratumumab is being tested as a potential addition to / alternative to lenalidomide in the setting of maintenance therapy (NCT03901963, AURIGA trial). The long-term toxicities of daratumumab are still under investigation, and while the overall safety signal suggests excellent tolerability, there is increasing evidence of a significant increase in infectious complications(133). There is the theoretical possibility that the effects on the natural killer cell population, for example, may contribute over time to the incidence of SM following MM(134, 135). In the context of any agent known to affect immune functioning, ongoing surveillance and detailed documentation of SM is essential.

7. Conclusion

While this is an exciting time to be a MM physician, with a steadily increasing armamentarium of efficacious therapies having acceptable short- and long-term toxicities, the risk of SM should remain a strong consideration when selecting therapies for individual patients. When considering all available information, it appears clear that the risk of death from SM is significantly lower than the risk of MM-related death, therefore the primary consideration should be optimal management of the MM. Currently available data does not support changing treatment decisions based purely on the risk of SM. However, there is increasing evidence that the combination of particular host, disease and treatment factors will increase the risk of SM for some individuals with certain treatments. Therefore, this risk should be integrated into the choice of regimen and should be considered when designing future clinical trials.

Acknowledgements

K.M. is supported by the Haematology Society of Australia and New Zealand New Investigator Scholarship and the Royal College of Pathologists of Australasia Mike and Carole Ralston Travelling Fellowship Award

Key abbreviations

AML	acute myeloid leukaemia
cf-DNA	cell free DNA
CH	clonal haematopoiesis
CIBMTR	Center of International Blood and Marrow Transplant Research
***dn*-MN**	*de novo* myeloid neoplasm
HDM-ASCT	high-dose melphalan- autologous stem cell transplant

HR	hazard ratio
IMiDs	immunomodulatory agents
MGUS	monoclonal gammopathy of undetermined significance
MDS	myelodysplastic syndrome
MM	multiple myeloma
MRD	minimal residual disease
OS	overall survival
PIs	proteasome inhibitors
PFS	progression-free survival
SEER	Surveillance, Epidemiology and End Results database
SIR	standardised incident rate
SM	second malignancy
TME	tumour microenvironment
t-MN	therapy-related myeloid neoplasm

References

1. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015;33(26):2863–9. [PubMed: 26240224]
2. Gonzalez-Calle V, Slack A, Keane N, Luft S, Pearce KE, Ketterling RP, et al. Evaluation of Revised International Staging System (R-ISS) for transplant-eligible multiple myeloma patients. Ann Hematol. 2018;97(8):1453–62. [PubMed: 29623394]
3. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. 2017;1(4):282–7. [PubMed: 29296944]
4. Turesson I, Bjorkholm M, Blimark CH, Kristinsson S, Velez R, Landgren O. Rapidly changing myeloma epidemiology in the general population: Increased incidence, older patients, and longer survival. European Journal of Haematology. 2018;101(2):237–44.
5. Mateos M-V, Leleu X, Palumbo A, Miguel J-FS. Initial treatment of transplant-ineligible patients in multiple myeloma. Expert Review of Hematology. 2014;7(1):67–77. [PubMed: 24308500]
6. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplantation. 2016;51(12):1565–8. [PubMed: 27595280]
7. Landgren O, Mastey D, Lesokhin AM, Smith EL, Shah UA, Mailankody S, et al. Long-Term Sustained Minimal Residual Disease (MRD) Negativity in Multiple Myeloma Patients Treated with Lenalidomide Maintenance Therapy: A Clinical and Correlative Phase 2 Study. Blood. 2019;134(Supplement_1):3127–.
8. Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma JAMA Oncology. 2015;1(6):746–54. [PubMed: 26181891]

9. Avet-Loiseau H, Corre J, Lauwers-Cances V, Chretien M-L, Robillard N, Leleu X, et al. Evaluation of Minimal Residual Disease (MRD) By Next Generation Sequencing (NGS) Is Highly Predictive of Progression Free Survival in the IFM/DFCI 2009 Trial. Blood. 2015;126(23):191–.
10. Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE, et al. Minimal Residual Disease Assessed by Multiparameter Flow Cytometry in Multiple Myeloma: Impact on Outcome in the Medical Research Council Myeloma IX Study. Journal of Clinical Oncology. 2013;31(20):2540–7. [PubMed: 23733781]
11. Kazandjian D, Korde N, Mailankody S, Hill E, Figg WD, Roschewski M, et al. Remission and Progression-Free Survival in Patients With Newly Diagnosed Multiple Myeloma Treated With Carfilzomib, Lenalidomide, and Dexamethasone: Five-Year Follow-up of a Phase 2 Clinical Trial. JAMA Oncology. 2018;4(12):1781–3. [PubMed: 30477009]
12. Engelhardt M, Ihorst G, Landgren O, Pantic M, Reinhardt H, Waldschmidt J, et al. Large registry analysis to accurately define second malignancy rates and risks in a well-characterized cohort of 744 consecutive multiple myeloma patients followed-up for 25 years. Haematologica. 2015;100(10):1340. [PubMed: 26160877]
13. Razavi P, Rand KA, Cozen W, Chanan-Khan A, Usmani S, 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. [PubMed: 23811785]
14. Mailankody S, Pfeiffer RM, Kristinsson SY, Korde N, Bjorkholm M, Goldin LR, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). Blood. 2011;118(15):4086–92. [PubMed: 21795746]
15. Radivoyevitch T, Dean RM, Shaw BE, Brazauskas R, Tecca HR, Molenaar RJ, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome after autotransplants for lymphomas and plasma cell myeloma. Leukemia Research. 2018;74:130–6. [PubMed: 30055822]
16. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958–1996: a search for common mechanisms. British Journal of Cancer. 2001;85(7):997–1005. [PubMed: 11592772]
17. Chakraborty S, Hauke RJ, Bonthu N, Tarantolo SR. Increased incidence of a second lymphoproliferative malignancy in patients with multiple myeloma--a SEER based study. Anticancer Res. 2012;32(10):4507–15. [PubMed: 23060579]
18. Tzeng HE, Lin CL, Tsai CH, Tang CH, Hwang WL, Cheng YW, et al. Time trend of multiple myeloma and associated secondary primary malignancies in Asian patients: a Taiwan population-based study. PLoS One. 2013;8(7):e68041. [PubMed: 23844152]
19. Chen T, Fallah M, Brenner H, Jansen L, Mai EK, Castro FA, et al. Risk of Second Primary Cancers in Multiple Myeloma Survivors in German and Swedish Cancer Registries. Sci Rep. 2016;6:22084–. [PubMed: 26908235]
20. Mahindra A, Raval G, Mehta P, Brazauskas R, Zhang MJ, Zhong X, et al. New cancers after autotransplantations for multiple myeloma. Biol Blood Marrow Transplant. 2015;21(4):738–45. [PubMed: 25555448]
21. Dimopoulos MA, Richardson PG, Brandenburg N, Yu Z, Weber DM, Niesvizky R, et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood. 2012;119(12):2764–7. [PubMed: 22323483]
22. Palumbo A, Bringhen S, Kumar SK, Lupparelli G, Usmani S, Waage A, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. The Lancet Oncology. 2014;15(3):333–42. [PubMed: 24525202]
23. Musto P, Anderson KC, Attal M, Richardson PG, Badros A, Hou J, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol. 2017;28(2):228–45. [PubMed: 27864218]
24. Costa LJ, Godby KN, Chhabra S, Cornell RF, Hari P, Bhatia S. Second primary malignancy after multiple myeloma-population trends and cause-specific mortality. British Journal of Haematology. 2018;182(4):513–20. [PubMed: 29974936]
25. Barth P, Castillo JJ, Olszewski AJ. Outcomes of secondary solid tumor malignancies among patients with myeloma: A population-based study. Cancer. 2019;125(4):550–8. [PubMed: 30452087]

26. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405. [PubMed: 27069254]
27. Pemmaraju N, Shah D, Kantarjian H, Orlowski RZ, Nogueras González GM, Baladandayuthapani V, et al. Characteristics and Outcomes of Patients With Multiple Myeloma Who Develop Therapy-Related Myelodysplastic Syndrome, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia. Clinical Lymphoma Myeloma and Leukemia. 2015;15(2):110–4.
28. Guru Murthy GS, Hamadani M, Dhakal B, Hari P, Atallah E. Incidence and survival of therapy related myeloid neoplasm in United States. Leukemia Research. 2018;71:95–9. [PubMed: 30048839]
29. Kayser S, Döhner K, Krauter J, Köhne C-H, Horst HA, Held G, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117(7):2137–45. [PubMed: 21127174]
30. Østgård LSG, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. Journal of Clinical Oncology. 2015;33(31):3641–9. [PubMed: 26304885]
31. Hulegårdh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Rangert Derolf Å, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: A report from the Swedish Acute Leukemia Registry. American Journal of Hematology. 2015;90(3):208–14. [PubMed: 25421221]
32. Zeidan AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: Why characterizing the beast is a prerequisite to taming it. Blood Reviews. 2019;34:1–15. [PubMed: 30314642]
33. Fernández-Caballero M, Salmerón D, Dolores Chirlaque M, Chen-Liang TH, Hurtado AM, García Malo MD, et al. Increasing therapy-related myeloid neoplasms in multiple myeloma. European Journal of Clinical Investigation. 2019;49(2):e13050. [PubMed: 30422316]
34. Fianchi L, Pagano L, Piciocchi A, Candoni A, Gaidano G, Breccia M, et al. Characteristics and outcome of therapy-related myeloid neoplasms: Report from the Italian network on secondary leukemias. American Journal of Hematology. 2015;90(5):E80–E5. [PubMed: 25653205]
35. Shih AH, Chung SS, Dolezal EK, Zhang S-J, Abdel-Wahab OI, Park CY, et al. Mutational analysis of therapy-related myelodysplastic syndromes and acute myelogenous leukemia. Haematologica. 2013;98(6):908. [PubMed: 23349305]
36. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. 2015;518(7540):552–5. [PubMed: 25487151]
37. Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367–76. [PubMed: 25550361]
38. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer. 2017;17(9):513–27. [PubMed: 28835720]
39. Chung A, Liedtke M. Therapy-related myeloid neoplasms after treatment for plasma-cell disorders. Best Practice & Research Clinical Haematology. 2019;32(1):54–64. [PubMed: 30927976]
40. Ok CY, Hasserjian RP, Fox PS, Stingo F, Zuo Z, Young KH, et al. Application of the International Prognostic Scoring System-Revised in therapy-related myelodysplastic syndromes and oligoblastic acute myeloid leukemia. Leukemia. 2014;28(1):185–9. [PubMed: 23787392]
41. Smith SM, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood. 2003;102(1):43–52. [PubMed: 12623843]
42. Castillo JJ, Olszewski AJ. Outcomes of secondary cancers among myeloma survivors. Journal of Clinical Oncology. 2017;35(15_suppl):8043–.
43. Landgren O, Graubard BI, Katzmann JA, Kyle RA, Ahmadizadeh I, Clark R, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12 482

persons from the National Health and Nutritional Examination Survey. Leukemia. 2014;28:1537. [PubMed: 24441287]

44. Landgren O, Graubard BI, Kumar S, Kyle RA, Katzmann JA, Murata K, et al. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance in 12372 individuals 10–49 years old: a population-based study from the National Health and Nutrition Examination Survey. Blood Cancer Journal. 2017;7(10):e618–e. [PubMed: 29053158]
45. Landgren O, Weiss BM. Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: support for genetic factors in pathogenesis. Leukemia. 2009;23(10):1691–7. [PubMed: 19587704]
46. Ailawadhi S, Swaika A, Razavi P, Yang D, Chanan-Khan A. Variable risk of second primary malignancy in multiple myeloma patients of different ethnic subgroups. Blood Cancer Journal. 2014;4(9):e243–e. [PubMed: 25192415]
47. Mitchell JS, Li N, Weinhold N, Försti A, Ali M, van Duin M, et al. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nature Communications. 2016;7(1):12050.
48. Chubb D, Weinhold N, Broderick P, Chen B, Johnson DC, Försti A, et al. Common variation at 3q26.2, 6p21.33, 17p11.2 and 22q13.1 influences multiple myeloma risk. Nature Genetics. 2013;45(10):1221–5. [PubMed: 23955597]
49. Morgan GJ, Johnson DC, Weinhold N, Goldschmidt H, Landgren O, Lynch HT, et al. Inherited genetic susceptibility to multiple myeloma. Leukemia. 2014;28(3):518–24. [PubMed: 24247655]
50. Hayden PJ, Tewari P, Morris DW, Staines A, Crowley D, Nieters A, et al. Variation in DNA repair genes XRCC3, XRCC4, XRCC5 and susceptibility to myeloma. Human Molecular Genetics. 2007;16(24):3117–27. [PubMed: 17901044]
51. Abou Zahr A, Kavi AM, Mukherjee S, Zeidan AM. Therapy-related myelodysplastic syndromes, or are they? Blood Reviews. 2017;31(3):119–28. [PubMed: 27923516]
52. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, et al. Cancer Survivorship—Genetic Susceptibility and Second Primary Cancers: Research Strategies and Recommendations. JNCI: Journal of the National Cancer Institute. 2006;98(1):15–25. [PubMed: 16391368]
53. Meric-Bernstam F, Brusco L, Daniels MS, Strong LC, Shaw KR, Lu KH, et al. Prevalence of incidental actionable germline mutations in 1,000 advanced cancer patients on a prospective somatic genomic profiling program. Journal of Clinical Oncology. 2015;33(15_suppl):1510–.
54. Janz S, Zhan F, Sun F, Cheng Y, Pisano M, Yang Y, et al. Germline Risk Contribution to Genomic Instability in Multiple Myeloma. Front Genet. 2019;10:424–. [PubMed: 31139207]
55. Schulz E, Valentin A, Ulz P, Beham-Schmid C, Lind K, Rupp V, et al. Germline mutations in the DNA damage response genes BRCA1, BRCA2, BARD1 and TP53 in patients with therapy related myeloid neoplasms. J Med Genet. 2012;49(7):422–8. [PubMed: 22652532]
56. Lynch HT, Ferrara K, Barlogie B, Coleman EA, Lynch JF, Weisenburger D, et al. Familial Myeloma. New England Journal of Medicine. 2008;359(2):152–7. [PubMed: 18614782]
57. Landgren O, Ma W, Kyle RA, Rajkumar SV, Korde N, Albitar M. Polymorphism of the erythropoietin gene promotor and the development of myelodysplastic syndromes subsequent to multiple myeloma. Leukemia. 2012;26(4):844–5. [PubMed: 21926963]
58. Andreotti G, Birmann BM, Cozen W, De Roos AJ, Chiu BCH, Costas L, et al. A pooled analysis of cigarette smoking and risk of multiple myeloma from the international multiple myeloma consortium. Cancer Epidemiol Biomarkers Prev. 2015;24(3):631–4. [PubMed: 25538226]
59. Psaltopoulou T, Sergentanis TN, Kanellias N, Kanavidis P, Terpos E, Dimopoulos MA. Tobacco smoking and risk of multiple myeloma: a meta-analysis of 40 observational studies. Int J Cancer. 2013;132(10):2413–31. [PubMed: 23047159]
60. Rota M, Porta L, Pelucchi C, Negri E, Bagnardi V, Bellocco R, et al. Alcohol drinking and multiple myeloma risk--a systematic review and meta-analysis of the dose-risk relationship. Eur J Cancer Prev. 2014;23(2):113–21. [PubMed: 24469244]
61. Andreotti G, Birmann B, De Roos AJ, Spinelli J, Cozen W, Camp NJ, et al. A pooled analysis of alcohol consumption and risk of multiple myeloma in the international multiple myeloma consortium. Cancer Epidemiol Biomarkers Prev. 2013;22(9):1620–7. [PubMed: 23964064]

62. Landgren O, Rajkumar SV, Pfeiffer RM, Kyle RA, Katzmann JA, Dispenzieri A, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. Blood. 2010;116(7):1056–9. [PubMed: 20421448]

63. Chang S-H, Luo S, Thomas TS, O'Brian KK, Colditz GA, Carlsson NP, et al. Obesity and the Transformation of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma: A Population-Based Cohort Study. JNCI: Journal of the National Cancer Institute. 2016;109(5).

64. Thordardottir M, Lindqvist EK, Lund SH, Costello R, Burton D, Korde N, et al. Obesity and risk of monoclonal gammopathy of undetermined significance and progression to multiple myeloma: a population-based study. Blood Adv. 2017;1(24):2186–92. [PubMed: 29296866]

65. Ostrand-Rosenberg S Myeloid derived-suppressor cells: their role in cancer and obesity. Curr Opin Immunol. 2018;51:68–75. [PubMed: 29544121]

66. Craver BM, El Alaoui K, Scherber RM, Fleischman AG. The Critical Role of Inflammation in the Pathogenesis and Progression of Myeloid Malignancies. Cancers (Basel). 2018;10(4):104.

67. Finn LE, Sproat LO, Heckman M, Jiang L, Diehl NN, Ketterling RP, et al. Association of obesity with cytogenetic risk in adult acute myeloid leukemia (AML). Journal of Clinical Oncology. 2014;32(15_suppl):7055–.

68. Jonsdottir G, Lund SH, Björkholm M, Turesson I, Hultcrantz M, Porwit A, et al. The impact of prior malignancies on second malignancies and survival in MM patients: a population-based study. Blood Adv. 2017;1(25):2392–8. [PubMed: 29296889]

69. Hasskarl J, Ihorst G, De Pasquale D, Schröttner P, Zerweck A, Wäsch R, et al. Association of multiple myeloma with different neoplasms: systematic analysis in consecutive patients with myeloma. Leukemia & Lymphoma. 2011;52(2):247–59. [PubMed: 21054148]

70. Landgren O, Shim YK, Michalek J, Costello R, Burton D, Ketchum N, et al. Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance: An Operation Ranch Hand Veteran Cohort Study. JAMA Oncology. 2015;1(8):1061–8. [PubMed: 26335650]

71. Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 2009;113(25):6386–91. [PubMed: 19387005]

72. Dosani T, Mailankody S, Korde N, Manasanch E, Bhutani M, Tageja N, et al. Host-related immunodeficiency in the development of multiple myeloma. Leukemia & Lymphoma. 2018;59(5):1127–32. [PubMed: 28792255]

73. Landgren O, Linet MS, McMaster ML, Gridley G, Hemminki K, Goldin LR. Familial characteristics of autoimmune and hematologic disorders in 8,406 multiple myeloma patients: A population-based case-control study. International Journal of Cancer. 2006;118(12):3095–8. [PubMed: 16395700]

74. Hemminki K, Liu X, Försti A, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. Journal of Hematology & Oncology 2012;5(1):59. [PubMed: 23031386]

75. Lindqvist EK, Landgren O, Lund SH, Turesson I, Hultcrantz M, Goldin L, et al. History of autoimmune disease is associated with impaired survival in multiple myeloma and monoclonal gammopathy of undetermined significance: a population-based study. Annals of Hematology. 2017;96(2):261–9. [PubMed: 27807648]

76. Ertz-Archambault N, Kosiorek H, Taylor GE, Kelemen K, Dueck A, Castro J, et al. Association of Therapy for Autoimmune Disease With Myelodysplastic Syndromes and Acute Myeloid Leukemia. JAMA Oncology. 2017;3(7):936–43. [PubMed: 28152123]

77. Takahashi K, Wang F, Kantarjian H, Doss D, Khanna K, Thompson E, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. The Lancet Oncology. 2017;18(1):100–11. [PubMed: 27923552]

78. Korde N, Liu QY, Kwok M, Manasanch EE, Simakova O, Mailankody S, et al. Early Myelodysplastic Changes Present in Substantial Proportion of Monoclonal Gammopathy of Unknown Significance (MGUS) and Smoldering Multiple Myeloma (SMM) Patients. Blood. 2012;120(21):1805–.

79. Matarraz S, Paiva B, Diez-Campelo M, López-Corral L, Pérez E, Mateos M-V, et al. Myelodysplasia-associated immunophenotypic alterations of bone marrow cells in myeloma: are

they present at diagnosis or are they induced by lenalidomide? Haematologica. 2012;97(10):1608–11. [PubMed: 22511492]

80. Matarraz S, Paiva B, Díez-Campelo M, Bárrena S, Jara-Acevedo M, Gutiérrez ML, et al. Immunophenotypic alterations of bone marrow myeloid cell compartments in multiple myeloma patients predict for myelodysplasia-associated cytogenetic alterations. Leukemia. 2014;28:1747. [PubMed: 24625552]
81. Razavi P, Li BT, Brown DN, Jung B, Hubbell E, Shen R, et al. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. Nature Medicine. 2019;25(12):1928–37.
82. Coombs CC, Zehir A, Devlin SM, Kishtagari A, Syed A, Jonsson P, et al. Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes. Cell Stem Cell. 2017;21(3):374–82.e4. [PubMed: 28803919]
83. Desai P, Roboz GJ. Clonal Hematopoiesis and therapy related MDS/AML. Best Pract Res Clin Haematol. 2019;32(1):13–23. [PubMed: 30927970]
84. Bolton KL, Ptashkin RN, Gao T, Braunstein L, Devlin SM, Kelly D, et al. Oncologic therapy shapes the fitness landscape of clonal hematopoiesis. bioRxiv. 2019:848739.
85. Landgren O, Hofmann JN, McShane CM, Santo L, Hultcrantz M, Korde N, et al. Association of Immune Marker Changes With Progression of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma. JAMA Oncology. 2019.
86. Talluri S, Samur MK, Nanjappa P, Yenumula C, Prabhala R, Shammas MA, et al. Immune Microenvironment Contributes to Dysregulation of Aid/Apobec Expression and Genomic Instability in Multiple Myeloma. Blood. 2017;130(Supplement 1):4333–.
87. Ghobrial IM, Detappe A, Anderson KC, Steensma DP. The bone-marrow niche in MDS and MGUS: implications for AML and MM. Nature Reviews Clinical Oncology. 2018;15(4):219–33.
88. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The Chemotherapy of Plasma-Cell Myeloma and the Incidence of Acute Leukemia. New England Journal of Medicine. 1979;301(14):743–8. [PubMed: 481481]
89. Cuzick J, Erskine S, Edelman D, Galton DA. A comparison of the incidence of the myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's working party on leukaemia in adults. British journal of cancer. 1987;55(5):523–9. [PubMed: 3300761]
90. Govindarajan R, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B, et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. Br J Haematol. 1996;95(2):349–53. [PubMed: 8904891]
91. Behjati S, Gundem G, Wedge DC, Roberts ND, Tarpey PS, Cooke SL, et al. Mutational signatures of ionizing radiation in second malignancies. Nature Communications. 2016;7(1):12605.
92. Rosenberg AS, Brunson AM, Tuscano JM, Jonas BA, Abedi M, Wun T, et al. Effect of Autologous Hematopoietic Stem Cell Transplant (aHSCT) on the Development of Second Primary Malignancies (SPM) in Multiple Myeloma Patients. Blood. 2017;130(Supplement 1):332–.
93. Barlogie B, Tricot G, Haessler J, van Rhee F, Cottler-Fox M, Anaissie E, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood. 2008;111(1):94–100. [PubMed: 17895401]
94. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500:415. [PubMed: 23945592]
95. Maura F, Rustad E, Yellapantula V, Bolli N, Leongamornlert D, Nadeu F, et al. Timing the initiation of multiple myeloma. Clinical Lymphoma, Myeloma and Leukemia. 2019;19(10):e6–e7.
96. Rustad E, Yellapantula V, Bolli N, Leongamornlert D, Nadeu F, Angelopoulos N, et al. Timing the Initiation of Multiple Myeloma. Cancer Cell. 2019.
97. Ahmedzai SH, Snowden JA, Ashcroft AJ, Cairns DA, Williams C, Hockaday A, et al. Patient-Reported Outcome Results From the Open-Label, Randomized Phase III Myeloma X Trial Evaluating Salvage Autologous Stem-Cell Transplantation in Relapsed Multiple Myeloma. Journal of Clinical Oncology. 2019;37(19):1617–28. [PubMed: 30969846]

98. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. New England Journal of Medicine. 2017;376(14):1311–20. [PubMed: 28379796]

99. Kazandjian D, Landgren O. Delaying the use of high-dose melphalan with stem cell rescue in multiple myeloma is ready for prime time. Clin Adv Hematol Oncol. 2019;17(10):559–68. [PubMed: 31730582]

100. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. New England Journal of Medicine. 2012;366(19):1782–91. [PubMed: 22571202]

101. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. New England Journal of Medicine. 2012;366(19):1770–81. [PubMed: 22571201]

102. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759–69. [PubMed: 22571200]

103. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(29):3279–89. [PubMed: 28742454]

104. Zhu YX, Braggio E, Shi C-X, Bruins LA, Schmidt JE, Van Wier S, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. Blood. 2011;118(18):4771–9. [PubMed: 21860026]

105. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia. 2010;24(1):22–32. [PubMed: 19907437]

106. Usmani SZ, Sexton R, Hoering A, Heuck CJ, Nair B, Waheed S, et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. Blood. 2012;120(8):1597–600. [PubMed: 22674807]

107. Moreau P, Dimopoulos MA, Richardson PG, Siegel DS, Cavo M, Corradini P, et al. Adverse event management in patients with relapsed and refractory multiple myeloma taking pomalidomide plus low-dose dexamethasone: A pooled analysis. European Journal of Haematology. 2017;99(3):199–206. [PubMed: 28504846]

108. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389(10068):519–27. [PubMed: 28017406]

109. Brioli A, Pezzi A, Derudas D, Petti MC, Zannetti BA, Ferrara F, Rocchi S, Nobile F, Baraldi AM, Musto P, Lanza F, Mancuso K, Canepa L, Catalano L, Lazzaro AD, Pinotti G, Boccadoro M, & Cavo M, editor Bortezomib (BOR)-Thalidomide-Dexamethasone (VTD) and High-Dose Melphalan (HDM) As First Line Treatment for Multiple Myeloma (MM) Is Associated with a Lower Rate of Second Primary Malignancies (SPMs) Compared to TD Plus HDM2014.

110. Chakraborty R, Muchtar E, Kumar SK, Buadi FK, Dingli D, Dispenzieri A, et al. Outcomes of maintenance therapy with lenalidomide or bortezomib in multiple myeloma in the setting of early autologous stem cell transplantation. Leukemia. 2018;32(3):712–8. [PubMed: 28848227]

111. Huang J, Phillips S, Byrne M, Chinratanalab W, Engelhardt BG, Goodman SA, et al. Lenalidomide vs bortezomib maintenance choice post-autologous hematopoietic cell transplantation for multiple myeloma. Bone Marrow Transplantation. 2018;53(6):701–7. [PubMed: 29703965]

112. Landgren O, Sonneveld P, Jakubowiak A, Mohty M, Iskander KS, Mezzi K, et al. Carfilzomib with immunomodulatory drugs for the treatment of newly diagnosed multiple myeloma. Leukemia. 2019;33(9):2127–43. [PubMed: 31341235]

113. Gay F, Cerrato C, Petrucci MT, Zambello R, Gamberi B, Ballanti S, et al. Efficacy of carfilzomib lenalidomide dexamethasone (KRd) with or without transplantation in newly diagnosed myeloma

according to risk status: Results from the FORTE trial. Journal of Clinical Oncology. 2019;37(15_suppl):8002–.

114. Landgren O, Thoren K, Hultcrantz M, Lesokhin AM, Lendvai N, Mailankody S, et al. Bone Marrow-Based and Longitudinal Blood-Based MRD Tracking in Newly Diagnosed Multiple Myeloma Patients Treated with Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (DKRd): A Correlative and Clinical Phase II Study. Blood. 2018;132(Supplement 1):3281–.
115. Corre J, Munshi N, Avet-Loiseau H. Genetics of multiple myeloma: another heterogeneity level? Blood. 2015;125(12):1870–6. [PubMed: 25628468]
116. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nature Reviews Cancer. 2012;12:335. [PubMed: 22495321]
117. Lohr Jens G, Stojanov P, Carter Scott L, Cruz-Gordillo P, Lawrence Michael S, Auclair D, et al. Widespread Genetic Heterogeneity in Multiple Myeloma: Implications for Targeted Therapy. Cancer Cell. 2014;25(1):91–101. [PubMed: 24434212]
118. Bolli N, Maura F, Minvielle S, Gloznik D, Szalat R, Fullam A, et al. Genomic patterns of progression in smoldering multiple myeloma. Nature Communications. 2018;9(1):3363.
119. Rustad EH, Yellapantula V, Glodzik D, Gundem G, Leongamornlert DA, Campbell PJ, et al. Revealing the Impact of Recurrent and Rare Structural Variations in Multiple Myeloma. Blood. 2019;134(Supplement_1):576–. [PubMed: 31395585]
120. Maura F, Petljak M, Lionetti M, Cifola I, Liang W, Pinatel E, et al. Biological and prognostic impact of APOBEC-induced mutations in the spectrum of plasma cell dyscrasias and multiple myeloma cell lines. Leukemia. 2018;32(4):1043–7.
121. Maura F, Bolli N, Angelopoulos N, Dawson KJ, Leongamornlert D, Martincorena I, et al. Genomic landscape and chronological reconstruction of driver events in multiple myeloma. Nature Communications. 2019;10(1):3835.
122. Reddi DM, Lu CM, Fedoriw G, Liu Y-C, Wang FF, Ely S, et al. Myeloid Neoplasms Secondary to Plasma Cell Myeloma: An Intrinsic Predisposition or Therapy-Related Phenomenon?: A Clinicopathologic Study of 41 Cases and Correlation of Cytogenetic Features With Treatment Regimens. American Journal of Clinical Pathology. 2012;138(6):855–66. [PubMed: 23161720]
123. Melchor L, Brioli A, Wardell CP, Murison A, Potter NE, Kaiser MF, et al. Single-cell genetic analysis reveals the composition of initiating clones and phylogenetic patterns of branching and parallel evolution in myeloma. Leukemia. 2014;28(8):1705–15. [PubMed: 24480973]
124. Mitra AK, Mukherjee UK, Harding T, Jang JS, Stessman H, Li Y, et al. Single-cell analysis of targeted transcriptome predicts drug sensitivity of single cells within human myeloma tumors. Leukemia. 2016;30(5):1094–102. [PubMed: 26710886]
125. Jang JS, Li Y, Mitra AK, Bi L, Abyzov A, van Wijnen AJ, et al. Molecular signatures of multiple myeloma progression through single cell RNA-Seq. Blood Cancer Journal. 2019;9(1):2. [PubMed: 30607001]
126. Lakshman A, Rajkumar SV, Buadi FK, Binder M, Gertz MA, Lacy MQ, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood cancer journal. 2018;8(6):59–. [PubMed: 29895887]
127. Mailankody S, Kazandjian D, Korde N, Roschewski M, Manasanch E, Bhutani M, et al. Baseline mutational patterns and sustained MRD negativity in patients with high-risk smoldering myeloma. Blood Adv. 2017;1(22):1911–8. [PubMed: 29296837]
128. Akhlaghi T, Rustad EH, Yellapantula VD, Korde N, Mailankody S, Lendvai N, et al. Identifying Ultra-High Risk Smoldering Multiple Myeloma. Blood. 2018;132(Suppl 1):3192.
129. Lonial S, Jacobus S, Fonseca R, Weiss M, Kumar S, Orlowski RZ, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. Journal of Clinical Oncology. 2019:JCO.19.01740.
130. Landgren O, Hultcrantz M, Lesokhin AM, Mailankody S, Hassoun H, Smith EL, et al. Weekly Carfilzomib, Lenalidomide, Dexamethasone and Daratumumab (wKRd-D) Combination Therapy Provides Unprecedented MRD Negativity Rates in Newly Diagnosed Multiple Myeloma: A Clinical and Correlative Phase 2 Study. Blood. 2019;134(Supplement_1):862–.
131. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma

XI): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology. 2019;20(1):57–73. [PubMed: 30559051]

132. Goldschmidt H, Mai EK, Dürig J, Scheid C, Weisel KC, Kunz C, et al. Response-Adapted Lenalidomide Maintenance in Newly Diagnosed, Transplant-Eligible Multiple Myeloma: Results from the Multicenter Phase III GMMG-MM5 Trial. Blood. 2017;130(Supplement 1):400–.
133. Nahi H, Chrobok M, Gran C, Lund J, Gruber A, Gahrton G, et al. Infectious complications and NK cell depletion following daratumumab treatment of Multiple Myeloma. PLOS ONE. 2019;14(2):e0211927. [PubMed: 30759167]
134. Habif G, Crinier A, André P, Vivier E, Narni-Mancinelli E. Targeting natural killer cells in solid tumors. Cellular & Molecular Immunology. 2019;16(5):415–22. [PubMed: 30911118]
135. Moon WY, Powis SJ. Does Natural Killer Cell Deficiency (NKD) Increase the Risk of Cancer? NKD May Increase the Risk of Some Virus Induced Cancer. Front Immunol. 2019;10:1703–. [PubMed: 31379882]

Practice points

- The risk of second malignancy after multiple myeloma diagnosis is low but is increasingly important in the context of improved survival.
- Risk-adapted treatment strategies should consider patient-, disease- and treatment-related factors.
- The rates of second malignancies after multiple myeloma will likely change as our treatment regimens evolve, suggesting ongoing risk-benefit analyses are necessary

Research Agenda

- Ongoing research includes the contribution of inherited defects in DNA-damage responses, clonal haematopoiesis and the tumour micro-environment to the development of second malignancies after multiple myeloma
- Serial comprehensive genomic analysis will better define disease- and treatment-related risk factors.
- Personalised risk- and response-adapted treatment regimens are in development for multiple myeloma and will likely affect the subsequent rate of second malignancies

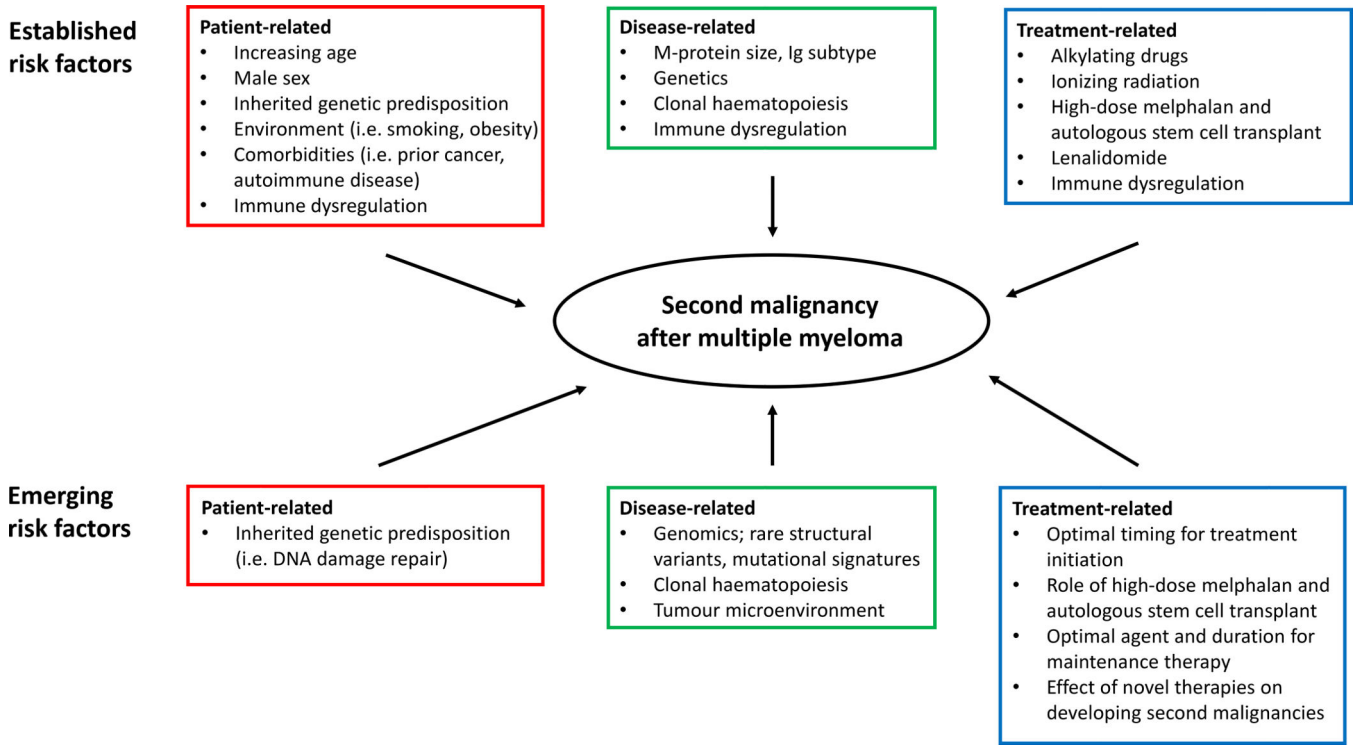

Figure 1.

Established and emerging risk factors for the development of second malignancy after multiple myeloma

Table 1.

Factors affecting risk for a second malignancy following a diagnosis of multiple myeloma

	Risk factor	References
Patient-related	Increasing age	11, 13, 18, 20, 23
	Male sex	13, 15, 18, 20
	Ethnicity	15, 41–44
	Genetics; single nucleotide polymorphisms, DNA damage repair, drug metabolism, CDKN2A mutation	36, 45–55
	Environment; smoking, obesity	18, 56–57, 60–65
	Comorbidities; prior cancer, autoimmune disease	66–67, 70–74
Disease-related	M-protein size and immunoglobulin subtype	12
	Clonal haematopoiesis	34, 75, 81
	Myeloma genetics	79–80
	Immune dysregulation	83
Treatment-related	Alkylating drugs	84–86
	Ionizing radiation	13, 87
	High-dose melphalan and autologous stem cell transplant	13, 86, 88–93
	Lenalidomide	20, 94–99
	Bortezomib	10, 102–105
Emerging areas for ongoing research	Myeloma genomics; rare structural variants, mutational signatures, defining the effect of clonal haematopoiesis	90, 116–120
	Tumour microenvironment	122–124
	Optimal timing for treatment initiation	125–128
	Role of autologous transplant	93
	Optimal duration and agent for maintenance	104–105
	Effect of novel therapies on second malignancy	130–132