Second malignancies after multiple myeloma: from 1960s to 2010s

Thomas, Anish; Mailankody, Sham; Korde, Neha; Kristinsson, Sigurdur Y.; Turesson, Ingemar; Landgren, Ola

Published in:
Blood

DOI:
10.1182/blood-2011-12-381426

2012

SECOND MALIGNANCIES FOLLOWING MULTIPLE MYELOMA: FROM 1960s TO 2010s

Anish Thomas 1, Sham Mailankody1, Neha Korde1, Sigurdur Y. Kristinsson2, Ingemar Turesson3, Ola Landgren1

1 Multiple Myeloma Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.
2 Department of Medicine, Karolinska University Hospital and Institutet, Stockholm, Sweden.
3 Division of Medicine, Skane University Hospital, Malmo, Sweden.

Address for correspondence: Dr. Ola Landgren, Multiple Myeloma Section, Metabolism Branch, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bldg 10/Room 13N240, Bethesda, MD, 20892. E-mail: landgreo@mail.nih.gov, Tel: +1-301-496-0670; Fax: +1-301-402-0172.

Word count: Abstract 200 words (max 200); text 3610 (max 5000); 70 references; 2 tables; 2 figures

Running title: Second tumors in myeloma

Key words: Multiple myeloma, secondary malignancy, treatment, lenalidomide, susceptibility genes, host factors, acute myeloid leukemia, AML, myelodysplastic syndromes, MDS

ABSTRACT

Based on small numbers, recent reports from three randomized trials have consistently demonstrated more hematologic malignancies in patients treated with lenalidomide as maintenance (vs. placebo). This fact has prompted concern and highlighted the association between multiple myeloma and second malignancies. Furthermore, an excess of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) following multiple myeloma has been known for over four decades. Most prior studies have been restricted due to small numbers of patients, inadequate follow-up, and limitations of ascertainment of second malignancies. Although the underlying biological mechanisms of AML/MDS after multiple myeloma are unknown, treatment-related factors are presumed to be responsible. Recently, an excess risk of AML/MDS was found among 5652 patients with IgG/IgA (but not IgM) monoclonal gammopathy of undetermined significance (MGUS), supporting a role for disease-related factors. Furthermore, there is evidence to suggest that polymorphisms in germline genes may contribute to a person's susceptibility to subsequent cancers, while the potential influence of environmental and behavioral factors remains poorly understood. This review discusses current knowledge regarding second malignancies following multiple myeloma and gives future directions for efforts designed to characterize underlying biological mechanisms, with the goal to maximize survival and minimize the risk for second malignancies for individual patients.

BACKGROUND

After decades of virtually no progress, multiple myeloma survival has improved significantly in the last 10 years, in younger patients even 2-3 fold.(1-3) In fact, multiple myeloma has seen more remarkable progress in treatment and patient outcomes than any other cancer in the last decade. With improvements in survival, a relatively new clinical challenge which has emerged is the risk of second malignancies. This pattern of increase in second malignancies has been observed in other cancers with available curative therapies and favorable outcomes. Survivors of testicular cancer are at up to 3-fold higher risk of developing a second malignancy than the general population.(4) Survivors of Hodgkin lymphoma have more than three times greater risk of solid tumors. Fifteen years after diagnosis, the cumulative mortality from second malignancies exceeds cumulative mortality from Hodgkin lymphoma.(5, 6) In the U.S. alone, the number of cancer survivors has tripled since 1971 and is growing by 2% each year; cancer survivors constitute 3.5% of the U.S. population.(7) In fact, second- or higher-order cancers account for 18% of incident cancers in the U.S. making them the third most common cancer diagnosis.(7) Based on the NCI SEER (Surveillance, Epidemiology and End Results) database, compared to the general population, cancer survivors have a 14% increased risk of developing a malignancy.(7)

In the late 1960s, based on a restricted number of patients, an association between multiple myeloma and leukemia was first reported.(8-10) In 1979, based on a clinical trial including 364 multiple myeloma patients, Bergsagel et al reported a greater than expected incidence of all forms of acute leukemia for patients treated with low-dose melphalan containing combinations of alkylating agents.(11) In the era where low-dose melphalan was the mainstay of multiple myeloma therapy, due to poor overall survival rates, the absolute number of multiple

myeloma patients at risk for acute leukemia was small. Although use of low-dose melphalan declined substantially with the advent of high-dose melphalan followed by autologous stem cell transplantation (ASCT) in the late 1980s, melphalan- based combinations continue to be used in ASCT- ineligible patients.(12) In the post-transplant era, several studies found that conventional chemotherapy preceding the transplant played a greater role in the development of myelodysplastic syndromes (MDS) and acute leukemia than myeloablative therapy used in conjunction with ASCT. In the last decade, agents with new mechanisms of action (such as, thalidomide, bortezomib and lenalidomide) and continuing improvements in supportive care have further improved response rates, progression free survival and overall survival in multiple myeloma. Recent preliminary reports of increased risk of second malignancies, predominantly MDS/acute leukemia, with lenalidomide have further highlighted this challenge in multiple myeloma patients.

Larger population-based studies support and expand on findings from smaller clinical studies showing that multiple myeloma patients have an increased risk of developing MDS/acute leukemia compared to the general population.(13-15) Based on the NCI SEER database, among 23,838 multiple myeloma diagnosed between 1973 and 2000, leukemia accounted for the largest cancer excesses, with acute myeloid leukemia (AML) constituting 80% of leukemia cases. Increased risks were also noted for Kaposi's sarcoma and chronic myeloid leukemia.(7) However, the overall risk of developing any type of a subsequent primary cancer was not increased. The increased risk of developing a new malignancy was limited to individuals diagnosed with multiple myeloma at ages younger than 70 years; subsequent cancer risk did not differ by gender, race, or initial therapy. It is to be noted that NCI SEER database did not capture

information on MDS until the introduction of International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) in 2001.(16)

Overall, based on a restricted number of investigations, most prior studies implicate treatment-related factors as the main contributing factor to development of second malignancies following multiple myeloma. However, the lack of molecular markers that are specific for therapy-induced cancer and inability to compare different treatment durations in a clinical trial setting limits our ability to define the impact of prior therapy in the etiology of a second malignancy. In fact, it seems reasonable to propose that second malignancies in multiple myeloma may not be attributable solely to prior treatment. Rather, the development of second malignancies may reflect combinations of influences including treatment-related, multiple myeloma-related, host-related, environmental and behavioral factors (Figure 1).(17) In this paper, we review and discuss our current understanding of second malignancies following multiple myeloma.

TREATMENT-RELATED FACTORS

The effects of treatment-related factors, including oral alkylating therapy on the development of malignancies following multiple myeloma have been assessed (Table 1).(11, 13, 14, 18-22) Bergsagel et al conducted the first prospective clinical study evaluating the value of a combination of three alkylating agents in the treatment of multiple myeloma: melphalan, cyclophosphamide and carmustine. In their study, the observed vs. expected incidence of all forms of acute leukemia was increased for all age groups.(11) In fact, the patterns are quite similar to investigations focusing on Hodgkin lymphoma24 and non-Hodgkin lymphoma(23)

showing MDS/acute leukemia to be associated with long-term alkylating therapy, and with a cumulative dose-response effect. Since these early observations, treatment-related factors including melphalan have been considered the main cause of excess of MDS/acute leukemia in multiple myeloma patients, although the biological mechanisms were not well defined. In a subsequent study, Cuzick et al. reported a positive association between the duration of melphalan treatment and the subsequent risk of developing leukemias.(22) In that study, the cumulative dose melphalan given up to three year period prior to leukemia diagnosis was reported to be the most important determinant of risk. However, this association has not held true in all studies. For example, a retrospective cohort study from the Finnish Leukemia Group found no significant association between the duration and cumulative doses of melphalan and AML risk subsequent to multiple myeloma.(13) Also, in another study, cyclophosphamide was found to be less leukemogenic than melphalan.(22, 24)

After the introduction of high-dose melphalan/ASCT, several studies addressed the relative contribution of myeloablative therapy used in conjunction with ASCT and conventional chemotherapy preceding the transplant toward development of MDS/AML. Govindarajan et al. compared two groups of patients with different exposure to alkylating agents preceding transplant. Group 1 had received no more than one cycle of standard alkylating therapy and group 2 had significantly prolonged exposure to chemotherapy, including alkylators prior to transplant. Both groups were treated with one course of high dose CTX to mobilize stem cells followed by 2 courses of high dose melphalan with autologous stem cell support. Despite a longer follow up (36 months vs. 29 months; $p= 0.05$), none of the patients in group 1 developed MDS, compared to 7 patients in group 2.(21) Other studies also demonstrated that conventional chemotherapy prior to ASCT is a more likely contributing factor of MDS/acute leukemia, rather

than pre-transplant myeloablative therapy, maintenance therapy or additional treatment after transplantation.(19) Furthermore, a recent population-based study based on 8740 myeloma patients diagnosed in Sweden (1986-2005), found the rates of MDS/AML before and after introduction of high-dose melphalan/ASCT to be very similar further supporting that the introduction of high dose melphalan as pre-transplant myeloablative therapy has not increased the risk of subsequent MDS/AML, beyond that of lower doses of melphalan.(15)

Radiotherapy may also have a potential role in development of second malignancies following multiple myeloma. In fact, about 40% of patients with multiple myeloma may require treatment with radiotherapy at some time during their illness.(25) Studies focusing on Hodgkin lymphoma and breast cancer have found an increased risk of second malignancies following radiotherapy, with a dose-response relationship between risk of second malignancy and radiation dose to the surrounding tissues, including the bone marrow.(17, 26, 27) For example, malignancies associated with loco-regional radiation for breast cancer include sarcomas, lung and esophageal cancers and AML.(27-29) At this time, to our knowledge, there is limited information on the association between radiotherapy and risk of subsequent malignancies in multiple myeloma.

Maintenance therapy has been evaluated in relation to risk of second malignancies in three recently reported multicenter randomized phase III trials (IFM 2005-02, CALGB 100104 and MM-015) (30-32) (Table 1). IFM 2005-02, CALGB 100104 explored the role of lenalidomide maintenance therapy after high-dose melphalan/ASCT.(30, 31) In both trials, lenalidomide at a dose of 10–15 mg given within 3–6 months of autologous transplantation was compared to placebo until disease progression. Unlike CALGB 100104, patients in IFM trial received lenalidomide induction for two months prior to maintenance dosing, had a longer

follow-up and no cross-over was permitted to lenalidomide arm at progression.32 In the IFM 2005-02 and CALGB 100104 trials, 5.5% and 6.5% of lenalidomide treated patients developed second malignancies compared to 1% and 2.5% in the respective control arms. The second malignancies reported include AML/MDS, Hodgkin lymphoma, B-cell ALL, colon, prostate, breast and esophageal cancers. MM-015 evaluated maintenance lenalidomide following combination of lenalidomide with melphalan and prednisone (MP) vs. fixed MP duration regimens in ≥65 year old transplant ineligible patients with newly diagnosed multiple myeloma.(32) This study also found an increase in the number of second cancers in lenalidomide treated patients, notably AML which was associated with complex baseline cytogenetics: two cases each were observed in the lenalidomide treated arms and none in the MP arm (0.7% vs. 0%). The SIR (standardized incidence ratio) for AML in the MP-lenalidomide followed by lenalidomide maintenance and placebo maintenance were 4.46 and 4.65 respectively compared to the NCI SEER database.(32) At this time, IFM 2005-02 and MM-015 have demonstrated a progression free survival benefit, although there was no improvement in overall survival for patients who received lenalidomide. CALGB 100104 demonstrated an overall survival improvement in lenalidomide treated patients with an overall survival rate at 23 months of 90% in the continuous lenalidomide arm compared to 83% in the placebo arm ($p<0.018$), despite 80% of patients crossing over to receive continuous lenalidomide.(31) Maintenance lenalidomide was discontinued in the IFM 2005-02 trial while patients on the other trials continue to receive lenalidomide with enhanced monitoring, while an ongoing safety review is completed.35

Among patients with relapsed/refractory multiple myeloma, two retrospective studies have evaluated the role of lenalidomide in relation to the risk of second malignancies.(33, 34) Based on 230 relapsed/refractory multiple myeloma patients treated with lenalidomide based

regimens, Reece et al found MDS/AML in 2.6% (6 patients) patients at a median of 76 months from the time of diagnosis of MM and 61 months from the time of initiation of lenalidomide.(33) Although the prior exposure to alkylating agents was similar in both groups, patients who developed AML/MDS were older [68 (54-76) vs. 61 (32-80)], less likely to have had high-dose melphalan/ASCT [2 (33%) vs. 149 (82%)] and had longer duration of treatment with lenalidomide [median number of cycles: 21 (9-35) vs. 9 (1-50)].(33) A post-hoc analysis of pooled data from phase III MM-009 and MM-010 trials revealed two MDS, eight solid tumors and no leukemias. Using NCI SEER data, no increase in incidence of solid tumors was noted compared to the general population.(34)

In parallel with the above mentioned studies reporting on lenalidomide maintenance and excess MDS/AML development in multiple myeloma, other investigations have been evaluating the role of lenalidomide treatment in the setting of MDS. For example, a recent study reported that lenalidomide used as treatment for 5q- MDS was not associated with AML progression.(35)

Taken together, mostly based on small numbers, prior studies have found various types of therapies (such as, oral alkylating therapy, myeloablative therapy used in conjunction with ASCT, radiotherapy and lenalidomide) to be associated an excess of second malignancies following multiple myeloma. Yet the exact underlying mechanisms remain to be determined and several studies to elucidate the underlying mechanisms are ongoing.

MULTIPLE MYELOMA-RELATED FACTORS

Although presenting with the same histologic picture, multiple myeloma displays a broad molecular range characterized by subgroups with unique gene expression profiles, which

correlate with clinical characteristics and patient survival. Moreover, additional molecular events including epigenetic changes and activation of molecular pathways occur during multiple myeloma progression and treatment.(36, 37)

In a recent population-based study from Sweden, based on 5652 patients with multiple myeloma precursor disease, monoclonal gammopathy of uncertain significance (MGUS), an 8-fold increased risk of developing MDS/AML was observed.(15) The elevated risk was confined to those with IgG/IgA (and not IgM) MGUS. Interestingly, MGUS patients with M-protein concentrations >1.5 g/dL (SIR=11.12) had higher risk than those with ≤1.5g/dL (SIR=4.67) suggesting that more active precursor disease has similar baseline risk for AML/MDS to that of active multiple myeloma.(15) Overall, these observations are important in that they support a role for disease related factors in MDS/AML following multiple myeloma and raises the question whether underlying molecular heterogeneities in multiple myeloma may be related to the risk of developing second malignancies. It is possible that certain molecular multiple myeloma subgroups are at a higher risk than others. For example, a potential mechanism could be selective pressure (i.e., a pre-existing non-dominant clone, unresponsive to treatment) leading to an increased susceptibility to developing second malignancies. A better understanding of underlying molecular mechanisms across multiple myeloma subgroups and risk of second malignancy will form the basis for modification and targeting therapies to specific subgroups, with the overall goal to minimize the risk of second malignancies.

HOST-RELATED FACTORS

Although we lack large well-designed studies at this time, based on work done on other cancer types, it seems reasonable to propose that host-related (including both genetic and non-

genetic) factors may play a role in the development of second malignancies following multiple myeloma. In fact, it has been estimated that genetic variations can account for up to 95% of variability in drug disposition and effects.(38) In addition to drug disposition and response to treatment, polymorphisms in genes encoding drug-metabolizing enzymes, DNA repair pathways, drug transporters and targets may also contribute to an individual's susceptibility for subsequent malignancies as well.(17, 39) For example, decreased production of glutathione S-transferase enzymes, GSTM1 and GSTT1 result from polymorphisms of respective genes which may be associated with an increased MDS risk in the presence of environmental mutagens and/or carcinogens exposure.(40) Similarly, polymorphisms in genes that regulate cellular responses to DNA damage can affect the risk of developing MDS/AML, presumably by influencing the survival of hematopoietic cells with proleukemogenic mutations.(41) Non-genetic host-factors which can modulate treatment effects include age, race, organ function, concomitant therapy, drug interactions, and myeloma itself.

Two studies (n=2418 and 82) observed that patients who eventually develop MDS or MDS-associated cytogenetic abnormalities (MDS-CAs) have a lower CD34 yield at collection, suggesting a pre-existing marrow abnormality likely a result of host or host- myeloma interaction.(11, 20) Similar observations have been reported in Hodgkin lymphoma and non-Hodgkin lymphoma, where cytogenetic abnormalities observed at the diagnosis of MDS/AML were already present in the morphologically normal pre-transplant bone marrow.(42, 43) Furthermore, the bone marrow microenvironment may be important in the pathogenesis of MDS/AML. MGUS and multiple myeloma are dependent on mutual interactions with cells and extracellular components of the bone marrow for survival and growth. Interactions of multiple myeloma cells with the bone marrow microenvironment activate a pleiotropic proliferative and

anti-apoptotic cascade including the NFκB signaling pathway resulting in multiple myeloma cell growth, survival, drug resistance and migration. Moreover, many of the growth factors secreted by multiple myeloma and bone marrow stromal cells stimulate osteoclastogenesis and angiogenesis.(36) It is conceivable that the resultant changes in bone marrow microenvironment may play a role in development of MDS/AML following multiple myeloma. Chromosome 5 abnormalities and clinical phenotype consistent with 5q- syndrome have been described in some patients with lenalidomide associated MDS.(33, 44) 5q- syndrome is a disorder of the human hematopoietic stem cell (HSC) with a combined lympho-myeloid potential and is known to represent an early event in MDS pathogenesis. Lenalidomide is approved for use in selected patients with 5q- with or without additional cytogenetic abnormalities. Rare and phenotypically distinct 5q- HSC that are selectively resistant to lenalidomide have been identified in MDS patients during complete clinical and cytogenetic remission.(45, 46) It is plausible that a sub-clone of lenalidomide resistant HSC may expand during treatment, resulting in MDS/AML. 5q- has also been described as part of a complex karyotype in secondary leukemias.(47, 48)

Recently, we found the G/G phenotype of single nucleotide polymorphism (SNP) rs1617640 in the erythropoietin promoter gene, which is associated with decreased erythropoietin expression, to be more common (27% vs. 12%) in multiple myeloma patients who developed MDS compared with patients who did not.(49) This suggests a role for susceptibility genes in the development of second malignancies following multiple myeloma. These results need to be confirmed in larger studies on a wider panel of genes.

To better understand the role of host genetics in defining susceptibility to second malignancies, it is important to identify susceptibility loci and alleles, and establish how these interact with exposure to affect cellular response to therapeutic exposures and the subsequent

risk of disease.(41) Genome-wide association studies and gene expression microarray analysis of groups of patients with and without second malignancies have identified several candidate SNP's which are associated with acute leukemia following other malignancies.(50-52) Identifying patients at risk for second malignancies at the time of diagnosis of multiple myeloma would enable personalizing treatment and post- therapy surveillance options to minimize this risk.

ENVIRONMENTAL FACTORS

Several proposed environmental risk factors are shared between multiple myeloma and second malignancies. For cancers that share etiologic factors with multiple myeloma, the pertinent genetic traits will likely have low to moderate penetrance and be driven by multiple gene–environment and gene–gene interactions.(17) For example, some, but not all prior studies indicate that exposure to ionizing radiation, especially at younger ages and at higher doses increases the risk of developing multiple myeloma and MGUS in addition to leukemias, MDS and solid tumors.(53-57) Also, prior studies have suggested that exposure to chlorinated solvents is associated with development of non-Hodgkin lymphoma, leukemia and multiple myeloma.(58, 59) Chronic antigen stimulation from prior autoimmune, infectious, inflammatory, allergic disorders and immune dysregulation may play a role in pathogenesis of both multiple myeloma and AML/MDS.(60-62) Recently, solid organ transplant patients receiving immunosuppressive therapy have been reported to be at risk for the development of AML.(63) In addition, socioeconomic status has been shown to influence survival in both multiple myeloma and AML, suggesting that life-style factors in these disorders are of importance.(64)

BEHAVIORAL FACTORS

Tobacco use and alcohol intake is causally related to multiple primary cancers. Multiple myeloma may share behavioral risk factors with other malignancies and multiple myeloma survivors exposed to these risk factors at a higher risk of subsequent malignancies. Interestingly, the commonly proposed behavioral risk factors (e.g. tobacco, alcohol and diet) for various types of cancers have not been associated with multiple myeloma.(65, 66) Nevertheless, obesity has been associated with an increased risk for both multiple myeloma and MGUS,(67, 68) and a slightly decreased risk for multiple myeloma has been reported to be associated with the consumption of cruciferous vegetable and fish.(69)

SUMMARY AND DISCUSSION

Despite being known for several decades, accurate estimates of incidence and pathogenesis of second malignancies following multiple myeloma are lacking. Current literature focusing on second malignancies following multiple myeloma is limited and should be interpreted with caution. For example, most prior studies are restricted due to small numbers of patients, inadequate follow-up, and limitations of ascertainment of second malignancies (Table 2). Largely due to insufficient data and a small number of studies, most of our current understanding of malignancies following multiple myeloma is modeled on experiences with other malignancies, such as Hodgkin lymphoma, and emphasizes the role of treatment.(11, 19-22) Based on current knowledge, it seems reasonable to propose that the development of second malignancies following multiple myeloma, most likely, is a multi-factorial process. Contributing

factors probably include various multiple myeloma treatments, multiple myeloma-related factors, host-related factors, as well as environmental and behavioral factors (Figure 1). Early works in this area and subsequent efforts have focused on the role of treatment-related factors such as alkylating agents.(11, 19-22) Due to the insufficient data, the role of non-treatment related factors remain largely unexplored. For example, based on small numbers of patients, there are indications that host genetic polymorphisms may play a role in pathogenesis of second malignancies.(49) Also, recent population-based data suggest that IgG/IgA MGUS patients may also be at an increased risk for AML/MDS.(15) These results support a role for host- and disease- related factors and, if validated in larger studies, they set the stage for future investigations designed to define underlying molecular mechanisms. Other non-treatment related factors like environment and behavior are also not well understood.

Based on small numbers, recent reports from three randomized trials have consistently demonstrated more hematologic malignancies in patients treated with lenalidomide as maintenance (vs. placebo).(30-32) Further studies are needed to better characterize underlying mechanisms of these observations. Beyond the underlying biology, the clinical implications of excess of second malignancies in multiple myeloma patients who receive lenalidomide need to be interpreted in the context of competing risks. On a clinical note, for most patients, multiple myeloma still remains an incurable malignancy and, on average, the general risk of dying is substantially higher than the risk of developing a second cancer (Figure 2). (70) That being said, although numbers are small, for individual patients who do develop AML/MDS following multiple myeloma, the outcomes are devastating. These two parallel perspectives (“on average” versus “individual patients”) highlight the complexity of clinical medicine in the era of modern therapy and correlative science. Furthermore, progression-free survival was significantly

prolonged in all three studies of lenalidomide maintenance and in one of these, the CALGB 100104 trial of lenalidomide maintenance after high-dose melphalan/ASCT there was also a significant overall survival benefit. In summary, these facts are tightly intertwined and there are multiple aspects to consider. Although there are few clear answers available at this time, in our opinion, clinicians need to discuss the risks and benefits with patients and stay updated as more data becomes available. Until we have access to better knowledge, in our opinion, in circumstances where the benefit of maintenance therapy in terms of overall survival is not well established, the risks versus any possible benefit should be taken more cautiously.

FUTURE DIRECTIONS

In the context of increasing overall survival in multiple myeloma, and the recently reported increase of second malignancies associated with use of lenalidomide (30-32), it is imperative that we re-address the association between multiple myeloma and leukemia which was first reported in the late 1960s.(8-10) Importantly, due to inherent problems related to the small number of cases, collaborative efforts are needed to better characterize molecular features of patients who develop second malignancies following multiple myeloma. Such efforts would allow us to better define the role of treatment and non-treatment related factors, and how they may influence each other. Ultimately, we could use such knowledge to identify high-risk and low-risk patients, and to tailor therapy, with the goal to maximize survival and minimize the risk for second malignancies for the individual patient.

ACKNOWLEDGEMENTS

This research was supported by the Intramural Research Program of the National Cancer Institute of the National Institutes of Health.

AUTHOR CONTRIBUTIONS

AT and OL drafted the manuscript. All authors were involved in the interpretation of the data, and reviewed and approved the submitted version of the manuscript.

CONFLICTS OF INTERESTS

None.

Legends

TABLE 1. Selected studies focusing on second malignancies following multiple myeloma

Legend: * These results come from interim analyses presented at the American Society of Hematology meeting in Orlando, Florida, December 2010. # Updated numbers from presentations at the International Myeloma Workshop in Paris, France, May 2011. At this time, the final analyses and written reports have not yet been published.
Abbreviations: MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; ASCT = autologous stem cell transplantation; NR = not reported; MPR-R = melphalan/ prednisone, revlimid (lenalidomide), with revlimid maintenance; MPR = melphalan/ prednisone, revlimid (lenalidomide), without revlimid maintenance; MP = melphalan/ prednisone, without revlimid maintenance.

TABLE 2. Selected study-related factors which may bias the estimated risk of second malignancies following multiple myeloma

FIGURE 1. Proposed model of second malignancies following multiple myeloma

Examples for the above listed categories include:
[1]Alkylating agents, Immunomodulatory agents, autologous stem cell transplant, radiation
[2]Molecular subtypes of disease, bi-clonal disease, bone marrow microenvironment
[3]Polymorphisms in germ line genes (e.g., drug metabolizing genes, erythropoietin promoter gene), chronic antigenic stimulation, genetic susceptibility with other malignancies
[4]Occupation, pesticides, chlorinated solvents
[5]Tobacco, obesity, alcohol, diet

FIGURE 2. Cumulative incidence of developing a second cancer and cumulative probability of death due to competing causes, following multiple myeloma

Legend: Data, which are based on 33,229 patients who received a diagnosis of multiple myeloma between 1973 and 2008 in the United State, are from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Reprinted with permission (Landgren et al, New Engl J Medicine, 2011(365);23:2242).

REFERENCES

1. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol. 2010;28(5):830-4. Epub 2009/12/30.
2. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20. Epub 2007/11/03.
3. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol. 2007;25(15):1993-9. Epub 2007/04/11.
4. Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. Journal of the National Cancer Institute. 2005;97(18):1354-65.
5. Mauch PM, Kalish LA, Marcus KC, Shulman LN, Krill E, Tarbell NJ, et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. The cancer journal from Scientific American. 1995;1(1):33-42.
6. Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2000;18(3):498-509.
7. Curtis RE FD, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF Jr, eds. , editor. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. . Bethesda, MD: NIH Publ. ; 2006.
8. Nordenson NG. Myelomatosis. A clinical review of 310 cases. Acta medica ScandinavicaSupplementum. 1966;445(Journal Article):178-86.
9. Osserman EF. In: Killander J, editor. Gamma Globulins: Structure and Control of Biosynthesis: Stockholm, Almqvist and Wiksell.; 1967. p. 573.
10. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukemia. The New England journal of medicine. 1970;283(21):1121-5.
11. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy on plasma-cell myeloma and the incidence of acute leukemia. The New England journal of medicine. 1979;301(14):743-8.
12. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. Mayo Clinic proceedingsMayo Clinic. 2010;85(3):225-30.
13. Acute leukaemia and other secondary neoplasms in patients treated with conventional chemotherapy for multiple myeloma: a Finnish Leukaemia Group study. European journal of haematology. 2000;65(2):123-7.
14. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. British journal of cancer. 2001;85(7):997-1005.
15. Mailankody S, Pfeiffer RM, Kristinsson SY, Korde N, Bjorkholm M, Goldin LR, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes following multiple myeloma and its precursor disease (MGUS). Blood. 2011. Epub 2011/07/29.

16. Conversion of Neoplasms by Topography and Morphology from the International Classification of Diseases for Oncology, second edition to International Classification of Diseases for Oncology, third edition. Cancer Statistics Branch, DCCPS, SEER Program, National Cancer Institute. 2001 [cited 2011. July 22]; Available from: Website. http://seer.cancer.gov/tools/conversion/ICDO2-3manual.pdf.
17. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, et al. Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. Journal of the National Cancer Institute. 2006;98(1):15-25.
18. Hasskarl J, Ihorst G, De Pasquale D, Schrottner P, Zerweck A, Wasch R, et al. Association of multiple myeloma with different neoplasms: systematic analysis in consecutive patients with myeloma. Leuk Lymphoma. 2011;52(2):247-59. Epub 2010/11/09.
19. Barlogie B, Tricot G, Haessler J, van Rhee F, Cottler-Fox M, Anaissie E, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood. 2008;111(1):94-100. Epub 2007/09/27.
20. Przepiorka D, Buadi F, McClune B, Franz G, Walsh W, White F. Myelodysplastic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma. Bone marrow transplantation. 2007;40(8):759-64.
21. Govindarajan R, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B, et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. British journal of haematology. 1996;95(2):349-53.
22. Cuzick J, Erskine S, Edelman D, Galton DA. A comparison of the incidence of the myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's working party on leukaemia in adults. British journal of cancer. 1987;55(5):523-9.
23. Pedersen-Bjergaard J, Ersboll J, Sorensen HM, Keiding N, Larsen SO, Philip P, et al. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. Annals of Internal Medicine. 1985;103(2):195-200.
24. Greene MH, Harris EL, Gershenson DM, Malkasian GD, Jr., Melton LJ, 3rd, Dembo AJ, et al. Melphalan may be a more potent leukemogen than cyclophosphamide. Annals of Internal Medicine. 1986;105(3):360-7.
25. Featherstone C, Delaney G, Jacob S, Barton M. Estimating the optimal utilization rates of radiotherapy for hematologic malignancies from a review of the evidence: part II-leukemia and myeloma. Cancer. 2005;103(2):393-401.
26. Sigurdson AJ, Jones IM. Second cancers after radiotherapy: any evidence for radiation-induced genomic instability? Oncogene. 2003;22(45):7018-27.
27. de Gonzalez AB, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. The lancet oncology. 2011;12(4):353-60.
28. Schaapveld M, Visser O, Louwman MJ, de Vries EG, Willemse PH, Otter R, et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(8):1239-46.

29. Berrington de Gonzalez A, Curtis RE, Gilbert E, Berg CD, Smith SA, Stovall M, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. British journal of cancer. 2010;102(1):220-6.
30. Attal M OP, Cances Lauwers V et al. , editor. Maintenance treatment with lenalidomide after transplantation for myeloma: analysis of secondary malignancies within the IFM 2005-02 trial. 13th International Myeloma Workshop; 2011; Paris.
31. Mccarthy P OK, Anderson K et al. . Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma CALGB ECOG BMT-CTN 100104. 13th International Myeloma Workshop; Paris2011.
32. Palumbo AP DM, Catalano J et al. , editor. Incidence of second primary malignancy in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance in newly diagnosed multiple myeloma patients age 65 or older [abstract]. J Clin Oncol. 2011;(suppl):29. : .
33. Reece DE M-KE, Goswami RS et al., editor. Incidence and characteristics of secondary myelodysplastic syndrome developing during lenalidomide-based regimens in relapsed and/or refractory multiple myeloma patients. 53rd American Society of Hematology Annual Meeting; 2010 December 4; Orlando, FL.
34. Dimopoulos MA OR, Niesvizky R et al. . Lenalidomide and dexamethasone treatment in relapsed/refractory multiple myeloma patients and risk of second primary malignancies: Analysis of MM-009/010 [abstract]. J Clin Oncol 2011;(suppl):29. 2011.
35. Kuendgen A, Lauseker M, List AF, Fenaux P, Giagounidis A, Brandenburg N, et al. Lenalidomide Treatment Is Not Related to AML Progression Risk but Is Associated with a Survival Benefit in RBC Transfusion-Dependent Patients with IPSS Low- or Int-1-Risk MDS with del5q: Results From a Comparative Study. Blood. 2011;118:(ASH Annual Meeting Abstracts; 119).
36. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nature reviewsCancer. 2007;7(8):585-98.
37. Zhan F, Sawyer J, Tricot G. The role of cytogenetics in myeloma. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2006;20(9):1484-6.
38. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics. 1998;8(4):283-9.
39. Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. The New England journal of medicine. 2003;348(6):538-49.
40. Dahabreh IJ, Giannouli S, Gota V, Voulgarelis M. GSTT1 and GSTM1 polymorphisms and myelodysplastic syndrome risk: a systematic review and meta-analysis. International journal of cancerJournal international du cancer. 2010;126(7):1716-23.
41. Allan JM, Travis LB. Mechanisms of therapy-related carcinogenesis. Nature reviewsCancer. 2005;5(12):943-55.
42. Abruzzese E, Radford JE, Miller JS, Vredenburgh JJ, Rao PN, Pettenati MJ, et al. Detection of abnormal pretransplant clones in progenitor cells of patients who developed myelodysplasia after autologous transplantation. Blood. 1999;94(5):1814-9.

43. Amigo ML, del Canizo MC, Hernandez JM, Gonzalez MB, Gutierrez N, Mateos MV, et al. Clonal myelodysplastic cells present in apheresis product before transplantation. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 1998;12(9):1497-9.
44. Goswami RS BD, Masih-Khan E et al., editor. Characteristics of patients presenting with secondary myelodysplastic syndrome during treatment with lenalidomide for relapsed/refractory multiple myeloma: 5q deletions can be observed. 53rd American Society of Hematology Annual Meeting; 2010 December 4; Orlando, FL. .
45. Tehranchi R, Woll PS, Anderson K, Buza-Vidas N, Mizukami T, Mead AJ, et al. Persistent malignant stem cells in del(5q) myelodysplasia in remission. The New England journal of medicine. 2010;363(11):1025-37.
46. Jadersten M, Saft L, Pellagatti A, Gohring G, Wainscoat JS, Boultwood J, et al. Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression. Haematologica. 2009;94(12):1762-6.
47. Boultwood J, Lewis S, Wainscoat JS. The 5q-syndrome. Blood. 1994;84(10):3253-60.
48. Boultwood J, Pellagatti A, McKenzie AN, Wainscoat JS. Advances in the 5q- syndrome. Blood. 2010;116(26):5803-11.
49. Landgren O. Multiple myeloma precursor disease: current clinical dilemma and future opportunities. Semin Hematol. 2011;48(1):1-3. Epub 2011/01/15.
50. Knight JA, Skol AD, Shinde A, Hastings D, Walgren RA, Shao J, et al. Genome-wide association study to identify novel loci associated with therapy-related myeloid leukemia susceptibility. Blood. 2009;113(22):5575-82.
51. Ellis NA, Huo D, Yildiz O, Worrillow LJ, Banerjee M, Le Beau MM, et al. MDM2 SNP309 and TP53 Arg72Pro interact to alter therapy-related acute myeloid leukemia susceptibility. Blood. 2008;112(3):741-9.
52. Yeoh EJ, Ross ME, Shurtleff SA, Williams WK, Patel D, Mahfouz R, et al. Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer cell. 2002;1(2):133-43.
53. Shimizu Y, Schull WJ, Kato H. Cancer risk among atomic bomb survivors. The RERF Life Span Study. Radiation Effects Research Foundation. JAMA : the journal of the American Medical Association. 1990;264(5):601-4.
54. Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiation research. 1994;137(2 Suppl):S68-97.
55. Iwanaga M, Hsu WL, Soda M, Takasaki Y, Tawara M, Joh T, et al. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: a retrospective cohort study of Nagasaki atomic bomb survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(4):428-34.
56. Iwanaga M, Tagawa M, Tsukasaki K, Matsuo T, Yokota K, Miyazaki Y, et al. Relationship between monoclonal gammopathy of undetermined significance and radiation exposure in Nagasaki atomic bomb survivors. Blood. 2009;113(8):1639-50. Epub 2008/10/14.
57. Landgren O. A role for ionizing radiation in myelomagenesis? Blood. 2009;113(8):1616-7.
58. Gold LS, Stewart PA, Milliken K, Purdue M, Severson R, Seixas N, et al. The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. Occupational and environmental medicine. 2011;68(6):391-9.

59. Sonoda T, Ishida T, Mori M, Sakai H, Noguchi M, Imai K. A case-control study of multiple myeloma in Japan: association with occupational factors. Asian Pacific journal of cancer prevention : APJCP. 2005;6(1):33-6.
60. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood. 2008;111(7):3388-94.
61. Kristinsson SY, Goldin LR, Bjorkholm M, Koshiol J, Turesson I, Landgren O. Genetic and immune-related factors in the pathogenesis of lymphoproliferative and plasma cell malignancies. Haematologica. 2009;94(11):1581-9.
62. Kristinsson SY, Bjorkholm M, Hultcrantz M, Derolf AR, Landgren O, Goldin LR. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(21):2897-903.
63. Gale RP, Opelz G. Commentary: does immune suppression increase risk of developing acute myeloid leukemia? Leukemia. 2011. Epub 2011/08/27.
64. Kristinsson SY, Derolf AR, Edgren G, Dickman PW, Bjorkholm M. Socioeconomic differences in patient survival are increasing for acute myeloid leukemia and multiple myeloma in sweden. J Clin Oncol. 2009;27(12):2073-80. Epub 2009/03/18.
65. Brown LM, Gibson R, Burmeister LF, Schuman LM, Everett GD, Blair A. Alcohol consumption and risk of leukemia, non-Hodgkin's lymphoma, and multiple myeloma. Leukemia research. 1992;16(10):979-84.
66. Kyle RA, Rajkumar SV. Epidemiology of the plasma-cell disorders. Best practice & researchClinical haematology. 2007;20(4):637-64.
67. Friedman GD, Herrinton LJ. Obesity and multiple myeloma. Cancer causes & control : CCC. 1994;5(5):479-83.
68. Landgren O, Rajkumar SV, Pfeiffer RM, Kyle RA, Katzmann JA, Dispenzieri A, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. Blood. 2010;116(7):1056-9. Epub 2010/04/28.
69. Brown LM, Gridley G, Pottern LM, Baris D, Swanso CA, Silverman DT, et al. Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. Cancer causes & control : CCC. 2001;12(2):117-25.
70. Landgren O, Thomas A, Mailankody S. Myeloma and second primary cancers. N Engl J Med. 2011;365(23):2241-2.

TABLE-1. Selected studies focusing on second malignancies following multiple myeloma

Study	Study design (study period)	Pts, n	Any second malignancy, %	Multiple myeloma to second malignancy, median time	Hematologic malignancy, n (%)	Solid tumor, n (%)
Mailankody et al., 2011	Population-based registry study (1986-2005)	8740	6.6%	45.3 months (AML/MDS)	69 (0.8%)	508 (5.8%)
Hasskarl et al, 2011	Retrospective study, single institution (1997-2008)	589	3%	35 months	6 (1.0%)	12 (2.0%)
Attal, et al., 2010*	Randomized phase III trial, maintenance lenalidomide vs. placebo after high-dose melphalan/ASCT	614	5.5% (lenalidomide maintenance) 1% (placebo)	44 months	[#] Lenalidomide maintenance: 11 (1.8%) [#] Placebo arm: 3 (0.5%)	[#] Lenalidomide maintenance: 12 (2.0%) [#] Placebo arm: 3 (0.5%)
McCarthy et al., 2010*	Randomized phase III trial, maintenance lenalidomide vs. placebo after high-dose melphalan/ASCT	460	6.5% (lenalidomide maintenance) 2.6% (placebo)	17.5 months after ASCT	[#] Lenalidomide maintenance: 8 (1.7%) [#] Placebo arm: 0 (0%)	[#] Lenalidomide maintenance: 10 (2.2%) [#] Placebo arm: 4 (0.9%)
Palumbo et al., 2010*	Randomized phase III trial, maintenance lenalidomide vs. placebo after low-dose melphalan/prednisone+/- lenalidomide	459	3.9% (lenalidomide maintenance) 1.3% (placebo)	25 months	[#] MPR-R arm: 7 (1.5%) [#] MPR arm: 5 (1.1%) [#] MP arm: 1 (0.2%)	[#] MPR-R: 5 (1.1%) [#] MPR: 4 (0.9%) [#] MP: 3 (0.7%)
Barlogie et al, 2008	Retrospective study, single institution (1989-2007)	2418	1.1%	NR	26 (1.1%)	NR
Przepiorka et al, 2007	Retrospective study, single institution (1996-2005)	82	12.2%	50 months	10 (12.2%)	NR
Dong et al, 2001	Population-based registry study (1958-1996)	8656	5.5%	2.9 years	83 (1.0%)	392 (4.5%)
Finnish Leukemia Group, 2000	Retrospective study based on patients from clinical trials (1979-1985)	432	9.2%	37 months (solid tumors) 56 months (acute leukemia)	17 (3.9%)	23 (5.3%)
Govindarajan et al, 1996	Prospective study (NR)	188	3.8%	63 months	7 (3.8%)	NR
Cuzick et al, 1987	Retrospective study based on patients from clinical trials (1964-1975)	648	1.9%	82 months	12 (1.9%)	NR
Bergsagel et al, 1979	Prospective study (1973-1977)	364	3.8%	NR	14 (3.8%)	NR
Kyle et al., 1970	Case series (1965-1966)	3	N/A	45 months	3 (N/A)	NR
Edwards and Zawadski, 1967	Case series (1950-1966)	8	N/A	10 years	1 (N/A)	NR

Nordenson, 1966	Retrospective study, multi institution (1932-1963)	310	2.3%	NR	7 (2.3%)	NR

TABLE 2. Selected study-related factors which may bias the estimated risk of second malignancies following multiple myeloma

Study-related factors
Short-term follow-up
Small sample sizes
Combinations and interactions between multiple drugs
Inadequate control group
Retrospective data collection
Under-reporting by clinicians
Survival difference (person-years) between experimental and surveillance arms

FIGURE 1. Proposed model of second malignancies following multiple myeloma

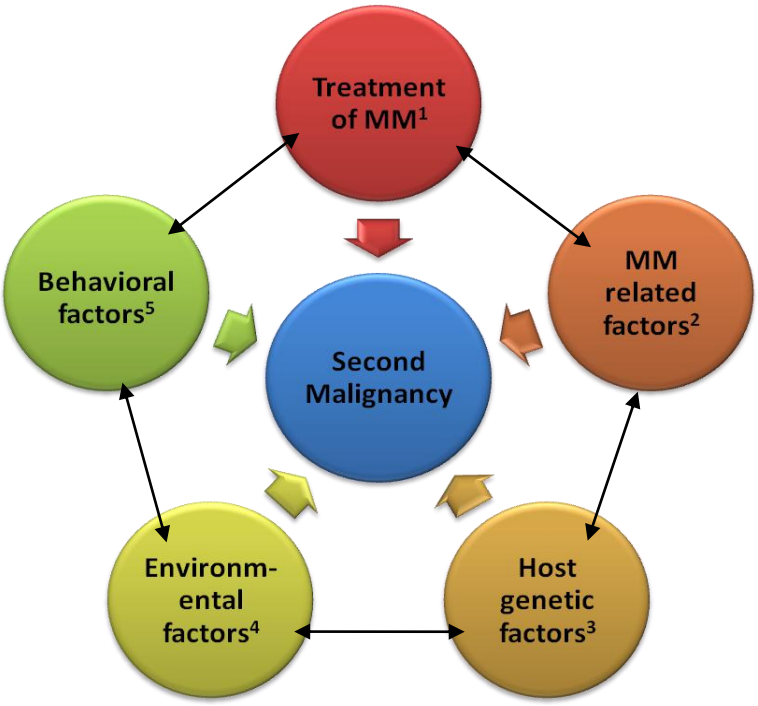
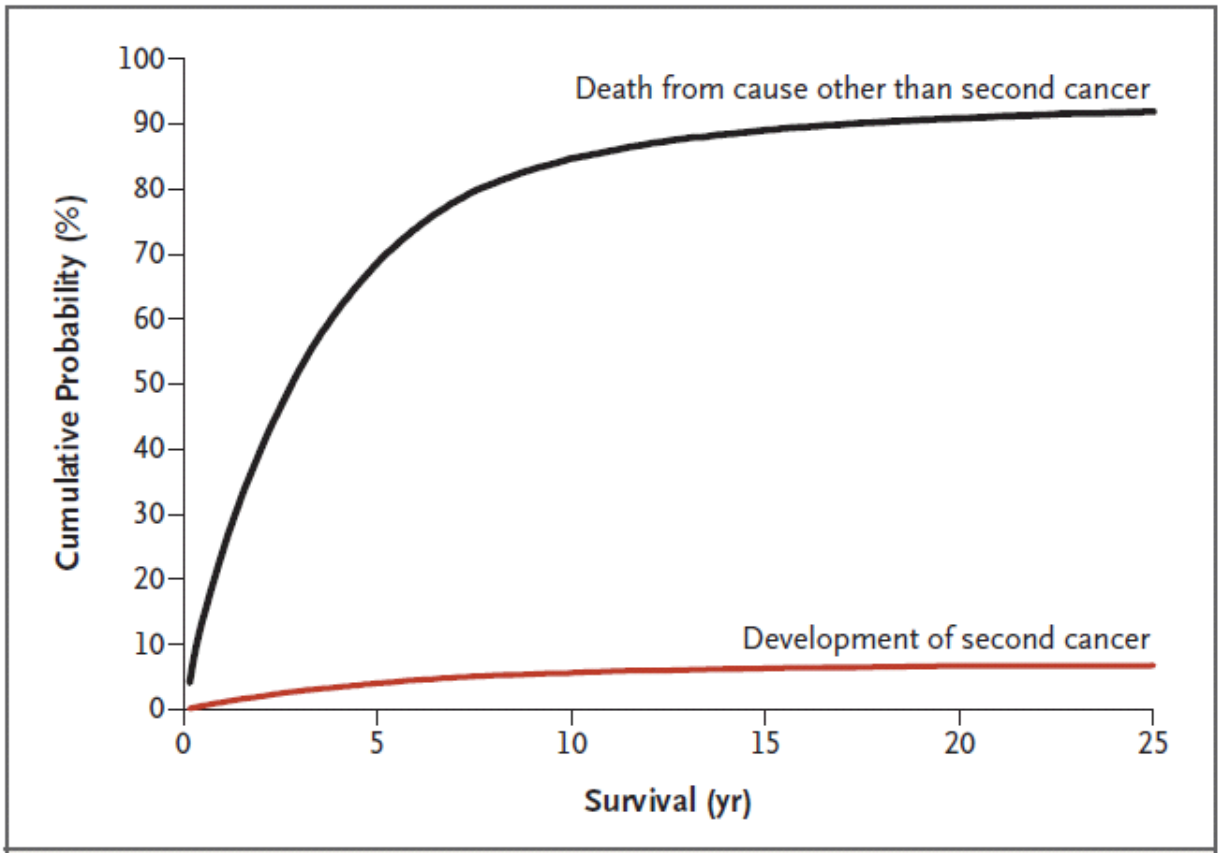


FIGURE 2. Cumulative incidence of developing a second cancer and cumulative probability of death due to competing causes, following multiple myeloma



Legend: Data, which are based on 33,229 patients who received a diagnosis of multiple myeloma between 1973 and 2008 in the United State, are from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Reprinted with permission (Landgren et al, New Engl J Medicine, 2011(365);23:2242). (70)