Second primary malignancies in multiple myeloma: an overview and IMWG consensus

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Second primary malignancies in multiple myeloma: an overview and IMWG consensus

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abstract

Background: Therapeutic advancements due to the introduction of autologous stem cell transplantation and ‘novel’ agents have significantly improved clinical outcomes for patients with multiple myeloma (MM). Increased life expectancy, however, has led to renewed concerns about the long-term risk of solid or hematologic second primary malignancies (SPMs). This review aims to disseminate the most up-to-date knowledge of possible host-, disease-, and treatment-related risk factors for the development of SPMs in patients with MM, and to provide practical recommendations to assist physicians.

Design:A panel of members of the International Myeloma Working Group reviewed the most relevant data published in the literature as full papers, or presented at meetings of the American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, or International Myeloma Workshop up to December 2015. The recommendations of the Panel, based on the findings of this literature review, are presented in this paper.

Results: The published literature indicates that, overall, the risk of SPMs in MM is low, multifactorial, and partially related to the length of patients’ survival and MM intrinsic susceptibility. Phase III trials and meta-analyses have reported an increase in SPMs when lenalidomide is administered to patients either following, or concurrently with, oral melphalan; however, the risk of death from MM or adverse events in these patients was significantly higher than the risk of death from SPMs. There is also no evidence of increased SPM incidence associated with lenalidomide plus high-dose intravenous melphalan, or with bortezomib plus oral melphalan, dexamethasone, or thalidomide.

Conclusion: Based on the available data, the Panel concludes that the potential risk of SPMs in MM should not alter the current therapeutic decision-making process. In particular, regimens such as lenalidomide plus dexamethasone should be preferred to prolonged exposure to oral melphalan plus lenalidomide.

key words: multiple myeloma, second primary malignancy, risk factors, lenalidomide, International Myeloma Working Group

key message

This in-depth review summarizes possible risk factors for second primary malignancies (SPMs) in multiple myeloma, and provides practical recommendations. Based on the most recent literature data, members of the International Myeloma Working Group conclude that concerns about the risk of SPMs, which is low and multifactorial, should not alter the current therapeutic decision-making process.

introduction

The potential for solid or hematologic second primary malignancies (SPMs) to develop in patients originally diagnosed with multiple myeloma (MM) has long been recognized. Forty-five years ago, Dr Robert Kyle and co-workers described the subsequent development of acute myeloid leukemia (AML) in four patients who had received prolonged melphalan treatment for MM or systemic amyloidosis [1]. Nine years later, other researchers reported a greater-than-expected incidence of AML (14 cases, 3.8%) among 364 patients with MM who had received low-dose melphalan in combination with other alkylating agents [2].

Subsequent Medical Research Council (MRC) studies strengthened the case for a link between prolonged exposure to alkylating agents and SPM development in patients with MM, reporting 5-, 8-, and 10-year prevalences of myelodysplastic syndromes (MDS) or AML in MM patients treated with melphalan or (albeit less consistently) cyclophosphamide of 3%, 10%, and 20%, respectively [3]. More recently, detailed pathological analysis of myeloid neoplasms secondary to MM (mainly MDS or AML) has furnished support for the hypothesis that alkylating agents exert a mutagenic effect on the pathogenesis of hematologic SPMs, with evidence of complex cytogenetic abnormalities/unbalanced aberrations of chromosomes 5/7 being particularly associated with melphalan/cyclophosphamide combinations [4].

Over the past decade, the successive introduction of high-dose melphalan followed by autologous stem cell transplantation (ASCT) as standard initial therapy in younger patients, and of the first generations of ‘novel’ agents, such as the immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and the proteasome inhibitor bortezomib, has improved clinical outcomes and life expectancy in MM, with current expected median survival ranging from 5 to 8 years [5–8]. However, increased life expectancy has rekindled concerns about the long-term risk

of solid or hematologic SPMs [9–11], particularly as the prognosis of many potential SPMs remains very poor in comparison with MM [12–15]. A recent Swedish, population-based study of 26,627 patients diagnosed with MM between 1958 and 2011 confirmed a statistically significant 2.3-fold (95% confidence interval [CI] 2.1–2.5) increased mortality risk in patients with SPMs versus a control group of MM patients without SPMs [16]. The randomized, phase III trials finding that lenalidomide maintenance therapy is associated with a significantly increased risk of SPMs (7%–8%) versus placebo (2%–3%), in both elderly [17] and transplant-eligible patients [18, 19], has further added to these concerns [20–22].

This paper aims to disseminate the latest knowledge of SPM risk factors in patients with MM, and provides practical recommendations and guidance to assist physicians in the management of patients with MM. In particular, a panel composed of members of the International Myeloma Working Group has considered the following questions:

1. What is the ‘true’ risk of SPM development in patients with MM?
2. What are the possible host- and disease-related risk factors for SPMs in patients with MM?
3. Do older and novel therapies increase the risk of SPM development in MM?

The recommendations of the Panel in relation to each of these questions are summarized in Table 1, and are presented in detail in the Supplementary Appendix. These recommendations are based on the most relevant data published in the literature as full papers (identified through the PubMed database) or presented at meetings of the American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, or International Myeloma Workshop, up to December 2015.

what is the ‘true’ risk of SPM development in patients with MM?

Table 2 summarizes several major population-based, cancer registry studies that investigated SPM incidence in patients with MM. These studies generally found no overall increase in SPM risk among patients with MM, but did identify an augmented incidence of MDS, AML and, to a lesser degree, non-Hodgkin lymphoma (NHL). In contrast, significant heterogeneity in the risk of different solid SPM subtypes was observed (Table 2).

It is not easy to draw firm conclusions about the ‘true’ risk of SPMs in MM, or to identify specific risk factors in a process that is likely to be multifactorial. Firstly, the estimated overall risk reported is relatively small: the cumulative incidence is 1%–10%, which is comparable with the incidence of cancer per year of life in the general population [31]. Consequently, some reports – particularly of uncontrolled/retrospective and post-hoc studies – may underestimate SPMs, as they are not specifically tracked during follow-up. Conversely, over-reporting may occur if SPMs are expected to be found in specific arms or subgroups of trials, or when appropriate screening is used to prospectively detect early SPMs. In general, well-designed, registry-based, population studies, which include individual treatment and long follow-up, may be a more effective means of determining therapy-associated SPM risk than some randomized trials, which are limited by inclusion and exclusion criteria, lower power, and treatment crossover.

Pre-existing or concomitant neoplasms could represent additional confounding factors (see below) [32–36]. On the other hand, recent studies indicate that SPM risk may be elevated as a ‘natural’ consequence of the increased survival achieved with current treatments, rather than as a direct result of the therapies themselves [9–11].

Finally, a correct diagnosis of ‘true’ SPM is mandatory. Recently, SPMs occurring in the UK MRC Myeloma XI study were reviewed by an ad-hoc independent committee according to pre-determined criteria [37]. Of 88 reported SPM cases, only 67 (76%) were confirmed as trial-related SPMs; the remaining cases were rejected because of: evidence that the second malignancy pre-existed prior to trial enrollment (57%); no evidence of malignancy found on further investigation (24%); reported non-malignant skin conditions (14%); and spontaneous resolution of cytopenias upon cessation of treatment (5%).

what are the possible host- and disease-related risk factors for SPMs in patients with MM?

SPM development is likely multicausal. In addition to specific treatments, possible risk factors may be classified as either host- or disease-related.

host-related risk factors

age and sex. Among potential host-related factors, older age and male sex have most commonly been associated with increased SPM incidence in patients with MM [18, 26, 38, 39]. Nevertheless, there are inconsistencies in the published data. Updated data from the Surveillance, Epidemiology, and End Results (SEER) program, for example, showed a decrease in total SPM risk with increasing age: MM patients <65 years of age had a 5-fold increased risk of developing AML versus those aged >75 years) [27]. Meanwhile, women with MM were found to be at significantly increased risk of leukemia versus men [27].

ethnicity. Several SEER-based analyses demonstrate an impact of ethnicity on the risk of SPM development in patients with MM [26, 40]. In an analysis of 2021 patients with MM and SPMs

(diagnosed between 1973 and 2008), Hispanic whites had a significantly decreased observed/expected (O/E) risk of developing overall (O/E 0.67; 95% CI 0.50–0.88), all solid-organ (0.66; 95% CI 0.48–0.89), lung/bronchus (0.34; 95% CI 0.08–0.88), and prostate SPMs (0.48; 95% CI 0.19–0.99). Non-Hispanic whites showed an increased O/E risk of developing melanoma of the skin (1.38; 95% CI 1.06–1.78), NHL (1.28; 95% CI 1.01–1.61), and AML (6.85; 95% CI 5.55–8.38). The O/E risk of developing SPMs of the kidney/renal pelvis (O/E 2.17; 95% CI 1.31–3.39) and AML (6.24; 95% CI 3.41–10.47) was increased among African Americans. The O/E risk of AML as a SPM was also found to be significantly increased among Asian Pacific Islanders (6.32; 95% CI 1.72–16.19) [40].

genetics. Genetic alterations and their interaction with environmental factors and/or therapy may contribute to familial and individual predisposition to MM and, possibly, to different SPMs [41–43]. Genotype studies have shown that germline mutations in the *CDKN2A* gene may predispose to both MM and other cancers [41]. Furthermore, the G/G phenotype of single nucleotide polymorphism (SNP) rs1617640 in the erythropoietin promoter gene has been found to be more common in individuals with MM who develop MDS versus those who do not [44], thus confirming a potential role for susceptibility genes in the development of SPMs in these patients. Other genetic polymorphisms have been found to be associated with an increased risk of MM [45], while conversely appearing to protect against potential solid SPMs, including prostate cancer [27, 46]. Genome-wide association studies and gene expression microarray analysis of groups of patients with or without SPMs have identified several other candidate SNPs that are associated with acute leukemia after other neoplasms [47, 48]. Studies investigating baseline whole bone marrow gene-expression profiling, proteomic analyses, and SNPs are currently ongoing, with the aim of identifying patients who may have a marked propensity to develop SPMs [43].

prior cancer. Studies have shown that prior or synchronously different malignancies (PSMs) are more common than SPMs in MM, occurring in 3%–24% of patients and thus representing a possible confounding factor when a diagnosis of SPM is suspected [33, 35, 36, 49–51]. While these tumors are often early-stage or good-prognosis neoplasms, the largest group (up to 90%) of invasive PSMs comprises prostate, gastric, colorectal, and breast cancers, while fewer hematologic malignancies (10%–27%) have been reported.

Patients with PSMs frequently have a history of chemotherapy, radiotherapy, and/or hormone therapy, which confers a poor prognosis. In these patients, MM potentially occurs as a SPM. Interestingly, in a large Swedish study, MM patients with PSMs at diagnosis were not at increased risk of developing a subsequent SPM versus MM patients without PSMs (overall response 1.19; 95% CI 0.97–1.46) [52]. These findings suggest that patients with MM and a PSM should not be denied the best available therapy because of fears of SPM development.

additional individual factors. Many additional socio-economic, occupational, lifestyle, and environmental factors could potentially play a role in the development of both SPMs and primary cancers. The potential involvement of such factors in the context of competing risks may be difficult to differentiate, especially if their real impact on the development of SPMs is small; consequently, no firm data have yet been produced in the setting of MM [10, 11, 53].

disease-related risk factors

That MM by itself (independent of MM therapy) may be a risk factor for SPM development was first hypothesized nearly 40 years ago [54]. Since then, baseline plasma cell cytogenetics, disease stage, and some MM subtypes have been associated with increased SPM incidence.

Interestingly, the risk of developing MDS/AML appears significantly increased in individuals with monoclonal gammopathy of undetermined significance (MGUS) versus the general population. For example, in a large, Swedish, population-based study, the risk of MDS/AML was increased 8-fold in the subset of 2293 patients with IgG or IgA isotype MGUS versus age- and sex-matched individuals from the general population [24]. Risk levels were increased in patients with raised M-component concentrations >1.5 g/dl versus those with lower levels, suggesting that the risk of MDS/AML development in MGUS patients with more extensive/advanced disease is similar to that in patients with symptomatic MM. An excess risk of non-melanoma skin cancer in MGUS, similar to that observed in symptomatic MM, was also seen.

A Mayo Clinic study systematically screened 17,315 individuals for the presence of MGUS [55]. Of the 605 patients found to have MGUS, seven were subsequently diagnosed with MDS, and two with AML (one of whom had antecedent MDS). Compared to 16,710 non-MGUS controls, these MGUS patients had a 2.4-fold significantly increased risk of developing MDS; the risk of AML was slightly, but not significantly, increased. No cases of acute lymphoblastic leukemia (ALL) were seen in the MGUS cohort. In a subanalysis, MDS occurred in patients with all Ig isotypes (including IgM), while AML was observed only in patients with IgA/IgG. Such results were not changed when ‘early’ MDS/AML patients, diagnosed within the first year following diagnosis of MGUS, were excluded.

Despite differences in study design and number of MGUS patients included, the Swedish and Mayo clinic findings both suggest a possible intrinsic causal role for plasma cell disorders, and a consequent inherent increased risk of MDS/AML that is independent of MM therapy. Recently, however, International Staging System stage and history of smoldering myeloma or MGUS were found to have no impact on SPM occurrence in a large, US disease registry study

[29]. Interestingly, plasma cell cytogenetic abnormalities were linked with an increased incidence of SPMs in symptomatic MM (hazard ratio [HR] = 1.64, $P < 0.05$), when modeled from study enrollment in the Total Therapy (TT) trials [56]. Furthermore, three of the patients who ultimately developed MDS/AML in the lenalidomide arm in the MM-015 trial were part of a group of 11 patients with plasma cell complex cytogenetics at baseline [57]. In contrast, predominantly favorable cytogenetics have been reported in patients who develop SPMs, suggesting that less aggressive MM and long disease latency may favor the manifestation of additional malignancies [30].

Tumor-induced immunodeficiency, deregulated release of cytokines, chronic inflammation, and common tumor cell precursors may also play an important role in increasing the susceptibility of MM patients to SPM development [58]. Immunologic defects may include quantitative and functional abnormalities in T-cell and B-cell compartments, natural killer and dendritic cell populations, and neutrophils, as well as abnormal cytokine production, modified membrane antigen/receptor expression, and impaired phagocytosis. Additionally, the possibility of transforming MM into a chronic entity, with multiple relapses and salvage therapies using older and newer drugs in sequence, may result in cumulative immunosuppression/dysfunction, further compromising immune surveillance against tumor cells. This could play a particularly significant role in increasing the risk of various skin cancers, including melanoma. MM pathogenesis could also modify sex hormone levels, which could explain the decreased risk of some hormone-related solid SPMs – including breast and prostate cancer – that is seen in MM. However, less frequent screening after MM diagnosis is another possible explanation for the reported reduced risk of these solid SPMs [27].

do older and novel therapies increase SPM risk in MM?

Early studies identified that prolonged exposure to melphalan increases the risk of hematologic SPM development (in particular, MDS/AML) in patients with MM, likely as a result of a direct mutagenic effect inducing DNA damage [1–4]. The MM treatment paradigm has evolved significantly over the past few years, and numerous studies have continued to investigate treatment-related risk factors for SPMs. The characteristics and findings of the key retrospective studies and prospective first-line phase III randomized trials that have gathered information on the impact of various anti-myeloma treatments on SPM incidence in patients with MM are summarized in Tables 3 and 4, respectively.

radiotherapy

Radiation dose and extended fields are supposed, but not well proven, factors favoring SPM development in patients with MM. Indeed, several solid SPMs have been described in MM patients following combination chemo-radiotherapy [10, 24, 49, 56]. However, compared with other malignancies in which loco-regional radiation treatments may induce SPMs in surrounding tissues (including bone marrow), information about the exact role of radiotherapy and risk of SPMs in MM is currently limited. Recent US Connect MM registry data did not support a possible relationship between radiotherapy and SPM incidence [29]; this could be due to the lower radiotherapy dose usually administered to patients with MM.

ASCT

Data suggest that secondary MDS/AML risk is increased following ASCT in patients with lymphoma (14.5% cumulative incidence up to 15 years) [72]. This risk is increased further by older age, male sex, obesity, and pre-transplant treatment with alkylating agents [13, 38]. In contrast to lymphoma patients, however, studies have found no significant increase in SPM incidence following ASCT in patients with MM [24, 27, 38, 73]. In particular, a recent

retrospective study in the USA found a similar incidence of new cancers in a large auto-transplantation cohort to that in age-, race-, and gender-adjusted comparison subjects, with an O/E ratio of 1.00 (99% CI 0.81–1.22) [38].

SPM rates in patients with MM post-ASCT may be attributable to 'conventional', alkylating agent-incorporating therapy prior to transplantation, rather than to the myeloablative therapy itself. For example, while investigating the possible role of high-dose melphalan in augmenting the risk of secondary MDS/AML in MM patients, Govindarajan et al. [61] observed seven MDS cases in 117 patients who had received extended courses of chemotherapy prior to tandem ASCT, whereas no cases were observed among 71 patients who received limited chemotherapy before ASCT [61]. The authors concluded that preceding treatments, and not conditioning with high-dose melphalan, were the likely cause of MDS post-ASCT.

The low risk of SPM development after ASCT in MM versus lymphoma patients may be partially explained by the earlier use of transplants in MM, the attention paid to avoiding pre-transplant stem-cell-damaging agents, and the cessation of total body irradiation during conditioning [74].

novel agents

IMiDs: thalidomide and lenalidomide. Initial population studies found no relationship between SPM incidence in MM and treatment with novel agents, including thalidomide and lenalidomide [24, 27, 60]. However, these studies were limited by a short follow-up period, lack of focus on SPMs, and the non-uniform use of novel agents during their first few years of availability. Several major studies have since indicated that lenalidomide may increase SPM risk, particularly in the maintenance setting [75]. These studies include three large, phase III,

placebo-controlled, randomized trials (IFM 2005-002, CALGB 100104, MM-015), all of which reported a significantly increased incidence of SPMs in newly diagnosed patients with MM who received lenalidomide maintenance versus similar patients who did not receive lenalidomide maintenance after either ASCT [18, 19, 76] or induction therapy [17, 77]. A recent update to CALGB 100104 confirmed that lenalidomide maintenance post-ASCT continued to be associated with an increased risk of SPMs versus placebo [78]; however, a post-hoc survey of this study raised the possibility that the entire patient population may have had an inherent risk for other malignancies, owing, at least in part, to risk factors such as age, prior tumors, prior therapies, and family history [50]. Interestingly, secondary ALL after lenalidomide treatment have been reported only rarely [18, 79].

A 2014 meta-analysis of seven randomized, controlled, phase III clinical trials that included lenalidomide as first-line therapy reported increased hematologic SPM incidence in newly diagnosed MM patients: 32/2620 (1.2%) versus 3/598 (0.5%) in patients treated (+L) or not treated (–L) with lenalidomide [39]. The cumulative incidence at 5 years was 3.1% (95% CI 1.9–4.3%) in the +L group versus 1.4% (95% CI 0.0–3.6%) in the –L group. In +L patients, SPM incidence increased linearly over time, and was significantly higher than in –L patients (HR = 3.8, 95% CI 1.15–12.62, $P = 0.029$). Co-exposure to lenalidomide and oral melphalan appeared to be the main driver of increased hematologic SPM risk (5-year cumulative incidence 3.9%), while lenalidomide plus cyclophosphamide (not estimable), lenalidomide alone (1.3%), and melphalan alone (1.4%) had no impact. The hematologic SPM risk associated with the combination of oral melphalan plus lenalidomide was also significantly increased versus intravenous melphalan and lenalidomide. In comparison with the situation in relation to hematologic SPMs, the distribution of solid SPMs was similar in +L and –L groups, with the exception of urinary tract tumors, which were more common in the +L group. This latter finding may be a consequence of the renal excretion of lenalidomide. Finally, it is worth noting that, in

the +L group, the risk of SPM-related mortality (2.4%) was significantly lower than the risk of death owing to either MM (26.5%) or treatment-related adverse events (9.8%) [39].

Several other studies have also suggested that, in patients with either newly diagnosed or relapsed/refractory MM, SPM risk may be increased with lenalidomide plus oral melphalan, but not with lenalidomide plus cyclophosphamide [80, 81] or dexamethasone [36, 64–66, 82]. As no increase in SPM incidence has been reported with lenalidomide in combination with dexamethasone, even on prolonged administration [66], a possible ‘protective’ effect of this drug might be considered. Different melphalan dose [67] and/or lenalidomide dosing schedules (3 weeks on, 1 week off versus continued treatment) could explain the lack of increased SPM incidence in some studies of lenalidomide maintenance therapy.

The actions of lenalidomide are complex, and the mechanism(s) by which it might favor SPM development remain undefined. Lenalidomide’s immunosuppressive activity, and its effects on the tumor microenvironment, may favor the escape/growth of abnormal clones that could result in the development of SPMs. Alternatively, treatment-related MDS/AML might be caused by a possible damaging stem-cell effect of lenalidomide. Cereblon, a molecular target for the anti-MM activity of lenalidomide, is a component of the E3 ubiquitin-ligase complex that is essential for nucleotide excision repair [83]. Inhibition of cereblon/DDB1 complex by lenalidomide impairs repair mechanisms after melphalan-induced DNA damage, and could therefore facilitate the development of SPMs [83].

Analysis of data from the TT2 trial showed a trend for increased solid SPM risk from the initiation of maintenance therapy in the TT plus thalidomide maintenance versus the TT without thalidomide arm [56]. This suggests an IMiD class effect, rather than a lenalidomide-specific

effect, associated with alkylator exposure. However, the absence of a randomized comparison and the number and variety of drugs used in the TT trials make it difficult to determine whether the thalidomide-associated increased SPM risk in TT2 is of similar magnitude to that seen with lenalidomide (see below).

bortezomib. Studies conducted to date indicate that bortezomib is associated with a low risk of SPM development. For example, after 54 months' follow-up, SPM incidence in elderly patients with MM who were treated with VMPT-VT (a four-drug combination comprising bortezomib, melphalan, prednisone, and thalidomide, followed by maintenance treatment with bortezomib plus thalidomide) was 0.9% versus 1.5% in similar patients treated with VMP (bortezomib, melphalan, and prednisone) [69]. In the phase III VISTA trial in patients with previously untreated MM, incidences of hematologic and solid tumor SPMs after 60.1 months' follow-up did not differ significantly between patients treated with VMP (1% and 5%, respectively) versus those treated with melphalan plus prednisone (1% and 3%, respectively), and were consistent with background rates [70].

Mature data on the incidence of SPMs were recently available for 299 patients enrolled in the phase III, multicenter, GIMEMA 26866138-MMY-3006 clinical trial that compared bortezomib, thalidomide, and dexamethasone (VTD) versus thalidomide plus dexamethasone (TD) as induction before, and consolidation after, a double ASCT [71]. The proportion of patients who developed SPMs was lower in the VTD (5%) than in the TD arm (11%, $P = 0.068$). Among those patients who developed SPMs, solid (75% versus 71%) and hematologic (25% versus 29%) SPM rates were similar in the two arms. In the overall population, SPM incidence was significantly reduced at 6 years among patients randomized to VTD versus TD (6% versus 13%; $P = 0.037$). When the analysis was performed according to SPM type, no statistically significant

difference could be demonstrated. These data suggest that bortezomib may be associated with a low risk of SPM development, and that this particular drug may even decrease the risk of SPMs due to thalidomide when used in combination. A large, single-institution, registry analysis of host-, myeloma-, and treatment-specific risks for SPMs in 744 consecutive MM patients recently confirmed that cumulative incidence rates for SPMs were decreased in bortezomib-treated patients [30].

other novel agents. Consolidated data examining the SPM risk associated with the second-generation proteasome inhibitor carfilzomib, the third-generation IMiD pomalidomide, and the histone-deacetylase inhibitor panobinostat are not yet available. However, none of the studies published to date reported an increased SPM risk in patients treated with these drugs [84–91]. In particular, the combination of carfilzomib, lenalidomide, and dexamethasone was not associated with an increased incidence of SPMs in relapsed MM (2.8%) versus lenalidomide plus dexamethasone (3.3%) [90].

SPM development following treatment with monoclonal antibodies was investigated in a recent phase III trial comparing the combination of elotuzumab (an anti-SLAMF7 monoclonal antibody), lenalidomide, and dexamethasone (elotuzumab group) versus lenalidomide plus dexamethasone (control group) in patients with relapsed or refractory MM [92]. SPMs developed in 35 of the 635 patients treated (5.5%): 22 (6.9%) in the elotuzumab group and 13 (4.1%) in the control group, without significant differences between the rates of hematologic SPMs and second solid tumors. After adjustment for exposure to study therapy, the second primary cancer incidence rate per 100 patient-years was 3.5 in the elotuzumab group versus 2.8 in the control group. No increase in SPM incidence was reported in a phase I study of single-agent daratumumab (an anti-CD38 monoclonal antibody) in MM [93].

summary

SPMs represent a relatively small, but clinically relevant, issue that must be considered and managed within the current treatment paradigms available to patients with MM. For individual patients with MM in whom a secondary hematologic or solid tumor is diagnosed, the clinical and psychological consequences may, indeed, be devastating. These two parallel perspectives (‘on average’ versus ‘individual patients’) should be carefully taken into consideration by any physician. Our goal should be to significantly reduce the impact of SPMs on MM patients by clarifying the biologic mechanisms involved, identifying associated risk factors, improving understanding of clinical behavior, and applying appropriate preventive strategies.

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tables

Table 1. Panel recommendations

Recommendation
What is the ‘true’ risk of SPM development in patients with MM?
• Well-designed, population-based studies suggest that the risk of SPMs in MM is low, and is partially related to the lengthening survival of patients with MM • The risk of SPMs should be evaluated in individual patients, according to patient-, disease-, and treatment-related factors • Additional and systematic data gathering is needed to determine the incidence and types of SPMs in patients with MM currently treated both in clinical trials and in the real-world setting • Ongoing trial protocols should be amended to include enhanced monitoring and precise measurement of secondary cancers (including non-invasive neoplasms), and include SPMs as an ‘a priori’ well-defined endpoint. These measures should be integral to the design of any future prospective clinical trials • Prospective population-based studies gathering information on the baseline characteristics and treatment of individual patients should also report SPM data • SPM data collected in clinical trials and observational studies should include details of the time to development, clinical and biologic characteristics, prognosis, and natural history of SPMs observed • SPM incidence rates should be adjusted for person-years at risk (that is, rate per 100 person/years) • Specific routine screening for SPMs, beyond that suggested for the general population, is not recommended. However, diagnostic measures that would aid the detection of suspected SPMs during daily clinical work-up should be considered, on a case-by-case basis, in long-term MM survivors. In particular, bone marrow examination with cytogenetic analyses (or FISH, if necessary) is recommended at baseline and in the event of unexplained blood count abnormalities in the real-life setting and in prospective observational and investigational studies • Every SPM case should be reviewed carefully to accurately assess the true impact of treatment on SPM development, and to prevent false inflation of reported SPM rates
What are the possible host- and disease-related risk factors for SPMs in patients with MM?
• The pathogenesis of SPMs in MM is likely to be multifactorial • Biologic samples from all MM patients included in clinical trials and, when possible, encountered in clinical practice, should be collected and stored for genetic analysis. Ideally, samples should yield DNA for genomic analysis or, better still, RNA for gene expression profiling. Collection of germline and tumor-related material, and re-banking of biologic samples during the course of the disease, are also recommended • Next-generation sequencing genomic studies designed to identify genetic profiles associated with increased SPM risk should be planned
Do older and novel therapies increase the risk of SPM development in MM?
• Based on the available evidence, the potential risk of SPMs in MM should not alter the current therapeutic decision-making process • Data regarding the use of ASCT in MM are reassuring, and the Panel recommends that first-line therapeutic approaches in eligible MM patients should always include ASCT conditioned with high-dose intravenous melphalan

- For the current approved indication of lenalidomide in the treatment of relapsed MM, the benefits of therapy clearly outweigh any risk of SPMs
- Similarly, in front-line therapy without concurrent oral melphalan, regimens such as lenalidomide plus dexamethasone (or alternatives such as cyclophosphamide or alkylating-free combinations) remain safe and effective options that should be considered for patients with MM, instead of oral melphalan in combination with lenalidomide
- In the maintenance setting, prolonged administration of lenalidomide where there is antecedent melphalan exposure should generally be avoided, with the important exception of high-dose melphalan used as a conditioning regimen for ASCT
- All patients initiating lenalidomide maintenance should undergo a baseline bone marrow examination with cytogenetics to ensure that there is no overt evidence of dysplasia or concerning cytogenetic abnormalities. There should also be a low threshold for careful bone marrow analysis with karyotyping for patients with unexplained cytopenias that persist despite lenalidomide withdrawal
- In cases where the overall survival benefit of maintenance therapy with lenalidomide is still not well established, the risks versus any possible benefits of treatment should be considered carefully
- The potential increased risk of SPMs should be adequately addressed through appropriate discussion with the patient with MM, bearing in mind current knowledge about treatment-associated risks and benefits
- Physicians should remain well informed about the latest data on the risk of SPMs in MM

ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization; MM, multiple myeloma; SPM, secondary primary malignancies.

Table 2. Key population-based registry studies evaluating the incidence of SPMs in patients with MM

Authors	Type of study	Study period	Patients (*N*)	All SPMs (*n*, %)	Hematologic SPMs (*n*, %)	Solid tumor SPMs (*n*, %)	Time from MM diagnosis to SPM development (median)	All SPMs SIR (95% CI)	Hematologic SPMs SIR (95% CI)	Solid tumor SPMs SIR (95% CI)
Dong et al. [23]	Population-based registry study	1958–1996	8656	475 (5.5)	83 (1.0)	392 (4.5)	2.9 y	NR	All HMs 2.19 (1.74–2.71); NHL 1.74 (1.12–2.57); AML 8.19 (5.70–11.4)	All STs 0.81 (0.70–0.90)
Mailankody et al. [24]	Population-based registry study	1986–2005	8740	577 (6.6)	69 (0.8)	508 (5.8)	45.3 mo MDS/AML	All SPMs 1.26 (1.16–1.36)	All HMs 2.04 (1.59–2.58); AML/MDS 11.51 (8.19–15.74)	All STs 1.19 (1.09–1.30); GI 1.30 (1.09–1.53); NMST 2.22 (1.74–2.80)
Youlden et al. [25]	Population-based registry study	1982–2001	2174	134 (0.6)	NR	NR	NR	Males 1.04 (0.84–1.27); females 0.89 (0.64–1.21)	NR	NR
Chakraborty et al. [26]	Selected population of MM patients with SPMs	1973–2008	3245 patients with MM as first of ≥ SPM	1657 (51.1)	214 (6.6)	1394 (43.0)	NR	All SPMs 0.99 (0.95–1.04)	All HMs 1.68 (1.46–1.92); all leukemias 3.07 (2.57–3.64); ALL 5.48 (NR); AML 7.01 (NR); CML 2.26 (NR)	All STs 0.94 (0.89–0.99); hypopharynx 0.0 (NR); esophagus 0.35 (NR); breast 0.76 (0.63–0.90); prostate 0.75 (NR); small intestine 2.03; skin, excluding basal/squamous carcinomas 1.43 (1.09–1.85); kidney 1.51 (1.13–1.98); KS 3.3 (1.06–7.69)

Razavi et al. [27]	Population-based registry study	1973–2008	36,491	2026, including 56 miscellaneous (5.5)	263 (0.7)	1707 (4.7)	5.2 y	All SPMs: 0.98 (0.94–1.02)	All HMs 1.63 (1.45–1.84); AML 6.51 (5.42–7.83); NHL 1.28 (1.04–1.57)	All STs 0.92 (0.88–0.97); esophagus 0.49 (0.28–0.87); lung 0.88 (0.78–0.99); breast 0.81 (0.69–0.94); prostate 0.69 (0.61–0.77); melanoma 1.36 (1.07–1.74); urinary bladder 1.22 (1.03–1.44); kidney/renal pelvis 1.30 (1.01–1.66); thyroid 1.63 (1.05–2.52)
Tzeng et al. [28]	Population-based registry study	1997–2009	3970	71 (1.8)	35 (0.9)	36 (0.9)	1.9 y	NR	All HMs 13.0 (7.79–21.6); NHL 7.72 (3.83–15.6); AML 23.9 (10.5–54.5)	All STs 0.57 (0.40–0.79); lung 0.28 (0.09–0.87)
Rifkin et al. [29]	US MM Registry study	2009–2012	1493 enrolled, 1443 treated	74 (5.1); invasive 51 (3.5); NMST 26 (1.8%)	14 (1.0)	37 (2.6)	NR	Incidence per 100/patient-y in 977 patients +L: invasive: 0.85 (0.61–1.19); incidence per 100/patient-y in 466 patients -L: invasive: 1.16 (0.72–1.86)	Incidence per 100/patient-y in 977 patients +L: invasive HMs: 0.17 (0.08–0.36); incidence per 100/patient-years in 466 patients -L: invasive HMs: 0.47 (0.22–0.99)	Incidence per 100/patient-y in 977 patients +L: invasive STs: 0.67 (0.46–0.98); NMST 0.50 (0.32–0.77); incidence per 100/patient-y in 466 patients -L: invasive STs: 0.68 (0.36–1.26); NMST 0.41 (0.18–0.91)

Engelhardt et al. [30]	Friburg University Registry study	1997–2011	744	49 (6.6)	17 (2.3)	32 (4.3)	NR	NR	NR	NR

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; GI, gastrointestinal; HM: hematologic malignancy; KS, Kaposi's sarcoma; +L, exposure to lenalidomide; -L, no exposure to lenalidomide; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; NHL, non-Hodgkin lymphomas; NMST, non-melanoma skin tumors; *n*, number; *NR*, not reported; SIR, standardized incidence rate; SPM, secondary primary malignancy; ST, solid tumor; y, years.

Table 3. Key retrospective studies that evaluated SPM incidence in patients with MM

Authors	Type of study	Study period (median follow-up)	Patients (*N*)	All SPMs (*n,* %)	Hematologic SPMs (*n,* %)	Solid tumor SPMs (*n,* %)	Time from MM diagnosis to SPM development (median)	Additional information
Cuzick et al. [3]	Retrospective study based on clinical trials (MRC)	1964–1975	648	12 (1.9)	12 (1.9) MDS, AML	NR	82 mo	Actuarial prevalence 3%, 10%, and 20% at 5, 8, and 10 y, respectively
Finnish Leukemia Group [15]	Retrospective study based on clinical trials	1979–1985 (16 y)	432	40 (9.3)	17 (3.9) AML, NHL	23 (5.3)	37 mo ST; 56 mo AML	O/E ratio 45.6 for AML, $P < 0.001$; 4.29 for NHL, P = ns; 0.75 for STs, P = ns
Munker et al. [35]	Retrospective, single-center study	1995–2010	197	5 (2.5)	1 (0.5)	4 (2.0)	NR	IR of SPMs or subsequent cancers: 2%, 4.8%, and 11.9% at 3, 5, and 10 y, respectively. 34 additional malignancies were diagnosed before MM diagnosis was made
Przepiorka et al. [59]	Retrospective, single-center study, ASCT	1996–2005	82	10 (12.2)	10 (12.2) MDS	NR	50 mo	5-y cumulative incidence 18%
Barlogie et al. [32]	Retrospective, single-center study, ASCT	1989–2007	2418	26 (1.1)	26 (1.1) MDS, AML	NR	NR	72 patients with transient MDS-associated cytogenetic abnormalities
Grudeva-Popova [33]	Retrospective, single-center study	1990–2010	332	5 (1.5)	NR	NR	6.6 y	Most additional cancers were present before the diagnosis of MM. Higher incidence of SPMs associated with longer survival
Hasskarl et al. [49]	Retrospective, single-center study	1997–2008	589	18 (3.1)	6 (1.0) MDS, AML, NHL	12 (2.0) 50% lung and prostate cancers	35 mo	IR 7.8%, 10.3%, and 11.6%, at 2, 5, and 10 y, respectively

Usmani et al. [56]	Retrospective, single-center study with multiple protocols	1998–2009	1148	73 (6.4)	36 (3.1) MDS, AML, NHL, ALL	37 (3.2) Prostate, NMST, breast, thyroid, bladder, colon, renal, lung	NR	HR = 0.63–1.30 (95% CI 0.18–2.67), without significant differences according to type of SPM (HMs or STs) or time of evaluation (enrollment vs maintenance)
Fenk et al. [60]	Retrospective, single-center study, ASCT	1994–2009	313	18 (5.8)	9 (2.8) MDS, AML, HL	9 (2.8) Breast, lung, others	56 mo	Cumulative incidence 19.7%; IR 0.7%, 5.8%, and 15.7% at 2, 5, and 10 y, respectively
Srivastava et al. [36]	Retrospective, single-center study (LD, ASCT 50%)	2003–2011 (4.2 y)	286	21 (6.6)	2 (0.7) AML	19 (6.6; 10 [3.5], excluding NMST) Melanoma, breast, others	44 mo	21 (9) SPMs/1120 person-y of follow-up from MM diagnosis
Govindaraja n et al. [61]	Retrospective, single-center study, ASCT	NR	188	7 (3.7)	7 (3.7) MDS	NR	63 mo	Prolonged CT before ASCT correlated with evidence of SPMs
Ormerod et al. [62]	Retrospective, single-center study, ASCT	1990–2010 (2995 d)	279	10 (3.6)	2 (0.7) MDS, ALL	8 (different types)	360 d	9 SPMs in patients +L
Rollison et al. [63]	Retrospective cohort study with nested case-control analysis (+L vs -L)	2004–2012 (40 mo)	1653	51 (3.1)	14 (0.8) 8 +L vs 6 -L	37 (2.2) 9 +L vs 28 -L; 14 different types	NR	IR of SPM 0.55 per 100 person-y with +L and 1.27 per 100 person-y with -L; HR = 0.44 (95% CI 0.24–0.80); HMs HR = 0.90 (95% CI 0.31–2.63); STs HR = 0.55 (95% CI 0.15–0.69)
Dimopoulos et al. [64]	Retrospective, pooled analysis of 11 clinical trials in RRMM treated with lenalidomide	2002–2008	3846	52 (1.3)	8 (0.2) MDS, NHL, AML	44 (1.1)		Overall IR of SPMs, including non-invasive skin cancers: 3.62. IR of invasive (both HMs and STs) SPMs: 2.08 (95% CI 1.60–2.60)

Dimopoulos et al. [64]	Retrospective, pooled analysis of 2 phase III randomized trials (LD vs placebo-dex)	2003–2008	703	23 (3.3)	2 (0.3) MDS (in +L)	17 (2.4) in +L (11 NMST); 4 (0.6) in -L (2 NMST)	1–45 mo	Overall IR of SPMs: 3.98 (95% CI 2.51–6.31) in +L vs 1.38 (95% CI 0.44–4.27) in -L; IR of NMST: 2.40 (95% CI 1.33–4.33) in +L vs 0.91 (95% CI 0.23–3.66) in -L; IRs of invasive SPMs: 1.71 (95% CI 0.86–3.43) in +L vs 0.91 (95% CI 0.23–3.66) in -L
Mahindra et al. [38]	Retrospective analysis in patients receiving ASCT	1990–2010	4161	163 (3.9)	O/E ratio 5.19 (99% CI 1.67–12.04; $P = 0.0004$) for AML	O//E ratio 3.58 (99% CI 1.82–6.29; $P < 0.0001$) for melanoma	NR	Crude IR 1.2 per 100 person-y; cumulative incidences of 2.6% (95% CI 2.09– 3.17), 4.2% (95% CI 3.49–5.00), and 6.1% (95% CI 5.08–7.24) at 3, 5, and 7 y, respectively

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; CI, confidence interval; CT, chemotherapy; d, days; HL, Hodgkin lymphoma; HM, hematologic malignancy; HR, hazard ratio; IR, incidence rate; +L, exposure to lenalidomide, -L no exposure to lenalidomide; LD, lenalidomide plus dexamethasone; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; MRC, Medical Research Council; NHL, non-Hodgkin lymphomas; NMST, non-melanoma skin tumors; NR, not reported; ns, not significant; O/E ratio, observed-to-expected ratio; RRMM, relapsed/refractory multiple myeloma; SPM, secondary primary malignancy; ST, solid tumor; y, years.

Table 4. Key first-line phase III trials that evaluated SPM incidence in MM patients

Authors	Type of study	Study period (median follow-up)	Enrolled patients (*N*)	All SPMs (*n*, %)	Hematologic SPMs (*n*, %)	Solid tumor SPMs (*n*, %)	Time from MM diagnosis to SPM development (median)	Additional information
Bergsagel et al. [2]	Comparison of different alkylating agent-based regimens	1973–1977	364	14 (3.8) AML	14 (3.8)	NR	NR	Actuarial risk of AML rapidly increased to 17.4% at 50 mo
Attal et al. [18]	Lenalidomide consolidation followed by lenalidomide vs placebo as maintenance after ASCT	2006–2008	614 (6 did not receive randomized treatment) (306 +L vs 302 -L)	All SPMs: 32 (10.4) +L vs 12 (4.0) -L; invasive SPMs: 23 (7.5) +L vs 9 (3.0) –L	13 (4.2) +L vs 5 (1.7) -L	10 (3.3) +L vs 4 (1.3) -L	NR	IR per 100 patient-y: 3.1 +L vs 1.2 -L (*P* = 0.002)
McCarthy et al. [19]	Lenalidomide vs placebo as maintenance after ASCT	2005–2009	460 (231 +L vs 229 -L)	18 (7.8) +L vs 6 (2.6) -L	8 (3.5) +L vs 1 (0.4) -L	10 (4.3) +L vs 5 (2.2) -L	HMs: 28 mo +L vs 30 mo -L; STs: 15 mo +L vs 21 mo -L	Overall, cumulative risk of SPMs was greater in +L than in placebo group (*P* = 0.0008)
Palumbo et al. [17]	MPR-R vs MPR vs MP in patients not eligible for ASCT	2007–2008	459 (152 MPR-R vs 153 MPR vs 154 MPT)	12 (7.9) MPR-R vs 9 (5.9) MPR vs 4 (2.6) MPT	7 (4.6) MPR-R vs 5 (3.3) MPR vs 1 (0.7) MPT	5 (3.3) MPR-R vs 4 (2.6) MPR vs 3 (1.9) MPT	NR	IR/100 patient-y: 1.4% for MPR-R vs 2.1% for MPR vs 0.7% for MP

Palumbo et al. [65]	RD followed by ASCT vs MPR, then lenalidomide maintenance vs no maintenance	2007–2009 (51.2 mo)	402 (273 randomized to consolidation: 141 ASCT vs 132 MPR; 251 randomized to L maintenance vs no maintenance: 57 ASCT +L vs 59 ASCT -L, and 59 MPR +L vs 56 MPR -L)	11 (2.7)	1 (0.2)	10 (2.5) 1 during induction; 5 in +L vs 4 in -L maintenance arm	NR	
Benboubker et al. [66]	RD until progression vs RD 18 cycles vs MPT in patients not eligible for ASCT	2008–2011 (37 mo)	1613 (535 RD, 541 RD 18 cycles, 547 MPT)	All SPMs (including NMST): 37 (7) RD until progression vs 44 (8.1) RD 18 cycles vs 47 (8.7) MPT; Invasive SPMs: 17 (3.2) RD until progression vs 30 (5.6) RD 18 cycles vs 27 (5.0) MPT	2 (0.4) RD until progression vs 2 (0.4) RD 18 cycles vs 12 (2.2) MPT (all MDS/ AML)	15 (2.8) RD until progression vs 29 (5.4) RD 18 cycles vs 15 (2.8) MPT	NR	IR/100 person-y (CI): ALL SPMs: RD until progression 2.76 (2–3.81) vs RD 18 cycles 3.33 (2.48–4.48) vs MPT 3.68 (2.76–4.89): HMs: RD until progression 0.14 (0.04–058) vs RD 18 cycles 0.14 (0.04–058) vs MPT 0.91 (0.52–1.61); STs: RD until progression: 1.09 (0.66–1.81) vs RD 18 cycles 2.15 (1.49–3.09) vs MPT 1.15 (0.69–1.90); NMST: RD until progression 1.62 (1.07–2.46) vs RD 18 cycles 1.25 (1.78–2.02) vs MPT 1.62 (1.05–2.48). Overall, IR of incidence of hematologic SPMs was significantly lower with RD (0.4%) vs MPT (2.2%).
Jones et al. [37]	CRD vs CTD (induction); bortezomib vs no consolidation; lenalidomide-based maintenance vs no maintenance[a]	2010–2015	2745	69 (2.5)	8 (0.3) MDS, AML, CML, HD	61 (2.2) including NMST	All SPMs: 15.6 mo (range 1.2–42.5); HMs: 18.2 mo (5.9–42.5)	Cumulative incidence (95% CI) of all SPMs: 0.65% (0.35, 0.97), 1.84% (1.26, 2.41), and 3.41% (2.49, 4.43) at 1, 2, and 3 years, respectively

Stewart et al. [67]	MPT-T vs MPR-R	2008–2011 (40.7 mo)	306 (298 received randomized treatment: 148 MPT-T vs 150 MPR-R)	All SPMs: 32 (10.7); 18 MPT-T (12.2) vs 14 MPR-R (9.3) excluding NMST: all SPMs: 22 (7.4); 14 MPT-T (9.5) vs 8 MPR-R (5.3)	14 (4.7) 10 MPT-T (6.7) vs 4 (2.6) MPR-R	18, including 9 NMST (6); invasive: 8 (2.7): 4 (2.7) MPT-T vs 4 (2.7) MPR-R	NR	IR/100 patient-y: total 4.06; MPT-T 4.56, vs MPR-R 3.56, excluding NMST: total 2.74; MPT-T 3.47 vs MPR-R 2.01
Zweegman et al. [68]	MPT-T vs MPR-R	2009–2012	560 (280 MPT-T vs 280 MPR-R)	Invasive, excluding NMST: 38 (6.8)	9 (1.6) AML/MDS: 3 (0.5) MPT-T vs 6 (1.1) MPR-R	29 (5.2) 18 (3.2) MPT-T vs 11 (2.0) MPR-R	NR	IR/100 patient-y: 3.3 (MPT-T) vs 2.4 (MPR-R), *P* = 0.33
Palumbo et al. [69]	VMPT-VT vs VMP	2006–2009 (54 mo)	511 (254 VMPT-VT vs 257 VMP)	0.9% VMPT-VT vs 1.5% VMP	NR	NR	NR	
San Miguel et al. [70]	VMP vs MP	2004–2006 (60.1 mo)	682 enrolled; 655 analyzed for SPMs (327 VMP vs 328 MP)	19 (5.8) VMP vs 13 (4.0) MP	3 (0.9) VMP vs 3 (0.9) MP	16 (4.9) VMP vs 10 (3.0) MP	HMs: 18–48 mo in the VMP arm, 1–35 mo in the MP arm; STs: 1–56 mo (22.7 median VMP and 30,3 MP)	Similar exposure-adjusted incidence rates: 0.017 VMP vs 0.013 MP per patient-y
Brioli et al. [71]	VTD vs TD followed by ASCT	2006–2008 (73 mo)	299 (148 VTD vs 151 TD)	25 (8.3); 5% VTD vs 11% TD	7 (2.3%); 1.3% VTD vs 3.2% TD	18 (6.0%); 3.8% VTD vs 7.8% TD	36 mo	IR for total population 1% at 1 y and 9.9% at 6 y

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; CI, confidence interval; CML, chronic myeloid leukemia; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; HD, Hodgkin's disease, HM: hematologic malignancy; IMWG, International Myeloma Working Group; IR, incidence rate; +L lenalidomide exposure; -L no lenalidomide exposure; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; MP, melphalan + prednisone; MPR, MP + lenalidomide (revlimid); MPR-R, MPR followed by lenalidomide maintenance; MPT, melphalan + prednisone + thalidomide; MPT-T, MPT folloved by thalidomide maintenance; NMST, non-melanoma skin tumors; NR, not reported; RD, lenalidomide + dexamethasone; SPM, secondary primary malignancy; ST, solid tumor; TD, thalidomide + prednisone; VGPR, very good partial response according to IMWG criteria; VMP, bortezomib + melphalan + prednisone; VMPT-VT, bortezomib + melphalan + prednisone + thalidomide followed by bortezomib + thalidomide maintenance; VTD, bortezomib + thalidomide + prednisone; y, years.
[a]Age-adjusted CRD vs CTD as induction; consolidation with bortezomib vs no consolidation (before ASCT in younger patients) if response < VGPR; lenalidomide-based maintenance vs no maintenance.

Supplementary appendix

Content

supplementary appendix – panel recommendations

what is the ‘true’ risk of SPM development in patients with MM?

panel recommendations

Well-designed population-based studies suggest that second primary malignancy (SPM) risk in multiple myeloma (MM) is low, and is partially related to the lengthening survival of patients with MM. The Panel recommends SPM risk evaluation in individual patients, according to patient-, disease-, and treatment-related factors, and stresses the need for accurate records of additional and systematic data gathering to determine the incidence and types of SPMs in patients currently receiving treatment in MM clinical trials and in the real-world setting. Ongoing clinical trial protocols should be amended to include enhanced monitoring and precise measurement of secondary cancers, including non-invasive neoplasms, which may represent a proof-of-principle of the cancer-promoting activity of specific treatments. New prospective trials with next-generation novel agents should also include SPMs as an ‘a priori’ well-defined endpoint. Additionally, the Panel recommends that careful monitoring for SPMs should be integral to these trials.

Future clinical investigations and real-life treatments should include bone marrow examinations with cytogenetic analyses (including fluorescence in situ hybridization [1], if necessary) at baseline. Additionally, prospective population-based studies, gathering information on the baseline characteristics and treatment of individual patients, should report SPM data that could provide important clinical and scientific information.

SPM incidence rates should be adjusted for person-years at risk (i.e. rate per 100 person/years), to reduce the possibility of SPM risk overestimation as a result of longer patient survival under current treatment regimens. Previous individual and family history of

malignancy should also be investigated. Finally, it will be important to collect data about time to development, clinical and biologic characteristics, prognosis, and the natural history of SPMs observed in future trials of novel agents. For MDS/AML in particular, efforts should be made to record the types of cytogenetic and molecular changes taking place, in order to evaluate whether they present with a pattern different from that observed in cases caused by cytotoxic chemotherapy or radiation.

In the light of available data, physicians should be extremely cautious when evaluating patient symptoms or findings indicative of a second malignancy. Specific routine screening for solid tumors, with the exception of those suggested for the general population, is not recommended in this setting. However, diagnostic measures that would aid the detection of a suspected SPM during routine clinical work-up should be considered, case by case, among long-term MM survivors. Similarly, despite the observed increased tumor risk among individuals with monoclonal gammopathy of undetermined significance (MGUS) [2], a premalignant condition thought almost always to precede the development of MM [3, 4], the Panel does not recommend additional screening for malignancies in such patients, with the exception of the follow-up recommended in the current International Myeloma Working Group (IMWG) guidelines [5], and the regular age-appropriate screening tests recommended for the general population. However, where unexplained abnormalities in blood counts arise, bone marrow examinations with cytogenetic analyses (or fluorescence in situ hybridization, if necessary) are recommended to investigate potential hematologic SPMs. Finally, a careful review process should be considered an important component of future clinical trials, to accurately assess the impact of treatment on SPM development, and to prevent false inflation of SPM rates.

what are the possible host- and disease-related risk factors for SPMs in patients with MM?

panel recommendations

While several host- and disease-related factors may contribute to the predisposition of patients with MM to SPMs, host genetics are likely to present an opportunity to define an individual's susceptibility to SPM development. The Panel recommends the collection of biologic samples from all MM patients included in clinical trials and, when possible, encountered in clinical practice, and their storage for genetic analysis. Ideally, samples should yield DNA for genomic analysis or, better still, RNA for gene expression profiling. Collection of germline and tumor-related material, and re-banking of biologic samples during the course of the disease, are also recommended. Next-generation sequencing genomic studies aimed at identifying genetic profiles associated with increased SPM risk should be planned. Genomic analysis will be particularly important in the context of patients with lower-risk MM or smoldering myeloma, as these patients have a longer life expectancy and would therefore benefit most from a risk-adaptive therapy approach. Indeed, identifying patients at risk for SPMs at the time of diagnosis of MM would enable personalized treatment and post-therapy surveillance options to minimize this risk.

do older and novel therapies increase SPM risk in MM?

panel recommendations

Based on the available evidence, the potential risk of SPMs in MM should not alter the current therapeutic decision-making process. Data regarding the use of autologous stem cell transplantation (ASCT) in MM are reassuring and, in the light of very recent clinical findings strongly confirming the benefits of this procedure, first-line therapeutic approaches in eligible MM patients should always include ASCT conditioned with high-dose intravenous melphalan.

While there appears to be no doubt that the use of bortezomib, either in the transplant setting or in elderly patients, is not associated with an increased risk of SPMs, the clinical implications of the increased SPM risk observed with lenalidomide therapy need to be carefully considered alongside the benefits of treatment. For most patients, MM remains an incurable malignancy and, on average, the risk of dying is substantially higher than the risk of developing a SPM. The benefits of lenalidomide therapy versus older, standard therapies for active MM in the first-line and relapsed settings are well documented, and include better and deeper responses, longer progression-free survival, and longer overall survival. In contrast, rates of mortality due to myeloma progression or treatment-related adverse events (mainly infection and cardiovascular events) in patients treated with lenalidomide are markedly higher than those due to SPMs. With this in mind, the Panel believes that, for the approved indication of lenalidomide in the treatment of relapsed MM, the benefits of treatment clearly outweigh any risk of SPMs. Similarly, in front-line therapy without concurrent oral melphalan, regimens such as lenalidomide plus dexamethasone (or alternatives such as cyclophosphamide or alkylating-free combinations) remain safe and effective options that should be considered for patients with MM, instead of oral melphalan in combination with lenalidomide.

In the maintenance setting, the risk/benefit analysis for lenalidomide is more complex. In particular, with the important exception of high-dose melphalan employed as a conditioning regimen for ASCT, prolonged administration of lenalidomide where there is antecedent melphalan exposure should generally be avoided. Data regarding patients receiving lenalidomide for more than 2 years are limited, and do not present a clear picture of the impact of treatment duration (and, presumably, of cumulative dose or schedule) on SPM risk. Long-term follow-up of a greater number of patients receiving lenalidomide for longer than 2 years is needed for reassurance regarding this point, particularly as

lenalidomide is still given until disease progression. Indeed, in circumstances where the overall survival benefit of maintenance therapy is not well established, the risks versus any possible benefits should still be considered carefully. For MM patients with other cancers, the few available data would suggest that lenalidomide, if indicated, should not be withheld because of concerns about subsequent cancer, irrespective of a prior cancer diagnosis. However, alternative therapies, if available, should be considered.

The Panel recommends that all patients initiating lenalidomide maintenance undergo a baseline bone marrow examination with cytogenetics to ensure there is no overt evidence of dysplasia or concerning cytogenetic abnormalities. There should also be a low threshold for a careful bone marrow analysis, with karyotyping for patients with unexplained cytopenias that persist despite lenalidomide withdrawal. Finally, the role of multiple salvage treatments in contributing to development of SPMs remains to be determined.

The above issues should be adequately addressed through appropriate discussion with the patient about the potential increased risk for SPMs. Informed decisions regarding therapy should be made in conjunction with the patient, bearing in mind current knowledge about treatment-associated risks and benefits. Physicians should remain well informed about the latest data on the risk of SPMs in MM.

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