Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS)

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Using population-based data from Sweden, we identified all multiple myeloma (MM) patients (n = 8740) and 5652 monoclonal gammopathy of undetermined significance (MGUS) patients diagnosed between 1986 and 2005. We calculated standardized incidence rates (SIRs) for all subsequent hematologic and nonhematologic malignancies for MM patients diagnosed before/after 1995 (introduction of high-dose melphalan/autologous stem cell transplantation [HDM-ASCT]) and 2000 (introduction of immunomodulatory drugs [IMiDs]), respectively. MM patients had an 11.51-fold (95% confidence interval: 8.19-15.74) increased risk of acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS); risk was very similar before/after 1995 and 2000, respectively. MGUS patients had an 8.01-fold (5.40-11.43) increased risk of AML/MDS. Risk was confined to IgG/IgA, while no IgM MGUS patients developed AML/MDS; patients with monoclonal-protein (M-protein) concentrations > 1.5 g/dL (SIR = 11.12; 3.61-25.96) had higher risk than those < 1.5 g/dL (SIR = 4.67; 1.71-10.16). An excess risk of nonmelanoma skin cancer was observed subsequent to both MM (SIR = 2.22; 1.74-2.80) and MGUS (SIR = 3.30; 2.76-3.90). Our novel observations of an excess risk for AML/MDS following IgG/IgA (but not IgM) MGUS, and the highest risk associated with M-protein concentrations > 1.5 g/dL, support a role for nontreatment-related factors in plasma cell dyscrasias. AML/MDS risk following MM was the same before/after the introduction of HDM-ASCT. Longer follow-up is needed to characterize second tumor risks in the IMiD era. (Blood. 2011;118(15):4086-4092)

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in Western countries.1 Before the introduction of alkylating agents, median survival time of MM patients was < 1 year.2 In the early 1960s, melphalan was discovered to have an anti-MM effect; until recently, the combination of melphalan and prednisone (MP) has remained the mainstay of therapy in MM.3 From 2000 (introduction of immunomodulatory drugs (IMiDs)) and subsequent hematologic and nonhematologic malignancies occurring before/after 1995 (introduction of HDM-ASCT) and 2000, respectively. MM patients had an 8.01-fold (5.40-11.43) increased risk of AML/MDS.

High-dose melphalan with autologous stem cell transplantation (HDM-ASCT) in younger patients with MM was first introduced in 2000 (introduction of immunomodulatory drugs (IMiDs)) and has increased the therapeutic options in MM and further improved response rates, progression-free survival, and overall survival.

For > 4 decades, an excess of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) have been reported following MM.15,16 Some previous population-based studies on patients with hematologic malignancies including MM have reported an increased incidence of second malignancies including myeloid leukemias.17,18 Although the underlying biologic mechanisms of AML/MDS following MM need to be better defined, treatment-related factors including the use of melphalan have been considered to be the main cause of the observed elevated risk.19-21 Based on small numbers, some studies have reported the risk of AML to increase with increasing cumulative melphalan dose, duration of melphalan therapy, or a combination; however, other investigators have found that the risk of AML in MM patients may be independent of cumulative melphalan dose.22,23 In the era of novel MM therapies, an increasing number of patients are living longer, and in turn will receive more types of MM therapies thus extending the natural course of their disease. Consequently, clinicians who treat and follow patients with MM have started to encounter long-term complications as the new challenge in clinical MM management. Indeed, preliminary analyses from recent randomized clinical trials have reported an increased incidence of second malignancies including AML/MDS in MM patients treated with maintenance lenalidomide.24-26

Using high-quality population-based data from Sweden, we have conducted the largest systematic evaluation to date focusing on second hematologic and nonhematologic malignancies following MM. By identifying all (n = 8740) MM patients diagnosed between 1986 and 2005 (follow-up until 2006), we were able to define patterns of second malignancies before and after the introduction of novel therapies, and to compare risks in relation to the Swedish general population. So far, most of the attention has been drawn to various MM treatments and their potential risk of causing second malignancies. However, as pointed out by Bergsagel et al in 1979,20 it is inherently complex to quantify the risks of...
Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multiple myeloma</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>8740 (100)</td>
<td>5652 (100)</td>
</tr>
<tr>
<td>65 years or younger, n (%)</td>
<td>2495 (29)</td>
<td>1585 (28)</td>
</tr>
<tr>
<td>Older than 65 years, n (%)</td>
<td>6245 (71)</td>
<td>4067 (72)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>4811 (55)</td>
<td>2845 (50)</td>
</tr>
<tr>
<td>Median age at diagnosis, y (interquartile range)</td>
<td>72 (64-79)</td>
<td>73 (63-80)</td>
</tr>
<tr>
<td>Median follow-up time, mo (interquartile range)</td>
<td>27.9 (10.3-54.0)</td>
<td>52.4 (22.4-92.6)</td>
</tr>
<tr>
<td>Year of diagnosis 1986-1994, n (%)</td>
<td>4228 (48)</td>
<td>1362 (24)</td>
</tr>
<tr>
<td>Year of diagnosis 1995-2005, n (%)</td>
<td>4512 (52)</td>
<td>4290 (76)</td>
</tr>
</tbody>
</table>

MGUS indicates monoclonal gammopathy of undetermined significance.

second tumors in relation to a given therapy because we do not know the baseline incidence of second malignancies in (untreated) MM patients. To overcome this problem, and to test the hypothesis that nontreatment-related factors may play a role in subsequent malignancies following plasma cell dyscrasias, we estimated the risk of subsequent hematologic and solid malignancies among 5652 monoclonal gammopathy of undetermined significance (MGUS) patients diagnosed during the same calendar period and compared risk patterns in relation to the Swedish general population.

Methods

Central registries, patients, and controls

Since the 1950s, Sweden has provided universal medical care for the entire population (independent of socioeconomic status and geographic region), currently approximately 9 million people. In contrast to many other countries, patients with lymphoproliferative malignancies in Sweden are usually diagnosed, treated, and followed clinically by physicians at a few hospital-based hematologic or oncology centers. The Nordic Myeloma Study Group (NMSG) was founded in 1987. In 1995, NMSG developed the first guidelines for the diagnosis and treatment of MM (updated in 2001 and 2006), and since 2009 there have been national guidelines in Sweden (latest update in 2011). These guidelines have been universally accepted and followed in Swedish hospitals. Given these facts, therapy for MM patients is very similar across the entire nation, independent of socioeconomic status, and geographic variations.

In Sweden, melphalan was introduced in the treatment of MM in the early 1960s. It was initially given as a continuous daily dose and, from the 1970s, was gradually exchanged for the combination with prednisone (MP). In a recent investigation, we obtained detailed information on the primary treatment on all MM patients diagnosed in Malmö (the third largest city in Sweden) between 1950 and 2005. In that study, we reported that among patients diagnosed after age 65 years, MP-like therapy was the most dominant primary treatment in all calendar periods. Among patients diagnosed at age 65 years or younger, vincristine-doxorubicin-dexamethasone (VAD)-like therapy (including other high-dose corticosteroid-based regimens) was introduced in the primary treatment in the mid-1990s, and was given to 96% of patients in the last calendar period.

Since 1958, all physicians and pathologists/cytologists in Sweden have been obliged by law to report each case of cancer diagnosed or treated to the Swedish Cancer Registry, which includes information on individual patient-based discharge diagnoses and discharge listings from all inpatient care, with a very high coverage. Using the nationwide Swedish Cancer Registry, which includes information on all incident cancers diagnosed since 1958 (including date of diagnosis and region/hospital where the diagnosis was made), we obtained data on all cancer diagnoses for all MGUS patients. Lastly, in accord with current diagnostic guidelines, we removed any MGUS patient with a recorded preceding lymphoproliferative malignancy.

For all MM and MGUS patients, we conducted record linkage with the Swedish Cancer Registry and the Swedish Cause of Death Registry to obtain data (until December 31, 2006) on second malignancies and of vital status, respectively. In addition, we obtained age- and sex-specific population incidence rates for all hematologic and nonhematologic malignancies from the Swedish Cancer Registry.

Approval was obtained from the Karolinska Institutional Review Board for this study. Informed consent was waived because we had no contact with study subjects. An exemption from institutional review board review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

Statistical analysis

To evaluate the risk of malignancies following MM and MGUS, respectively, we calculated standardized incidence ratios (SIRs; observed cancers in the patient cohorts divided by the expected numbers from the general
population) with 95% confidence intervals (CIs) for all subsequent hematologic and nonhematologic tumors overall and separately. Expected numbers of events were calculated by applying age- and sex-specific population incidence rates to the person-years observed among our cases. We evaluated the risk of every individual malignancy as well as defined organ-specific subgroups. For all malignancies where we found statistical associations, we conducted sensitivity analyses excluding malignancies diagnosed within a year of MGUS and MM diagnosis, respectively. In all our analyses, SIRs and 95% CIs were based on the first malignancy after MM and MGUS, respectively.

To assess the role of novel MM therapies in relation to the development of second malignancies, the analysis for younger (65 years or younger) patients were stratified before and after the year 1995 (when HDM-ASCT was introduced as standard treatment for younger MM patients in Sweden). We also conducted exploratory analyses stratified before and after year 2000 (when immunomodulatory drugs [IMiDs] were introduced in Sweden).

Results

All (n = 8740) MM patients (median age 72 years; 55% males) diagnosed in Sweden between 1986 and 2005 (follow-up until 2006) were included (Table 1). During the same calendar-period, we identified 5652 MGUS patients (median age 73 years, 50% males; Table 1).

Malignancies subsequent to MM

Sixty-nine and 508 of the MM patients were diagnosed with a second hematologic and nonhematologic malignancy, respectively (Figure 1; supplemental Appendix, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). Twenty-eight (4.6%) second malignancies were diagnosed within a month of MM diagnosis; the most common tumor types were prostate (n = 11) and renal cancer (n = 5). Risk estimates for second malignancies following MM were virtually unchanged when cases diagnosed within a month were excluded from the analysis (not shown).

Compared with the Swedish population, MM patients had a 1.26-fold (95% CI 1.16-1.36) increased risk of developing any second malignancy (Figure 1). Hematologic second malignancies were 2.04-fold (95% CI 1.59-2.58) more common, and most of the excess risk was contributed by AML/MDS (SIR 11.51, 95% CI 8.19-15.74, incidence 139.0 per 100 000 person-years; Figure 1). In sensitivity analysis excluding malignancies diagnosed within a year of MM diagnosis, the risk of AML/MDS following MM was very similar (SIR 13.47; 95% CI 9.33-18.82; n = 34). The median time to AML/MDS diagnosis following MM was 45.3 months (interquartile range: 29.8-73.3 months; Figure 2). Furthermore, among MM patients who developed a subsequent
nonhematologic malignancy, there were 2 individuals who developed AML/MDS as a third malignancy (following lung and prostate cancer, respectively).

Nonhematologic second malignancies were 1.19-fold (95% CI 1.09-1.30) more common following MM (Figure 1). There was an increased risk for gastrointestinal malignancies (SIR = 1.30; 95% CI 1.09-1.53) and nonmelanoma skin cancer (SIR = 2.22, 95% CI 1.74-2.80).

We analyzed risk for AML/MDS among younger (< 65 years) MM patients diagnosed before/after 1995 (introduction of HDMAST for patients < 65 years), and risks were not significantly different (SIR = 33.34; 95% CI 12.23-72.57 vs SIR = 23.19; 95% CI 11.98-40.50). Similarly, risks for AML/MDS among MM patients (including all age groups) diagnosed before/after 2000 (introduction of IMiDs) were not significantly different (SIR = 13.51; 95% CI 8.83-19.80 vs SIR = 8.35; 95% CI 4.17-14.94).

Malignancies subsequent to MGUS

Seven hundred ninety-two and 710 of the MGUS patients were diagnosed with a subsequent hematologic and nonhematologic malignancy, respectively (Figure 1; supplemental Appendix). As expected, the most common malignancy diagnosed after MGUS was MM (n = 532, 9.4%; SIR = 79.86, 95% CI 73.21-86.94). In further accord with the literature, MGUS patients (dominantly IgM isotype) were diagnosed with a subsequent diagnosis of Waldenström macroglobulinemia (WM)/non-Hodgkin lymphomas (NHL; SIR = 12.85, 95% CI: 11.08-14.81). Eighty-six (7.1%) second malignancies were diagnosed within a month of MGUS diagnosis (46 of these were MM). With the exception of lymphoproliferative hematologic malignancies, risk estimates for malignancies diagnosed subsequent to MGUS were virtually unchanged when patients diagnosed with a malignancy within a month after MGUS diagnosis were excluded (not shown).

We observed an elevated risk for AML/MDS following MGUS (SIR = 8.01, 95% CI 5.40-11.43, incidence 102.0 per 100,000 person-years; Figure 1); none of these MGUS patients developed MM following AML/MDS. When excluding malignancies diagnosed within a year of MGUS diagnosis, the risk of AML/MDS following MGUS was very similar (SIR = 5.13; 95% CI 2.93-8.34; n = 16). The median time to AML/MDS diagnosis following MGUS was 14.4 months (interquartile range: 6.0-87.6 months; Figure 2). The excess AML/MDS risk was confined to patients with IgG/IgA MGUS (n = 13/2293) and none of the IgM MGUS (n = 0/559) patients developed AML/MDS (Table 2). Based on small numbers, we found more pronounced AML/MDS risk among MGUS patients with M-protein concentrations > 1.5 g/dL (SIR = 11.12; 95% CI 3.61-25.96) versus < 1.5 g/dL (SIR = 4.67, 95% CI 1.71-10.16; Table 2). Lastly, we observed an increased risk for myeloproliferative neoplasms/polycythemia vera (SIR = 5.32; 95% CI 2.91-8.92) subsequent to MGUS (Figure 1); the analysis excluding malignancies diagnosed within a year of MGUS diagnosis revealed virtually the same results (SIR = 4.54, 95% CI 2.18-8.35; n = 10).

Compared with the Swedish population, MGUS patients had a 1.56-fold (95% CI 1.44-1.68) increased risk of developing a nonhematologic malignancy (Figure 1). We found increased risk for nonmelanoma skin (SIR = 2.04; 95% CI 1.63-2.51), endocrine (SIR = 3.34; 95% CI 1.78-5.71), and breast cancer (SIR = 1.32; 95% CI 1.02-1.69). In analysis excluding malignancies diagnosed within a year of MGUS diagnosis, the risks were very similar (data not shown). In addition, MGUS patients had an increased risk of the following organ-specific subgroups: kidney and urinary tract (SIR = 1.58; 95% CI 1.21-2.04), respiratory (SIR = 1.42; 95% CI 1.05-1.89), male reproductive system (SIR = 1.32; 95% CI 1.11-1.57), and gastrointestinal cancer (SIR = 1.25; 95% CI 1.05-1.48). However, no specific malignancy was significantly increased within these organ-specific subgroups. When excluding malignancies diagnosed within a year of MGUS diagnosis, none of the organ-specific subgroups were found to be at significantly increased risk (data not shown).

**Discussion**

In this largest systematic evaluation of second malignancies following MM to date, we were able to expand our current knowledge regarding the risk of developing AML/MDS. In accord with prior studies, compared with the general population, we found MM patients to have an 11-fold increased risk of developing AML/MDS reflected in an incidence of 139.0 per 100,000 person-years. On average, AML/MDS occurred approximately 4 years after MM diagnosis.

In our study, we conducted analyses designed to study patterns of second primary malignancies in relation to the introduction of HDMAST (year of 1995 in Sweden). More specifically, we estimated the risk for AML/MDS before and after 1995, and found the patterns to be very similar. We have speculated that the observed lack of difference over time could potentially reflect the fact that before the introduction of HDMAST, MM patients typically received oral melphalan in combination with steroids. Thus, it may be that lower doses of extended oral melphalan therapy and melphalan concentrated to 1 or 2 high-dose courses could have similar impact on the risk of developing AML/MDS. Unfortunately, because of lack of detailed treatment information for individual patients, we were unable to further examine the role of melphalan dosing in the context of second malignancies. It is possible that the observed patterns are influenced by temporal variations in exposures to other types of therapies. In our exploratory analyses focusing on the introduction of IMiDs (year 2000 in Sweden), we found the risk patterns for AML/MDS to be very similar over time. However, since the actual usage of IMiD therapy in Sweden during the study period was relatively low and the follow-up time was restricted, the analysis focusing on the introduction of IMiDs should be interpreted with caution. Clearly, there is a need for future analysis when more mature data become available.

For the first time, to our knowledge, we found IgG/IgA (but not IgM) MGUS patients to have an increased risk of developing...
AML/MDS. None of these MGUS patients developed MM following AML/MDS. This observation is important in that it supports a role for nontreatment-related factors in the causation of AML/MDS in plasma cell dyscrasias. Given that the risk of AML/MDS was higher subsequent to MM compared with MGUS, we have speculated that there may be an interaction between underlying plasma cell disease and treatment-related factors. Alternatively, it is possible that more proliferative plasma cell dyscrasias (ie, MM) carry a higher risk than precursor states (ie, MGUS). In further support for this hypothesis, based on small numbers, AML/MDS risk was higher in MGUS patients with M-protein concentrations > 1.5 g/dL (vs < 1.5 g/dL). To assess the potential influence of detection bias (ie, underlying disease processes which led to the medical work-up for MGUS), we conducted sensitivity analysis excluding malignancies diagnosed within a year of MGUS diagnosis. As expected, we found MGUS patients being diagnosed with AML/MDS during that first year (Figure 2). Importantly, in the sensitivity analysis (excluding malignancies diagnosed within a year of MGUS diagnosis), we estimated the risk of AML/MDS following to be very similar to the risk calculated in the main analysis. In addition, based on small numbers, the absolute number of AML/MDS following MGUS remained elevated during the > 10 years of follow-up (Figure 2).

As expected, we found MM to be the most common malignancy subsequent to MGUS. Recently, it has been shown that virtually all MM patients are preceded by MGUS. Also in accord with the literature, we found the risk of WM/NHL to be highly elevated following to be very similar to the risk calculated in the main analysis. In addition, based on small numbers, the absolute number of AML/MDS following MGUS remained elevated during the > 10 years of follow-up (Figure 2).

When we evaluated the risk of nonhematologic malignancies subsequent to MM and MGUS, we found melanoma skin cancer to be increased compared with the general population (SIR = 2.22 and SIR = 3.30). Given the consistent findings between MM and MGUS, this may represent a true biologic association. Furthermore, compared with the general population, MGUS patients had an increased risk for endocrine malignancies (n = 20); 17 of these patients had parathyroid cancer. We have speculated that this observation most likely is because of the fact that serum calcium levels are closely monitored for MGUS patients (ie, detection bias). We also found MGUS patients, but not MM patients, to have an increased risk for malignancies involving certain organ-specific subgroups, including: kidney and urinary, respiratory, and male reproductive system. However, no specific malignancy was significantly increased. Furthermore, when we assessed organ-specific subgroups and we excluded malignancies detected within 1 year of MGUS diagnosis, the risk estimates were no longer statistically significant. Based on these facts, although true biologic associations cannot be excluded, we feel that these patterns, most likely, reflect increased surveillance of patients with MGUS, or they could be spurious findings because of multiple statistical testing.

Our study has several strengths, including the large sample size and use of high-quality data from Sweden. The study included a stable population with access to standardized health care during the entire study period. By using the nationwide register-based design, we were able to rule out recall bias and ensure a generalizability of our findings. As described in detail in “Central registries, patients, and controls,” the MGUS patients in our study were diagnosed at hematology/oncology outpatient units. In accordance with clinical practice in Sweden, most MGUS patients typically underwent a BM examination as part of the clinical work-up. In a recent validation study, we have reported that ascertainment and diagnostic accuracy for lymphoproliferative disorders (including MM) is very high (> 90%-95%) in Sweden. Also our study has some limitations. For the MM cohort, we lack detailed clinical and treatment data, as well as information on the molecular subtype of MM. Because the MGUS patients come from a clinical cohort established from a national hospital network in Sweden, and not from a screening study, one has to be cautious and consider various types of potential bias. For example, it cannot be ruled out that the observed excess of AML/MDS following MM is, at least in part, because of underlying disease processes which led to the medical work-up for MGUS (ie, detection bias). Furthermore, given the fact that MGUS patients are followed clinically, and CBC tests are part of the standard annual monitoring, it may have contributed to the detection of, at least some, earlier MDS cases (ie, surveillance bias). As discussed above, in the main analysis (but not the sensitivity analysis), we found the risk of certain organ-specific subgroups of nonhematologic malignancies to be increased, and this may represent some bias. However, there was no association between MGUS and subsequent risk of chronic lymphocytic leukemia (CLL)/chronic myeloid leukemia (CML). One future strategy to assess the potential influence of detection and surveillance bias may be the launching of a large record-linkage study based on a screened MGUS population, and to compare patterns of malignancies with population rates from the National Cancer Institute (NCI) SEER database. However, such an effort would have other important limitations. For example, the NCI SEER database does not include information on MDS cases until 2001 when the ICD-O-3 coding went into effect, and, as for any large database, there were a few years of delay until the reporting became entirely consistent. Thus, at this time, the possibilities to accurately quantify the risk of MDS following MGUS—compared with the general US population—are very limited. In addition, the M-protein concentrations are relatively lower in a screened MGUS population (the median M-protein concentration is 0.5 g/dL and 0.8 g/dL in the Olmsted county screening study and the present study, respectively). Because our study found higher AML/MDS risk among MGUS patients with higher M-concentrations, the clinical value of a screened MGUS population becomes harder to interpret in the context of subsequent risk of developing AML/MDS.

The present study was designed and launched during the spring of 2010. At the annual American Society of Hematology meeting in December 2010, preliminary analyses from 3 randomized clinical trials were presented, suggesting that maintenance therapy with lenalidomide may increase the risk of second malignancies in MM. Based on available interim data from these trials, AML/MDS has been observed as the most prominent second malignancies. Currently, there are ongoing efforts designed to review and confirm the cases, and to characterize underlying mechanisms. The results from the present study are important in the context of these clinical trials. For example, it is possible that MM patients who subsequently develop second malignancies carry certain disease- and host-related characteristics that remain to be defined. Our novel findings that IgG/IgA (and not IgM) MGUS
have an increased risk of AML/MDS, and the greatest risk is among MGUS patients with M-protein concentrations > 1.5 g/dL (vs < 1.5 g/dL), suggest that nontreatment-related factors play an etiologic role in the development of AML/MDS following MM, likely in combination with treatment factors. Our observation that AML/MDS risk following MM is the same before and after the introduction of HD-MACSCT suggests that administration of melphalan over a longer time period, or concentrated to 1 or 2 high-dose courses, carries similar risks. Although we did exploratory analysis on the patterns of AML/MDS after the introduction of IMiDs, our database had limitations in terms of follow-up, and the use of IMiDs given as maintenance therapy has been very limited in Sweden. Future studies are needed to uncover underlying biologic mechanisms of our findings.

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Authorship

Contribution: S.M. and O.L. initiated and designed the study; S.Y.K., M.B., I.T., and O.L. provided data; all authors were involved in the interpretation of the results; S.M. and O.L. drafted the manuscript; and all authors reviewed and approved the submitted version of the manuscript.

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