

ORIGINAL ARTICLE

Multiple myeloma in association with second malignancy

J.Grudeva-Popova¹, I.Nenova¹, M.Spasova², M.Yaneva³, E.Beleva¹, N.Ananoshtev⁴

¹Department of Oncology and Hematology, ²Department of Pediatrics and Medical Genetics, ³Radiotherapy Department – University Multiprofile Hospital for Active Treatment “Sv. Georgi”, Plovdiv; ⁴Comprehensive Oncology Hospital, Plovdiv, Bulgaria

Summary

Purpose: To look at the frequency of second primary malignancies (SECMAL) in patients with multiple myeloma (MM).

Methods: The medical files of 332 patients with MM (whole group), diagnosed and treated at the University Multiprofile Hospital for Active Treatment “Sv. Georgi” and the Comprehensive Oncology Hospital “Plovdiv” for a 20-year period (1990-2010) were retrospectively analyzed. MM patients with SECMAL constituted the study group. A control group comprised patients with solid tumors associated with SECMAL. This group derived from a sample of 21768 patients with solid tumors.

Results: In the study group, SECMAL was diagnosed in 4.52% (N=15) of the patients, while in the control group this figure was 5.09% (N=1108) ($p>0.05$). The diagnosis of MM preceded the occurrence of SECMAL in 35.71% of the study

group patients, the median interval being 6.6 years (range 5-14). More frequently the diagnosis of the solid tumor preceded the occurrence of MM (66.67%). Breast cancer and gastric cancer were encountered with the highest frequency (26.67% each). The median survival (77.2 months, range 44-129) was significantly longer in the group with MM and SECMAL compared to the whole group with MM (median 38.6 months, range 10-58; $p<0.05$).

Conclusion: The rate of MM with other malignant diseases is comparable with the frequency of SECMAL in other lymphoproliferative disorders and solid tumors. The occurrence of SECMAL during the clinical course of MM is not a frequent event and is expected in the rare cases with longer survival.

Key words: multiple myeloma, risk factors, second malignancy, survival

Introduction

SECMAL is usually diagnosed during the long observation period of potentially curable patients with oncologic diseases with significant life expectancy. Analysis of these cases gives important information about the role of numerous genetic, immunologic and environmental factors (including previous chemo/radiotherapy) in carcinogenesis. Cases of SECMAL have been first reported in 1927 in patients cured of Hodgkin's disease [1]. In most cases SECMAL is considered as a consequence of the treatment of the first malignant disease.

The association of MM with other malignancies has been described only rarely in case

reports, and larger studies do not appear in the current literature. Ormerod et al. have reported 3.5% of SECMAL in a group of 279 MM patients [2]. The occurrence of secondary myelodysplastic syndrome and acute myeloblastic leukemia during the natural course of MM had long been documented. Some authors have reported higher risk of secondary lymphoproliferative malignancies vs carcinomas in the setting of MM [3]. The significance of myeloma-specific factors as well as the immunomodulatory treatment administered have been largely discussed [4]. In a meta-analysis of 11 clinical trials (3846 MM cases) a trend was found towards higher incidence rate in lenalidomide-treated patients vs dexamethasone ones [5].

The purpose of the current study was look for the frequency and analyze the cases with SECMAL associated with MM.

Methods

We retrospectively analyzed 332 patients with MM (whole group), diagnosed and treated at the University Multiprofile Hospital for Active Treatment "Sv. Georgi" and the Comprehensive Oncology Hospital "Plovdiv" for a 20-year period (1990-2010). MM patients with SECMAL constituted the study group. The mean follow-up time of the patients in this group was 6.34 years (range 2.7-8.9).

The control group comprised 1108 patients with solid tumors associated with SECMAL. This group derived from a sample of 21768 patients with solid tumors, registered at the Comprehensive Oncology Hospital "Plovdiv" for a 5-year period (1998-2002). The study and the control groups were comparable in their basic demographic characteristics.

The frequency of the association MM-SECMAL and the survival rate in the study group were also compared to size-matched groups of patients with lymphomas associated with SECMAL (149 patients with Hodgkin's disease and 113 patients with chronic lymphocytic leukemia / CLL). These patients were enrolled in our previous studies with published results [6,7].

Statistics

Data were analyzed by means of descriptive, variation and comparative analysis. Survival was estimated by Kaplan-Meier method [8]. Quantitative variables were presented as medians and ranges and compared between groups using Student's t-test. A p-value < 0.05 was regarded as statistically significant. The statistical package SPSS, v.19 was used in all analyses.

Results

Frequency of the association of MM with SECMAL

The study group included 15 cases (4.52%) of MM associated with SECMAL. The median patient age was 64 years (range 42-78) and there was a slight female predominance in the male-to-female ratio (females: 53.85%).

In the control group of patients with malignant solid tumors (N=1108) the established frequency of SECMAL was 5.09%. The difference between the groups was not statistically significant ($p > 0.05$).

The most common malignant diseases associated with MM were breast and gastric cancer, followed by skin carcinoma. All other types of malignancies are shown in Table 1.

Table 1. Types of malignant diseases associated with multiple myeloma

Type of malignancy	N (%)
Breast cancer	4 (26.67)
Prostate cancer	1 (6.67)
Gastric cancer	4 (26.67)
Colon/ rectal cancer	1 (6.67)
Laryngeal cancer	1 (6.67)
Skin carcinoma	2 (13.33)
Essential thrombocythemia	1 (6.67)
Endometrial cancer	1 (6.67)

Time of occurrence of the SECMAL in MM

MM preceded the occurrence of SECMAL in 33.33% of the study group patients. These cases comprised only 1.5% of the whole group of patients with MM. The time interval between the diagnosis of MM and SECMAL ranged from 5 to 14 years (median 6.6). The malignant solid tumor preceded MM in 66.67% of the cases in the study group (range 1-14 years; median 4.5) (Figure 1).

Comparison of the frequency of the association MM/SECMAL with the frequency of association with other malignant lymphoproliferative disorders/ SECMAL

MM was associated with SECMAL in 4.52% of the cases. CLL was associated with SECMAL in 7.96% of the cases ($p > 0.05$). SECMAL developed during the course of CLL in 66.7% of these patients. Hodgkin's disease was associated with SECMAL in 2.68% ($p > 0.05$) of the cases. SECMAL developed later in the course of Hodgkin's disease in 75% of the patients.

The frequency of the association of these 3 malignant lymphoproliferative entities with SECMAL

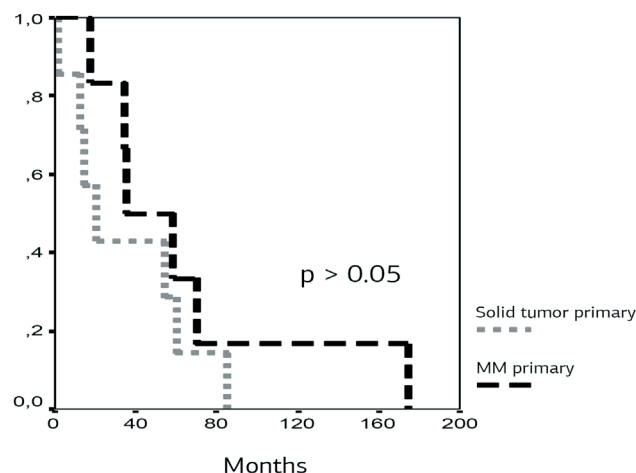


Figure 1. Time to occurrence of SECMAL depending on the primary tumor (MM or solid tumor).

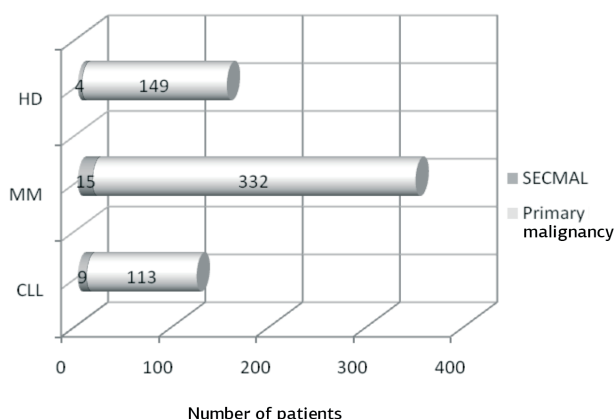


Figure 2. Comparison of the frequency of the association MM/SECMAL with the frequency of association with other malignant lymphoproliferative disorders/SECMAL (Hodgkin's disease/HD, chronic lymphocytic leukemia/CLL).

MAL did not differ significantly ($p > 0.05$). In most cases the SECMAL occurred late (after 5 years) in the course of CLL (57.5% of the patients) and Hodgkin's disease (74.5% of the patients). Regarding the association MM/SECMAL we observed the opposite phenomenon – more frequent occurrence of MM during the course of the treated solid malignant tumor (Figure 2).

Survival

The median survival of the whole group of patients with MM was 38.6 months (range 10-58). The patients of the study group survived significantly longer (median 77.2 months, range 44-134; $p < 0.05$). Comparison between the survival of the subgroups showed significantly longer survival for the patients with preceding MM (median 79.7 months) vs. those with preceding malignant solid tumor (median 55 months; $p < 0.05$). The survival between the whole group of patients with MM and the study group ($N=15$) differed significantly ($p < 0.05$). This difference was more pronounced when compared with the survival of the subgroup with preceding MM and subsequent occurrence of SECMAL ($p = 0.023$) (Figure 3).

Discussion

Table 2. Epidemiological data on the annual frequency of some malignant diseases

Malignancy	Annual frequency
Breast cancer	5-200/100 000
Hodgkin's lymphoma	2.41 /100 000
Chronic lymphocytic leukemia	3.79/100 000
Multiple myeloma	4.62/ 100 000

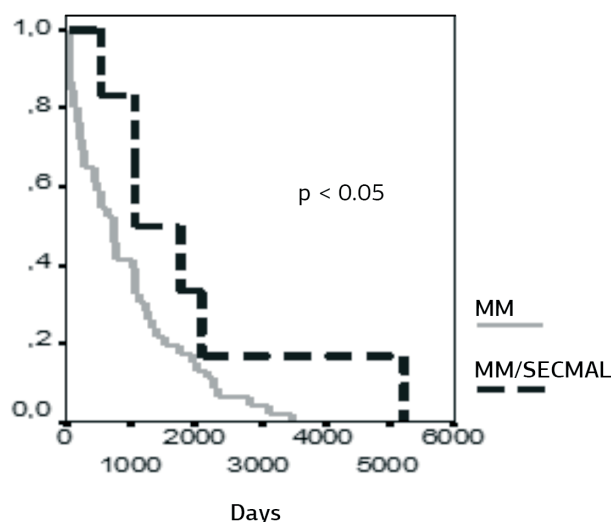


Figure 3. Cumulative survival of patients with multiple myeloma (MM) and the study group with MM and SECMAL.

The association of two or more malignant diseases is well studied in carcinomas (e.g. breast cancer) and some lymphoid malignancies (Hodgkin's disease and CLL) [9-12]. There are sporadic case reports of MM associated with CLL - we came across 6 clinical cases [9]. In 1998 Giles et al. had reported MM only in 0.1% of the patients with CLL. A debated cause was chemotherapy with purine analogues, which possibly could worsen immunosuppression [12]. There are only scant observations of the occurrence of SECMAL during the course of MM [13,14].

To our opinion possible explanations for this lack of interest on this topic are:

1. The relatively low frequency of MM in the general population. It is lower compared to solid tumors, but comparable to the frequency of other lymphoproliferative disorders. Epidemiological data of the frequency of some malignant diseases are shown in Table 2 [15,16].
2. The moderate survival and older age of the patients with MM.

The median survival in a cohort of 10551 patients with MM was 3.7 years and some authors had found it lower than that of other malignancies [13]. Nowadays, the 5-year survival of patients with MM reaches 25-30%. In comparison, the survival of breast cancer, colon cancer, prostate cancer and Hodgkin's disease patients exceeds 90% [14].

Our data show that the survival of the study group patients with MM and subsequent occurrence of SECMAL was significantly longer than that of the rest of MM patients. Only 1.8% of the patients with MM presented with SECMAL after a period of 5-14 years. The mean age of these patients was 64 years.

The following facts should be considered when analyzing the potential etiopathogenetic factors for occurrence of SECMAL in MM:

1. It is well-known that radiation and chemotherapy could induce genomic instability and may possibly trigger the development of SECMAL on a background of immune deficiency. Studies of cancer patients treated with irradiation had shown increasing risk of SECMAL if therapy had been conducted in childhood and with higher cumulative radiation doses. Highly proliferating tissues during irradiation are predominantly affected (mainly the thyroid gland and breast). The risk of SECMAL appears to be higher if a larger surface is exposed to comparatively low fractionated dose (intensity-modulated radiation therapy) [16].
2. A genetic predisposition also plays a role - disruptions of the genes responsible for the renewal of stem cells (SNPs) have been identified. Other genetic disorders (BRCA1 and 2) have been related with impaired function of proteins which participate in DNA repair [17].

Our data showed that solid tumors (predominantly gastric cancer and breast cancer) more frequently preceded MM (66.67%). It is a well-known fact that treatment schedule for these carcinomas incorporates:

1. Polychemotherapy protocols, which include cytotoxic drugs with proven mutagenic capacity (alkylating agents, epipodophyllotoxins, hormones) [18]. Some studies had shown higher relative risk for a therapy-related leukemia when epipodophyllotoxins and vinca alkaloids were incorporated in treatment protocols in the childhood [19]. The relationship between tamoxifen therapy for breast cancer and later occurrence of an endometrial carcinoma has been also discussed [20,21].
2. Radiation therapy, especially in young age, in-

creases the relative risk for leukemia [17,19]. In the setting of breast cancer the definitive post-operative radiation therapy is usually applied at a dose 50-60 Gy, which is delivered to large fields involving hematopoietically active spongy bones.

To our opinion most cases which associate solid tumors and MM belong to the group of the so-called therapy-related SECMAL. It is possible to discuss the causative role of the preceding polychemotherapy for cancers in the occurrence of MM with regard to the long latent period between the two diagnoses (up to 14 years).

Cases with initially diagnosed MM, in which immune dysregulation could be incriminated for the occurrence of SECMAL, are less frequent. Another possible explanation for this rarer association could be the use of alkylating agents-containing regimens with proven mutagenic effect for the therapy of MM. The probable occurrence of SECMAL in this setting usually requires a latent period of 5-14 years, which is a rarely achieved survival duration in MM. On the other hand, radiation therapy for MM is aimed at pain control (15-25 Gy) and stabilization (40 Gy) and is delivered to limited fields without involvement of extensive areas of active hematopoiesis.

Conclusion

1. The frequency of the association of MM with other malignant diseases was 4.52%, comparable to the frequency of SECMAL in CLL, Hodgkin's disease and malignant solid tumors.
2. Only 1.5% of the MM patients developed SECMAL. The occurrence of SECMAL during the course of MM was not a frequent event and could be expected in the rare cases with longer survival.
3. MM as a SECMAL was a probable event during the course of the malignant solid tumors (breast cancer and gastric cancer).

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