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Characteristics and outcomes of patients with multiple myeloma (MM) who develop therapy (t)-related myelodysplastic syndrome (MDS), t-chronic myelomonocytic leukemia (CMML), or t-acute myeloid leukemia (AML)

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Abstract

Background—There has been significant improvement in the outcome of patients with MM. However, there has also been an increased risk of t-MN. Little is known about the characteristics and outcomes of patients with t-MN.

Methods—Patients with MM treated at our institution between 1993 and 2011 were reviewed. We identified 47 patients who were diagnosed with t-MN. The primary objective of this study was to evaluate the time to develop t-MN their response to treatment and overall survival.

Results—Median age of patients at diagnosis of MM was 65 years. Thirty two (68.0%) received initial treatment with conventional chemotherapeutic agents. Seven (14.9%) patients received treatment with novel agents such as lenalidomide, thalidomide or bortezomib. Eight (17.0%) patients were treated with a combination of novel and conventional agents. Twenty (42.6%) patients underwent high-dose chemotherapy and autologous hematopoietic stem cell

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transplantation (auto-HCT). Median time from the diagnosis of MM to t-MN was 7 years 95%CI [5.0 – 28.0]. Thirty-three (70.2%) patients developed t-MDS, 11 (23.4%) t-AML, and 3 (6.4%) t-CMML. Median age at diagnosis of t-MN was 65 years. Twenty-six (78.8%) patients with t-MDS, nine (81.8%) patients with t-AML and one (33.3%) patients with t-CMML had complex/high risk cytogenetics. Median OS for all 47 patients after diagnosis of t-MN was 6.3 months 95%CI [4.0 – 8.7].

Conclusion—Development of t-MN in patients with MM is associated with poor outcomes. These patients in general have complex cytogenetic abnormalities, short CR and OS. Better understanding of disease biology and novel therapeutic approaches are warranted.

Keywords

therapy-related myeloid neoplasm; multiple myeloma; myelodysplastic syndrome; acute myeloid leukemia; second primary neoplasm

Introduction

Tremendous improvements have been made in the treatment of multiple myeloma (MM) over the past decade. This has led to improved survival in both newly diagnosed and relapsed patients [1]. As these patients live longer they have an increased risk of developing secondary primary malignancies (SPM) such as therapy (t)-related myelodysplastic syndrome (MDS), t-chronic myelomonocytic leukemia (CMML) or t-acute myeloid leukemia (AML) [therapy-related myeloid neoplasm, t-MN] [2]. Various mechanisms have been postulated to be involved in this pathogenesis. These include myeloma-related factors such as type and level of monoclonal (M) protein [2], host-related factors such as age and gender [3] and treatment-related factors, such as use of melphalan and newer immunomodulatory agents such as lenalidomide and thalidomide [3, 4]. Although, in general, these patients have poor survival once diagnosed with t-MN, little is known about their disease characteristics and outcomes. We therefore aimed to study the characteristics and outcome of patients who developed t-MN as SPM after the treatment of MM. We reviewed our database of patients with MM who were treated at our institution between 1993 and 2011. We identified 49 patients who were diagnosed to have t-MN and were also treated at our institution. The primary objective of this study was to evaluate the time to develop t-MN, their response to treatment and overall survival.

Methods

Summary statistics were used to describe the study population. Time to development of t-MN was calculated in years from the date of diagnosis of MM to the diagnosis of t-MN. Overall survival (OS) was calculated from the date of diagnosis of t-MN to death or the last follow-up date. Patients who were alive at their last follow-up were censored on that date. The Kaplan-Meier product limit method was used to estimate the median time to event [5]. Univariate Cox proportional hazards regression was used to identify any association with each of the variables and time to t-MN [6]. For each factor, medians, hazard ratios (HRs), their 95% confidence intervals (CI), and proportional hazards regression p-values are presented in tables. Similar analyses were performed for OS. A p-value of < 0.05 was

considered significant for this analysis. Statistical analysis was performed using STATA/SE version 13.1 statistical software (Stata Corp. LP, College Station, TX).

Results

A total of 1386 MM patients were seen at our institution from 1993–2011. Out of these, 47 patients (3.4%) were diagnosed and treated for t-MN at our institution and therefore included in this analysis. Table 1 shows the demographic and clinical characteristics of all 47 patients. Median age at diagnosis of MM was 58 years with 38 males and 9 females. Median M protein concentration was 2.8 gm/dl (n = 26) and median beta₂-microglobulin concentration (B2-MCG) was 3.8 (1.2–24.5). IgG M spike was the most common (n = 26) with IgA M spike in 6 patients and light chain disease in 4 patients.

Thirty two (68.0%) received initial treatment with conventional chemotherapeutic agents such as melphalan, cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, idarubicin, thiotepe, busulfan, carmustine or cytarabine. Seven (14.9%) patients received treatment with novel agents such as lenalidomide, thalidomide and bortezomib. Eight (17.0%) patients were treated with combination of novel and conventional agents. Fourteen (29.8%) patients also received radiation therapy to the affected areas. Twenty (42.6%) patients underwent high-dose chemotherapy and autologous hematopoietic stem cell transplantation (auto-HCT). Fourteen patients received maintenance therapy after auto-HCT; eight received novel agents, three received conventional agents, and two received dexamethasone.

Median time from the diagnosis of MM to t-MN was 7 years 95%CI [5.0 – 8.0]. Thirty-three (70.2%) patients developed t-MDS, 3 (6.4%) t-CMML and 11 (23.4%) t-AML. Median age at diagnosis of t-MN was 65 years. Twenty-six (78.8%) patients with t-MDS, nine (81.8%) patients with t-AML and one (33.3%) patient with t-CMML had complex/high risk cytogenetics. Most common cytogenetic abnormalities involved chromosome 5 and 7. Molecular abnormalities identified included: *JAK2* V617F mutation: 1, *MLL* gene mutation: 1, *RAS* mutation: 1 and *FLT3*-ITD and *NPM1* mutation: 1. After the diagnosis of t-MN, 14 (29.8%) did not receive any treatment, whereas 33 (70.2%) patients received at least 1 cycle of induction chemotherapy either with conventional chemotherapeutic agents or investigational drugs. Five out of these 33 patients underwent an allogeneic stem cell transplant. Out of the patients who did not undergo allogeneic stem cell transplant, nine patients (22.0%) achieved complete remission (CR) and their median duration of CR approximately 4 months [1 – 62]. Median overall survival (OS) of patients treated only with chemotherapy was 7.2 months 95%CI [4.0–10.6]. Out of the five patients who received an allogeneic stem cell transplant, three achieved CR. Median OS in this subgroup of patients was 18.3 months [14.8– Not Estimable]. Median OS for all 47 patients after diagnosis of t-MN was 6.3 months 95%CI [4.0 – 8.7].

Table 2 shows the univariate Cox proportional hazard models for time to development of t-MN. Several factors showed significant relationships with t-MN. The patient's age at diagnosis of MM, the M protein concentration, serum albumin level, are significant predictors for t-MN (p<0.05). Table 3 shows the multivariate analysis for time to

development of t-MN. Age at diagnosis of MM, initial treatment for MM and type of monoclonal spike were significantly associated with t-MN. Figure 1 shows OS for the entire cohort from the time of diagnosis of t- MN. Figure 2 shows the OS for the patients who received allogeneic stem cell transplant vs those did not.

Discussion

With greatly improved survival in patients with multiple myeloma over the last two decades, development of SPM has emerged as a challenging problem. The overall incidence of SPM after multiple myeloma is low. Analysis of 36,491 MM patients from the surveillance, epidemiology, and end results program (SEER) database showed that there was no overall increased risk of SPM, however there was specific site associated increased risk. Risk of colorectal cancer was increased by 50 % and risk for AML was increased by seven times. However there was no difference in the risk of AML before and after introduction of autologous stem cell transplant and novel therapies for MM [7].

Development of secondary leukemia in patients with MM has been known since the 1970's [8]. In one series, a total of 58 patients were reported to have both MM and acute myeloblastic or myelomonocytic leukemia. Eleven patients had both of these diagnoses simultaneously. 44 patients were treated with melphalan and other cytotoxic agents thus implicating their role in the pathogenesis of acute leukemia. However three patients did not receive any treatment raising the question of myeloma-related factors in the pathogenesis of leukemia [8]. Mittelman et al reported another series of 100 MM patients out of which nine developed MDS. Their clinical course was characterized by increasing pancytopenia and none of these patients had evidence of MM at the time of diagnosis of MDS [9]. Their disease course was characterized by an initial hypercellular bone marrow followed by rapidly evolving hypocellular marrow. Median OS was 5 months from the diagnosis of MDS and no patients with IgA Myeloma developed MDS. Thus it was largely believed that treatment with melphalan and other conventional chemotherapeutics played a key role in the development of secondary MDS/AML. However, high dose melphalan with autologous stem cell transplant has not been shown to have increased risk in the absence of preceding chemotherapy [10]. Analysis by Fenk et al also suggests that observed incidence of SPM after high dose chemotherapy seems to be related to the disease itself and the additional genotoxic stress from chemotherapy [11]. In recent years with the advent of novel agents the life expectancy of MM patients has improved tremendously. However treatment with lenalidomide, both in maintenance and relapsed/refractory MM settings has been shown to be associated with increased risk of SPM [12–15]. A recently published meta-analysis suggests that this risk is observed when lenalidomide is combined with melphalan in treatment of newly diagnosed multiple myeloma patients [16].

Usmani et al also recently reported the risk factors for development of t-MDS and t-AML in patients treated with total therapy (TT) 2 and 3 [17]. Out of 1080 patients treated in TT 2 and 3 about 11 % patients developed MDS associated cytogenetic abnormalities (MDS-CA) and 3 % patients developed clinical MDS/AML. MDS-CA often preceded development of clinical MDS/AML. Risk factors for MDS-CA included treatment with TT3b and lenalidomide, 65 years of age, male gender, beta₂-microglobulin > 5.5 mg/dl, and MM

relapse. Patients treated on TT3a and TT3b developed clinical MDS/AML more frequently thus suggesting the role of thalidomide and lenalidomide in the pathogenesis. Our results are essentially consistent with earlier reports. The incidence of t-MDS, t-CMML or t-AML was 3.5%, which is similar to the report by Usmani et al who reported a 3% incidence after TT2 and 3. Similarly, older and heavily pretreated patients were at a greater risk of the development of SPM. Host related factors may also play a role in development of t-MDS/t-AML after treatment for MM. Patients who developed MDS-CA after autologous stem cell transplant had lower CD34 yield at collection thus suggesting an abnormal bone marrow microenvironment [18]. Similarly G/G genotype of nucleotide polymorphism (SNP) rs1617640 in the erythropoietin (EPO) promoter has been found to be more common in patients with MM who develop MDS [19] suggesting a role of susceptibility genes in development of SPM.

Once patients with MM develop t-AML their outcome is dismal with overall survival reported to be less than 3 months [20]. This is similar to patients with non-Hodgkin's lymphoma who develop t-MDS with median survival of few months despite high dose chemotherapy and allogeneic stem cell transplant [21]. Similarly t-CMML has recently been described as being associated with high risk cytogenetics and poor outcomes [22]. Our results again highlight the relatively poor outcome of these patients with a median OS of only 6 months. However, a select group of patients that could proceed to an allo-HCT can achieve a longer remission. The future goal should be to identify transplant-eligible patients early, and to proceed to an allo-HCT if they have a suitable donor.

Conclusion

The development of t-MN in patients with MM, although rare, is associated with a poor outcome, regardless of specific treatment for the MM. These patients in general have complex cytogenetic abnormalities, chemo-resistant disease, a short CR and short OS. A better understanding of disease biology, novel therapeutic approaches, and the use of allo-HCT whenever possible may help in improving future outcomes.

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Clinical Practice Points

- Improvements in the treatment of multiple myeloma has led to observed increase in occurrence of treatment-related second primary malignancies (SPM), particularly t-MDS, t-CMML, t-AML. [therapy-related myeloid neoplasm, or t-MN]
- Most of these patients have complex cytogenetics at the time of diagnosis of t-MN and survival after diagnosis of SPM with t-MN is usually measured in months, representing a clinically aggressive disease course for this unique subgroup.
- Novel therapies for t-MN developing in patients with multiple myeloma are needed in the future.

Figure 1.
Overall Survival for the entire group (n=47) from the time of diagnosis of t-MN

Figure 2.
Overall survival in patients who received allogeneic stem cell transplant vs no allogeneic stem cell transplant

Table 1
Baseline characteristics

	Median (Range)	Number of patients
Median age at diagnosis of MM	65.0 (46.0–83.0)	47
Median M protein concentration (gm/dl)	2.8 (0.1–7.6)	26
Type of M spike		
IgA (kappa or lamda)		6
IgG (kappa or lamda)		26
Light chain disease		4
Median B2-MCG concentration	3.8 (1.2–24.5)	18
Initial Treatment for MM		
Conventional agents		32
Novel agents		7
Both		8
Auto-HCT for MM		
No		27
Yes		20
Maintenance treatment irrespective of Auto-HCT		
No		26
Conventional agents		12
Novel agents		8
Both		1
Type of t-MN		
t-MDS		33
t-AML		11
t-CMML		3
Cytogenetic data for t-MN		
Not available		2
Low risk		5
Intermediate risk		5
High risk		37
Allogeneic SCT for t-MN		
No		42
MRD		2
MUD		3
Complete Remission (t-MN)		

	Median (Range)	Number of patients
No		34
Yes		12

Table 2

Univariate Analysis for Time for time to t-MN

	N	Events	HR	95% CI for HR	p-value
Age at diagnosis	45	45	1.07	(1.04–1.11)	<0.001
BM biopsy - % plasma cells	24	24	1.00	(0.98–1.02)	0.858
M protein concentration at diagnosis (gm/dl)/Bence Jones proteinuria (g/d)	25	25	0.82	(0.66–1.01)	0.061
Albumin (gm/dl)	16	16	3.86	(1.27–11.74)	0.017
B2-MCG	17	17	1.03	(0.92–1.15)	0.604
M spike					
IgG (Kappa or Lambda)	26	26			
IgA (Kappa or Lambda)	4	4	3.51	(1.12–11.08)	0.032
Light Chain	4	4	3.24	(1.04–10.13)	0.043
Initial treatment for MM					
Conventional agents	31	31			
Novel agents	6	6	2.08	(0.82–5.28)	0.122
Both	8	8	2.21	(0.99–4.92)	0.052
Cytogenetics for t-MN					
Low risk	4	4			
Intermediate risk	3	3	1.98	(0.44–9.00)	0.375
High risk	36	36	1.20	(0.42–3.40)	0.730
Allogeneic SCT for t-MN					
No	40	40			
MRD	2	2	0.57	(0.14–2.40)	0.447
MUD	3	3	0.64	(0.20–2.10)	0.462
CR					
No	33	33			
Yes	11	11	0.97	(0.48–1.95)	0.928

Table 3

Multivariate Analysis for Time to t-MN

	HR	95% CI	p-value
Age at diagnosis	1.09	(1.04, 1.15)	0.001
Initial Rx for Multiple Myeloma			
Conventional agents			
Novel agents	0.31	(0.08, 1.15)	0.081
Both	1.08	(0.40, 2.94)	0.883
M spike			
IgG (Kappa or Lambda)			
IgA (Kappa or Lambda)	3.96	(1.16, 13.54)	0.028
Light Chain	4.71	(1.17, 18.92)	0.029