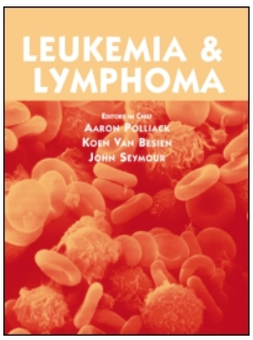

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REVIEW

Secondary malignancies in patients with multiple myeloma, Waldenström macroglobulinemia and monoclonal gammopathy of undetermined significance

Jorge J. Castillo[a] and Morie A. Gertz[b]

[a]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [b]Division of Hematology, Mayo Clinic, Rochester, MN, USA

ABSTRACT

In recent years, the survival of patients with plasma cell dyscrasias has improved due to improvements in anticancer and supportive therapy. However, the risk of secondary malignancies has increased, thought to be due to a combination of environmental and disease-related factors, as well as treatment. In the present review, we evaluate the risk of secondary malignancies in patients with monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM) and Waldenström macroglobulinemia (WM). Patients with MGUS appear to have a higher risk of developing myeloid malignancies such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In patients with MM, the risk of AML, acute lymphoblastic leukemia and some solid tumors appears increased. Finally, in WM patients, there seems to be increased risk of AML, diffuse large B-cell lymphoma, thyroid cancer and melanoma.

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Myeloma; Waldenström macroglobulinemia; MGUS; secondary malignancies

Introduction

The relation between plasma cell dyscrasias and secondary malignancies was identified and initially described 46 years ago. Kyle and colleagues described three patients with multiple myeloma (MM) and one with amyloidosis, who developed acute myelogenous leukemia (AML) after having received prolonged courses of melphalan.[1] Subsequently, in the context of a randomized controlled study evaluating regimens containing melphalan, cyclophosphamide, carmustine and prednisone in over 300 patients with MM, the 4-year risk of developing acute leukemia was reported at 17%.[2] Based on these data, and additional studies,[3,4] the relation between chemotherapy exposure and secondary malignancies in patients with MM was suggested.

With the advent of high-dose melphalan followed by autologous stem cell transplant (HDM-ASCT), additional data supported an increase in the risk of secondary malignancies, specifically myelodysplastic syndrome (MDS) and AML.[5,6] However, some studies have suggested that the duration of the preceding therapy was strongly associated with the development of MDS after HDM-ASCT rather than the ASCT-supported myeloablative treatment itself.[7] Finally, with the introduction of novel agents into the MM treatment field,[8–10] the concern for secondary malignancies has reawakened.

The purpose of this review is to evaluate on the published literature the association between plasma cell dyscrasias and secondary malignancies. We specifically focused on population-based and large prospective and/or retrospective studies evaluating the increased risk of secondary malignancies in patients with MM, Waldenström macroglobulinemia (WM) and monoclonal gammopathy of unknown significance (MGUS).

Risk of secondary malignancies in patients with MM

Evidence from population-based studies

The result of our systematic review of the literature identified several population-based studies that have reported on the incidence of secondary malignancies in patients with MM.[11–16] A list of selected studies and main results are shown in Table 1. Two studies from the US have not been included in Table 1 as they reported results from the SEER database,[17,18] which is represented by the study by Razavi and

CONTACT Jorge J. Castillo Jorgej_castillo@dfci.harvard.edu 450 Brookline Ave, Mayer 221, Boston, MA 02215, USA

Table 1. Selected population-based studies evaluating the incidence of secondary malignancies in patients with myeloma.

	Storm	Dong	Mailankody	Razavi	Tzeng	Chen	
Country	Denmark	Sweden	Sweden	USA	Taiwan	Germany	Sweden
Period	1943–1980	1958–1998	1986–2005	1973–2008	1997–2009	1997–2010	1997–2010
Total cohort	NA	8656	8740	36,491	3970	18,735	7560
N of secondary cancers	NA	475	577	2021	71	752	349
Esophagus			SIR 1.3	SIR 0.5	NS	NS	NS
Small intestine				SIR 2.0	NS		
Colorectal				NS		SIR 0.7	NS
Hepatobiliary				NS		NS	NS
Lung			SIR 0.7	NS	IRR 0.2	SIR 0.8	NS
Melanoma			NS	SIR 1.4	NS	NS	NS
Non-melanoma skin cancer			SIR 2.2	NS	NS	NS	NS
Breast			NS	SIR 0.8	NS	SIR 0.7	NS
Uterus			NS	NS		SIR 0.4	NS
Prostate			NS	SIR 0.7	NS	SIR 0.7	NS
Urinary bladder			SIR 1.3	SIR 1.2	NS	SIR 0.5	NS
Kidney				SIR 1.3	NS	NS	NS
Central nervous system		NS		NS		NS	NS
Thyroid				SIR 1.6	NS		
Hodgkin lymphoma		NS		NS			
Non-Hodgkin lymphoma		SIR 1.7	NS	SIR 1.3	IRR 7.6	NS	NS
Acute myeloid leukemia	RR 9.1	SIR 8.9	SIR 11.5	SIR 6.5	IRR 16.3	SIR 4.9	SIR 2.3
Acute lymphocytic leukemia		NS		SIR 5.1	SIR 10.5		

RR: relative risk; SIR: standardized incidence ratio; IRR: incidence rate ratio; NS: not significant; NA: not available.

colleagues.[13] All the studies originated from representative cohorts, in which the observed number of events was compared against the number of events expected in the general population from which the cohort originated. Also, all the studies estimated the incidence of secondary cancers adjusting for common factors such as age and sex, among other factors. Finally, all studies had a median follow-up of longer than 10 years, which allows for the outcome of interest, in this case the incidence of secondary cancers, to occur. Overall, all the studies were considered of high quality and with low risk of bias.

The risk of other hematologic malignancies appears strikingly increased in patients with MM, specifically AML, whose risk is consistently elevated in all the studies reviewed with risk ratios between 3 and 20-fold higher than the general population. Although the risk of AML can be partially explained by exposure to therapy, a number of cases of AML have presented concurrently to or shortly thereafter the diagnosis of MM, raising the likely possibility of an inherent susceptibility in patients with MM to developing other hematological malignancies. It is possible that the risk of AML in patients with MM would, in part, be associated with exposure to therapy. Unfortunately, the majority of these population-based studies do not specify the treatment modalities that patients received.

With regards to other hematological malignancies, it is of interest that the risk of acute lymphoblastic leukemia (ALL) appears increased in patients with MM, although at a lower degree than AML.[11,13] The risk of non-Hodgkin lymphoma (NHL) also appears slightly increased in patients with MM.[13,15,16] There are no additional data, however, on the subtypes of NHL that occur most commonly in MM patients. The risk of Hodgkin lymphoma does not appear increased in MM patients.[12,13,16]

With regards to the incidence of solid tumors, the results are inconsistent. One study found a mildly increased risk (20–40%) of developing genitourinary cancers, melanoma and thyroid cancer in patients with MM,[13] while the incidence of these cancers did not appear increased in other studies.[11,15] In another study, the risk of head and neck, urinary and non-melanoma skin cancers was increased while the risk of melanoma did not seem increased.[16] It is interesting to note, however, that the incidence of the most common solid tumors, such as breast, colon, lung and prostate appears consistently decreased in patients with MM when compared with the general population.[11,13,15,16] There are several potential explanations for this apparent 'protective' effect of MM on the most commonly detected solid tumors. It is possible that the diagnosis and treatment of MM affects the screening rates for other malignancies. Another possibility is that due to these studies' large sample size, small statistically significant differences, although clinically irrelevant, are identified. Missing data can also account for this finding. Finally, it is possible there is a true biological predisposition for solid tumors in patients with MM either associated with germinal polymorphisms or due to therapy. One example is the presence of *MTHFR* gene polymorphisms, which have been

associated with an increased risk of MM in one study, and a decreased risk of prostate cancer in another. [19,20]

The risk of any solid tumor was lower in patients older than 75 than in patients younger than 65 years in a population-based study from the US.[13] This finding was reproduced in the study by Tzeng and colleagues.[15] An explanation for these findings is difficult and unlikely to be satisfactory. It could well be that the risk of secondary malignancies is similar between younger and older MM patients. However, younger patients with MM tend to have longer survival than older patients, providing an "opportunity" for these malignancies to develop and be detected. On the other hand, the risk of lung and urinary bladder cancer was higher in patients older than 75 than in patients younger than 65 years.[13] This finding would suggest a biological difference in the risk of secondary malignancies in older patients with MM but it would need further confirmation.

According to the study by Razavi and colleagues, there were no major differences between the risks of solid or hematologic malignancies between men and women.[13] Similarly, in the study by Tzeng and colleagues, the risk of secondary malignancies did not appear different between men and women.[15] There was a mildly increased risk of cancers of the small intestine, urinary bladder, kidney and melanoma in men but not in women.[13] The risk of ALL and AML was similarly increased in both sexes. Overall, current data do not support differences in the risk of secondary malignancies in men or women living with MM.

A SEER-based study evaluated the risk of secondary malignancies in patients with MM according to their ethnicity.[21] The study suggested that the risk varies based on the ethnicity of the patient. For example, the overall risk was decreased in Hispanic whites (HR 0.67, 95% CI 0.50–0.88) while it was not increased in non-Hispanic whites, blacks or Asian/Pacific Islanders. The risk of solid tumors was also decreased in Hispanic and non-Hispanic whites (HR 0.66, 95% CI 0.48–0.89, and HR 0.90, 95% CI 0.85–0.95, respectively) while the risk was not increased in blacks and Asian/Pacific Islanders. Finally, the risk of AML is increased about 6-fold in non-Hispanic whites, blacks and Asian/Pacific Islanders but only 1.5-fold in Hispanic whites. It is important to note that less than 5% of the cases of secondary malignancies occurred in blacks and Hispanic whites, respectively, rendering estimates potentially inaccurate. The study, however, provides interesting insights on the heterogeneous effect of ethnicity on the incidence of secondary malignancies in MM patients. Such differences are likely associated with heterogeneous genetic backgrounds as well as environmental exposures.

The study by Dong and colleagues report no changes in the risk of all secondary malignancies based on years of latency from MM diagnosis.[12] However, the risk of myeloid leukemia was increased by 9-fold 1–9 years after MM diagnosis and remained elevated by 7-fold after >9 years from MM diagnosis. In the study by Razavi and colleagues, the risk of colorectal and bladder increased only after 5 years of diagnosis of MM.[13] On the other hand, the risk of AML was mildly increased within 2 years of MM diagnosis but was increased 9 and 11-fold between 2–5 years and >5 years after MM diagnosis. Interestingly, the risk of AML appeared to have decreased based on the year of diagnosis from 13-fold in 1973–1977 to 3-fold in 2003–2008.[13] The decreased risk in AML was similar in patients younger and older than 65 years. A similar finding was reported by Chen and colleagues with the risk of AML decreasing from 10-fold in 1997–2003 to 3.5-fold between 2004 and 2010 in German population.[11] The risk of AML decreased from 4-fold to 2-fold in those same periods in the Swedish population.[11] The dramatic increase in the risk of AML years after the diagnosis of MM supports an exposure triggering the development of leukemia such as MM-directed therapy. It is interesting, however, to see that such a risk has decreased in recent years. A likely explanation is that MM patients might have lower rates of exposure to alkylators and other chemotherapeutic agents in recent years. This finding pairs up with the approval of novel agents in recent years, such as proteasome inhibitors and IMIDs, which have modified the therapeutic approach to MM patients. On the other hand, a Swedish study showed that the risk of AML/MDS in MM patients did not increase after 1995, the year in which autologous transplants became standard of care for eligible patients with MM, or after 2000, the year in which IMIDs were introduced in Sweden.[16]

As patients with MM are living longer, it would be of interest to evaluate the survival of patients with MM who develop secondary malignancies. However, data are scant in this regard. A Swedish study showed that MM patients who developed a secondary malignancy had a higher risk of death than MM patients who did not develop a secondary malignancy (HR 2.3, 95% CI 2.1-2.5).[22] With regards to patients who develop AML/MDS, the risk of death was increased 9-fold when compared to MM patients without a secondary malignancy, and 2-fold when compared to patients without MM who develop *de novo* AML/MDS. There was no difference in survival between MM

patients who develop AML/MDS and patients without MM who develop secondary AML/MDS.

As expected with large registry-based population studies, most of these studies did not evaluate the risk of secondary malignancies associated with specific therapeutic modalities. Also, given the large sample size in these studies, it is likely that some statistically significant associations do not precisely translate into findings of clinical significance. Conversely, subgroup analyzes could have suffered from small sample size and therefore might have failed to identify clinically significant associations.

Evidence from prospective and retrospective studies

In 2012, three separate randomized controlled studies reported an increased rate of secondary malignancies in patients exposed to lenalidomide.[8–10] The study by Attal and colleagues assigned 614 patients younger than 65 years who had undergone ASCT to lenalidomide ($n = 307$) or placebo ($n = 307$) until relapse.[10] With a median follow-up from time of MM diagnosis of 55 months, the incidence of secondary malignancies in patients exposed to lenalidomide was 3.2 per 100 patient-years versus 1.2 per 100 patient-years in the placebo arm ($p = 0.002$). The study by McCarty and colleagues assigned 460 patients younger than 71 years who had achieved at least stable disease for 100 days after ASCT to lenalidomide ($n = 231$) versus placebo ($n = 229$) until disease progression.[9] After a median follow-up time of 34 months, 8% of the patients in the lenalidomide group developed a secondary malignancy (3.5% hematologic and 4.3% solid) versus 2.6% in the placebo group (0.4% hematologic and 2.2% solid). Finally, the study by Palumbo and colleagues randomly assigned 459 patients 65 years or older to melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R; $n = 152$), or melphalan-prednisone-lenalidomide (MPR; $n = 153$) or melphalan-prednisone (MP; $n = 150$) without maintenance.[8] With a median follow-up period of 30 months, the 3-year estimated rate of secondary malignancies was 7%, 7% and 3%, respectively. The rate of secondary hematologic malignancies was increased in the MPR-R and MPR arms when compared with the MP arm. The rate of solid tumors was similar in the three arms.

Given those previous findings, Palumbo and colleagues performed a meta-analysis of seven randomized controlled studies aimed at describing the risk of second cancers in patients with MM treated with lenalidomide.[23] All the studies originated from Europe or the US, and included a total of 3218 patients (2620 received lenalidomide and 598 did not) enrolled between the years 2000 and 2012. In comparison, patients who were treated with lenalidomide were younger (median age 67 vs. 69 years) and had shorter follow-up time (median 25 vs. 28 months) than patients who were not treated with lenalidomide. The 5-year cumulative incidence of second malignancies in patients who received lenalidomide was 6.9% versus 4.8% in patients who did not, with a hazard ratio (HR) of 1.55 (95% CI 1.03–2.34; $p = 0.04$). The 5-year cumulative incidence of hematologic cancers was also increased in lenalidomide-exposed patients (3.1% vs. 1.4%, respectively), with a HR of 3.8 (95% CI 1.15–12.6; $p = 0.03$). Of the 32 patients treated with lenalidomide who developed second hematologic cancers, 16 (50%) had AML, 7 (22%) myelodysplastic syndrome (MDS) and 4 (13%) ALL. There was no difference in the incidence of second solid cancers between patients who were treated with lenalidomide or not (3.8% vs. 3.4%, respectively), with a HR of 1.1 (95% CI 0.62-2.00; $p = 0.72$). Of the 82 lenalidomide-exposed patients who developed a second solid cancer, 27 (40%) had noninvasive skin cancer, 15 (18%) gastrointestinal, and 13 (16%) urinary tract cancers. The distribution of second solid cancers in patients treated with lenalidomide was similar to patients who were not, with the exception of a higher rate of urinary tract cancers (16% vs. 4%, respectively).

However, exposure to lenalidomide was not associated with an increased risk of secondary malignancies in other studies, as shown in a study based on data from Connect MM, a United States-based multicenter prospective cohort registry.[24] The study included 1,450 MM patients, and with a median follow-up of 33.5 months, 4% of the patients developed a secondary malignancy with an incidence rate of 1.62 per 100 patient-years. Hematologic (MDS, AML and ALL) and solid malignancies (lung, prostate, breast, colon, melanoma and pancreas) were observed in 1.2% and 2.8% of patients, respectively. There was no difference in the 3-year cumulative incidence of secondary malignancies regardless of exposure to melphalan, lenalidomide, none or both agents. It is important to note that this was not a randomized study and that the follow-up time is short.

An analysis from the VISTA study evaluated the risk of secondary malignancies in patients with MM exposed to bortezomib-melphalan-prednisone ($n = 344$) versus melphalan-prednisone ($n = 388$).[25] After a median follow-up of 5 years, the rate of proportion of hematologic malignancies was not different at 1% in each group. The 5-year rate of solid tumors was not different as well at 5% and 3%, respectively.

A pooled analysis of four phase III randomized controlled studies in MM patients evaluated the risk of secondary malignancies seen with bortezomib-containing regimens.[26] A total of 25 cases of secondary malignancies (5 hematologic and 20 solid) were seen in 1718 bortezomib-treated patients. The incidence rate of secondary malignancies was not different than the rate reported by 2004–2008 SEER data. A German retrospective registry study followed 744 patients with MM over 25 years.[27] The cumulative incidence rates for hematologic and solid malignancies were 2% and 4%, respectively. In their multivariate analysis, exposure to bortezomib was associated with a lower rate of developing a secondary malignancy (HR 0.24, 95% CI 0.07–0.81; $p = 0.02$). There was a mildly increased risk of secondary malignancies in MM patients exposed to lenalidomide but it was not statistically significant (HR 1.56, 95% CI 0.65–3.73; $p = 0.32$). Exposure to anthracyclines or alkylating agents was not associated with an increased risk of secondary malignancies.

Data on the incidence of secondary malignancies in MM patients exposed to carfilzomib, pomalidomide or ixazomib are currently unavailable.

Risk of secondary malignancies in patients with WM

An initial retrospective cohort study evaluated the occurrence of secondary malignancies in 924 patients with WM.[28] A total of 225 cases (24%) developed a secondary malignancy, although over 60% of the cases were seen before the diagnosis of WM was made. In that study, the most common secondary malignancies were breast, skin, hematologic, melanoma, lung and thyroid malignancies. Hematologic secondary malignancies included 13 cases of DLBCL and 4 cases of AML, all recognized after the diagnosis of WM. Of note, this study did not have a comparator group and was mainly descriptive. In a sub-study, the risk of MDS/AML appeared increased specifically in patients who were exposed to nucleoside analogs.[29] In a smaller Italian study on 230 WM patients, 32 patients (14%) developed a secondary malignancy with a 10-year cumulative incidence of solid and hematologic cancers of 12% and 6%, respectively.[30] The risk of secondary malignancies was 1.7-fold higher than the general population; the risk of secondary hematologic malignancy was increased 4-fold. Of interest was the 9-fold increase in the risk of DLBCL and the 8-fold increased risk for MDS/AML. In a follow-up study, the risk of secondary malignancies was 5-fold higher in treated versus untreated WM patients.[31] Finally, in a randomized study that evaluated 414 patients who were exposed to fludarabine ($n = 207$) and chlorambucil ($n = 207$), of which 80% were WM,[32] the 6-year cumulative incidence of secondary malignancies was higher in the chlorambucil arm (21%) versus the fludarabine arm (4%). Fourteen and six secondary solid and hematologic malignancies were seen in the chlorambucil arm versus four and one in the fludarabine arm, respectively.

These findings prompted an evaluation of the SEER database evaluating 4,676 patients with WM to characterize the incidence of secondary malignancies in this population.[33] A total of 681 cases (15%) were identified, 484 solid and 174 hematologic, all identified after the diagnosis of WM. The cumulative incidence of secondary malignancies was 10% at 5 years and 16% at 10 years with an overall standardized incidence ratio (SIR) of 1.49 and a median time to secondary malignancy of 3.7 years. With regards to solid malignancies, thyroid (SIR 2.7), melanoma (SIR 1.9) and lung cancer (SIR 1.5) were more commonly seen in WM patients than in the general population. The risk of aggressive lymphomas (SIR 4.6) and acute leukemia (SIR 3.2) was also increased in WM patients. The risk of secondary malignancies was higher in WM patients younger than 65 years than in 65 years or older. There were no differences in secondary malignancies incidence based on sex or race. Based on years of latency from WM diagnosis, the risk of solid and hematologic tumors was higher 5 years after WM diagnosis than within 5 years of diagnosis. There was no difference in epochs before or after the year 2000.

The outcome of patients with WM who develop secondary malignancies was also evaluated in a population-based study including 6865 WM patients in the SEER-18 cohort.[34] In that analysis, the overall survival of WM patients who developed colorectal cancer (HR 2), melanoma (HR 2.6) and aggressive lymphoma (HR 1.4) was worse than the general population who developed those same cancers. The worse outcome observed in these patients was not explained by more advanced stage or higher histological grade at the time of diagnosis. These findings support that an underlying WM might prevent patients from receiving appropriate palliative and/or curative treatments.

Risk of secondary malignancies in patients with MGUS

There is clear evidence that MGUS is a pre-malignant condition. As such, a small proportion of patients with non-IgM MGUS can progress into MM at a rate of approximately 1% per year, while IgM MGUS patients

can progress into WM or amyloidosis at a rate of 1.5% per year.[35,36] The evidence supporting an increased risk of other secondary malignancies in patients with MGUS is scarce.

A large Swedish population-based study evaluated 5652 patients diagnosed with MGUS following strict diagnostic criteria.[16] As expected, the risk of MM was increased in comparison with the general population. Ten percent of MGUS patients who developed a hematologic malignancy developed MM (SIR 80), and 3% developed WM or NHL (SIR 13). The risk of AML/MDS was increased 8-fold when compared with the general population. Interestingly, the incidence of AML/MDS was seen exclusively in non-IgM MGUS patients. Also, the risk of AML/MDS was higher if monoclonal protein concentration was higher than 1.5 g/dl (SIR 11) versus less than 1.5 g/dl (SIR 4.7). The risk of solid malignancies was mildly increased (SIR 1.6) with an increase in non-melanoma skin (SIR 2.0), endocrine (SIR 3.3) and breast cancer (SIR 1.3). The risk of other solid malignancies, such as male genitourinary, respiratory and gastrointestinal cancers were mildly increased. The increased risk disappeared after eliminating secondary solid tumors diagnosed within 1 year of MGUS diagnosis.

A Mayo Clinic population-based analysis compared the incidence of MDS and acute leukemia in 605 patients older than 50 years with MGUS versus 16,710 individuals who tested negative for MGUS based on serum protein electrophoresis with immunofixation.[37] MGUS patients had a 2.4-fold increase in the risk of developing MDS with a slightly increased risk of AML (RR 1.36). No cases of ALL were observed in the MGUS group. Specifically, the risk of MDS also appeared increased in patients with IgM MGUS (RR 1.85) but it was not statistically significant.

A smaller Swedish study followed 728 patients with MGUS for a median of 10 years to evaluate the risk of developing lymphoid and myeloid malignancies.[38] As expected, most of the lymphoid malignancies were MM. There was an incidence of MDS/AML of 1.4% at 10 years. These results support an increased risk of myeloid malignancies in MGUS patients but the study did not provide a comparator group for a formal comparison.

Conclusion

The current data supports an increased risk of MDS/AML in patients with MM, WM and MGUS. Although exposure to alkylating agents, nucleoside analogs, IMIDs and/or HDM-ASCT might increase the risk of secondary myeloid malignancies, there is evidence that patients with MGUS, who are typically not exposed to these agents, also have an increased risk of those same malignancies. The present data strongly suggest an inherent increased propensity of developing myeloid malignancies, which is present irrespective of therapy exposure. Furthermore, a prospective study on 80 patients with smoldering MM and MGUS found that 20% of these individuals had dyspoietic morphological features in their bone marrow biopsies such as hypolobated megakaryocytes, micromegakaryocytes, and higher numbers of CD34 + myeloblasts.[39] The data also suggest, however weakly, that there might be an additive effect associated with the use of combination regimens. It is important to note that the outcome of the patients with MM who develop AML secondary to MM-directed therapy might be worse than the general population developing those same malignancies, and does not differ from the outcome of patients with secondary AML. However, additional studies are needed to confirm those findings and concerns.

The risk of other secondary hematologic malignancies or solid tumors is less well established but current studies support an increased risk of NHL, gastrointestinal and genitourinary cancers. The biology behind such relationships remains elusive. An interesting finding is the “protective” effect of MM for the development of common solid tumors such as breast, lung and prostate cancers. Explanations are unlikely to be satisfactory and might include genetic predisposition, environmental exposures, decreased rate of screening in plasma cell dyscrasia survivors, or a truly decreased incidence of those cancers due to therapy or other unexplained biological mechanisms. Despite the current evidence, screening for breast, prostate, lung and colorectal cancer should be followed as recommended by international guidelines.

Finally, it is important to recognize the survival benefit experienced by patients with MM and WM in the last decades, likely due to the advent of more effective, less toxic targeted agents. Treatment decisions, therefore, should be based on balanced discussions between patients and physicians with regards to the benefits and potential toxicities associated with each treatment option. Additional research is needed, not only to estimate the actual economic and social burden of secondary malignancies associated with therapy for plasma cell dyscrasias, but also to develop therapies with a lower risk of secondary malignancies, if possible. In the meantime, data continue accumulating on a wide variety of highly effective novel treatment options that are likely to change the landscape of therapy and improve response and survival of patients with plasma cell dyscrasias.

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ORCID

Jorge J. Castillo http://orcid.org/0000-0001-9490-7532

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