Multiple Myeloma and Thromboembolism in the Perspective of Age and Performance

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Abstract

Introduction: The relation with cancer and thromboembolism (TE) are well documented. Within cancer types, hematological malignancies, especially Multiple Myeloma (MM) show a propensity towards TE with its disease biology, disease burden and treatments. We aimed to evaluate the risk factors of TE and MM with a perspective of age and clinical performance.

Methods: Data regarding Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance scores, patient, disease and treatment related properties of patients with MM between 2010 and 2016 were recorded.

Results: Of the 125 MM patients, 60 were female (48%) while 65 were male (52%). Median age was 65 years. TE was observed in 28 patients (22.4%). In patients <65 years, poor ECOG and Karnofsky scores were strongly related with TE (p values 0.003 and 0.000). Polypharmacy and LDH elevation were observed to be risk factors in all ages (p values 0.002 and 0.000). In patients with poor ECOG (p=0.005 and 0.037) and Karnofsky performance (p=0.002 and 0.003) while radiotherapy and pneumonia during TE episodes were observed to be risk factors for TE regardless of age and performance (p values 0.016 and 0.000). Antimicrobial use during TE episode was observed to be a risk factor in younger patients (p=0.000) who are fit by both scales while bed rest and presence of fractures were observed as risk factors in younger patients with poor performance scores.

Conclusion: Performance assessment should be considered as fundamental for TE evaluation and adequate prophylactic treatment for TE should be commenced in frail young patients.

Keywords: Multiple myeloma; Thromboembolism; Performance

Introduction

Thromboembolic (TE) events in patients with cancer are reported to be as high as 20% [1]. Bed rest, hospitalization and immobilization, surgery, chemotherapy and disease biology are demonstrated to contribute in the development of TE. Besides the increase in mortality, TE events are related with an extra treatment burden, interventions, decreased quality of life and major delays in treatment. Simply in the physician’s regard, cancer patients with TE are supposedly had higher complications and mortality [1-3]. Among malignant diseases, myeloma has a distinct propensity towards TE [4]. Beginning from monoclonal gammopathy of uncertain significance (MGUS) [5], all clonal plasma cell disorders, with certain degrees of monoclonal plasma cell infiltration, show predisposition for venous and arterial TE. Regarding the pathogenesis of this predisposition, disease biology plays the leading role. Increased expression and coagulant activity of tissue factor, vascular endothelial growth factor (VEGF) are demonstrated to play a role in TE development. Likewise, dysregulation of thrombospondin, a matrix originated glycoprotein with antiangiogenic properties, increased coagulation factor VIII and von Willebrand factor (vWF) production and increased cytokines and cytokine related protein C resistance are also documented diversities towards TE proclivity [6-7]. With a special reference to altered vWF activity, ABO blood group status has also been studied in patients with cancer and pregnancy [8]. With the commencement of immunomodulatory drugs (IMIDs) like thalidomide and lenalidomide, the desired effect of antiangiogenic and anti-inflammatory effects have shown unfavorable aspects not when used as single agents but combined with corticosteroids or cytotoxic chemotherapy [9]. Besides disease biology itself. Simple but timeless risk factors like accelerated atherosclerosis, bed rest. Hospitalization and immobilization, fractures, chemotherapy, radiotherapy, polypharmacy and especially age are expected, but usually underestimated. In our study, we aimed to evaluate the conventional risk factors of TE with clinical and thorough but daily and accessible data with risk stratification and perspective.

Methods

Data of patients diagnosed and treated as overt multiple myeloma between 2010 and 2016 in the Department of Hematology, Trakya University Faculty of Medicine were recorded from their files in a retrospective manner. Data of sex, age, Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance scores, nutritional status assessed with body mass index (BMI), previous history of TE, hyperlipidemia, hypertension, smoking status, Framingham 10 years’ cardiovascular risk score, presence of lower extremity varices, pneumonia at the time of TE episode, myeloma subtype, international staging system (ISS), Durie Salmon (DS) stage, hypercalcemia, increased lactate dehydrogenase (LDH) level at presentation, vertebral
fractures and need for radiotherapy, bed rest, polypharmacy, ABO blood group, cytogenetics of myeloma evaluated with fluorescent in situ hybridization (FISH), and use of anthracyclines, IMIDs, and prophylaxis for arterial or venous TE were recorded from their files. Ethical approval was obtained from the Local Ethical Committee.

Statistics

All supposed risk factors for TE were compared with X² test and Pearson correlation while the distribution of clinical data were evaluated with Fisher’s exact test. A two-tailed p value of <0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Of the 125 MM patients, 60 were female (48%) while 65 were male (52%). Median age was 65 years (37-87). 45 patients had IgA (36%) while 78 had IgG (62.4%) and 2 had light chain disease. 82 patients had kappa light chain (65.6%) while 43 had lambda (34.4%). 14 patients had Durie Salmon Stage 1 disease (11.2%). 43 had DS Stage 2 disease (34.4%) and 68 had DS Stage 3 disease (54.4%). 4 patients had IS Stage I disease (3.2%) while 53 had Stage II (42.4%) and 68 had Stage III disease (54.4%). Regarding genetics. 28 patients had standard karyotyping while 24 had 17p deletion (19.2%). 4 had t(4.14) (3.2%). 3 had t(11.14) (2.4%). 6 had t(14.16) (4.8%). 16 had 11q deletion (12.8%). 11 had 13q deletion (8.8%). 2 patients stated a previous TE and adequate period of anticoagulant therapy, irrelevant with the current MM diagnosis. All patients with TE were on acetylsalicylic acid or low molecular weight heparin (LMWH). TE was observed in 28 patients (22.4%) during the course of the disease. Mostly pulmonary embolism (PE) (57.14%). 39.2% patients had DVT. ATE was observed in 27 patients (21.6%) with a dominiance of MI (55.5% of the episodes). Stroke was observed in 37% of the ATE episodes. 64 patients received anthracyclin (51.2%). 66 patients received IMIDs (52.8%). 65 patient had received radiotherapy (52%). 83 patients had hypercalcemia with the first presentation (66.4%). 65 patients had elevated LDH levels (52%). 65 patients had fractures (52%). 49 patients had BMI <21 (39.2%) while 52 had BMI 21-25 (41.6%) and 24 patients had >25 (19.2%). Regarding blood groups. 62 patients had group O (49.6%). 43 had A (34.4%). 13 had B (10.4%) and 7 had AB (5.6%). 67 patient had polypharmacy (53.6%). 52 patient had hypertension (41.6%) with a need of blood pressure lowering treatment. 16 patient had hyperlipidemia (12.8%) with a need of lipid lowering treatment. 21 patient had pneumonia during the TE attack (16.8%). 38 patients were receiving antimicrobials during TE episode (30.4%). Regarding performance status. 44 patients were in need of bed rest more than half of the day (35.2%). 23 patients had ECOG 1 (18.4%) while 35 had ECOG 2 (28%). 27 had ECOG 3 (21.6%). 40 patients had ECOG 4 (32%). Assessed with Karnofsky performance system. 72 patients (57.6%) were poor. with a need of regular and consistent assistance. General features were summarized in Table 1. Disease type (heavy/light chain types). ABO blood groups, use of anthracyclin or IMIDs, BMI and nutritional status, genetical profile determined by FISH and presence of hypercalcemia with the initial evaluation were not related with TE. IS and DS stages (p=0.010 and 0.031), polypharmacy and use of antimicrobials during episode (p=0.000 and 0.004), radiotherapy (p=0.016), pneumonia during episode (p=0.005), LDH elevation and fractures (p=0.000 and 0.000) were related with VTE.

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Heavy chain</strong></td>
<td></td>
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<tr>
<td>IgG</td>
<td>78 (62.4%)</td>
</tr>
<tr>
<td>IgA</td>
<td>45 (36%)</td>
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<tr>
<td><strong>Light chain</strong></td>
<td></td>
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<tr>
<td>Kappa</td>
<td>82 (65.6%)</td>
</tr>
<tr>
<td>Lambda</td>
<td>43 (34.4%)</td>
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<tr>
<td><strong>ISS stage</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>2</td>
<td>53 (42.4%)</td>
</tr>
<tr>
<td>3</td>
<td>54.4%</td>
</tr>
<tr>
<td><strong>Durie salmon stage</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14 (11.2%)</td>
</tr>
<tr>
<td>2</td>
<td>43 (34.4%)</td>
</tr>
<tr>
<td>3</td>
<td>68 (54.4%)</td>
</tr>
<tr>
<td><strong>Fracture</strong></td>
<td>65 (52%)</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>83 (66.4%)</td>
</tr>
<tr>
<td><strong>LDH elevation</strong></td>
<td>65 (52%)</td>
</tr>
<tr>
<td><strong>VTE</strong></td>
<td>28 (22.4%)</td>
</tr>
<tr>
<td><strong>ATE</strong></td>
<td>26 (20.8%)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>16 (12.8%)</td>
</tr>
</tbody>
</table>
BP treatment 52 (41.6%)
LL treatment 29 (23.2%)
Radiotherapy 65 (52%)
Polypharmacy 67 (53.6%)
Nutrition
Normal 68 (54.4%)
Malnurtrated 57 (45.6%)
ECOG
1 23 (18.4%)
2 35 (28%)
3 27 (21.6%)
4 40 (32%)
Bed rest 44 (35.2%)
Comorbidity 58 (46.4%)
Anthracyclin 64 (51.2%)
IMIDs 66 (52.8%)
Genetics
Del 17p 24 (19.2%)
Del 11q 16 (12.8%)
Del 13q 11 (8.8%)
Hypodiploidy 33 (26.4%)
t(4,14) 4 (3.2%)
t(11,14) 3 (2.4%)
t(14,16) 6 (4.8%)
Normal 28 (22.4%)

Table 1: General Characteristics of patients.

TE-Age and Performance Association

In patients <65 years, poor ECOG performance scores (3 and 4, poor) and Karnofsky scores (≤ 50, poor) were strongly related with TE (p values 0.003 and 0.000). In patients who are ≥ 65 years, no relation was observed between performance and VTE.

With a stratification of age groups as <65 years and ≥ 65 years with Karnofsky performance evaluation poor as ≤ 50 and fit >50, polypharmacy was observed to be a risk factor in all ages (p=0.002), in poor ECOG performance (p=0.005) and Karnofsky performance (p=0.002) while radiotherapy and pneumonia during TE episodes were observed to be risk factors for TE regardless of age and performance (p values 0.016 and 0.000). Antimicrobial use during TE episode was observed to be a risk factor in younger patients (p=0.000) who are fit by both scales while bedrest and presence of fractures were observed as risk factors in younger patients with poor performance scores. LDH elevation was observed as a risk factor for TE, regardless of age in patients with poor performance. No relation was observed with TE and disease type, stage, genetical profile, presence of varices, hypercalcemia, taking blood pressure or lipid lowering treatments, nutritional status or combination treatments with anthracyclins or IMIDs with age or performance. Risk assessment of VTE with respect to age and performance is summarized in Table 2.
Pneumonia during episode | p=0.005 | independent of age | p=0.005 | independent of | p=0.005 | independent of performance |
--- | --- | --- | --- | --- | --- | --- |
Bedrest | p=0.02 | p=0.017 | not significant | p=0.015 | not significant | p=0.02 | not significant |
Antimicrobial treatments | p=0.000 | p=0.000 | not significant | p=0.005 | not significant | p=0.000 | not significant |
Fracture | p=0.000 | p=0.000 | not significant | p=0.001 | not significant | p=0.042 | not significant |
LDH elevation | p=0.000 | p=0.000 | independent of age | p=0.037 | not significant | p=0.003 | not significant |

Table 2: Thromboembolism risk factors with respect to age and performance.

**Discussion**

As described by Virchow, TE generally develops due to an alteration in blood flow such as stasis, vascular endothelial injury, or an impairment in the balance of blood components such as acquired or inherited hypercoagulable states [10]. In almost two third of the episodes, a risk factor may be identified. Besides known risk factors like prothrombin gene and factor V Leiden mutations, Protein S, C and antithrombin III deficiencies and antiphospholipid syndrome; presence of a central venous catheter, trauma, immobility more than 48 hours of surgery in the last month, hospitalization, malignancy, infection or surgery in three months' time, use of erythropoietins and blood transfusion are additional acquired and contemporary thrombotic risk factors. Previous TE history is a major risk factor for recurrence and family history is an additional and independent risk factor for TE [11]. Cancer and TE association is well documented and demonstrated. Production of procoagulant cytokines, disease burden, and treatment related endothelial injury and general clinical deterioration are general risk factors for TE. TE may develop even before the cancer diagnosis or during the course of the disease. Within cancer types, the risk of TE in hematological malignancies is similar with solid tumors [2]. The increased risk of thrombosis in MM is multifactorial. To better identify the potential, contributing factors of thrombosis may be categorized as patient related, disease and course related and treatment related. Patient related factors are age, sex, obesity, immobilization and genetic predisposition. Disease and course related factors are fractures and immobilization, hyperviscosity due to high tumor burden, interleukin-6 associated coagulopathy, light chain disease, chromosome 11 abnormalities, coagulation pathway abnormalities such as increases in von Willebrand factor/Factor VIII levels, acquired activated protein C resistance, chemotheraphy regimes especially in combination with corticosteroids, anthracyclines and antiangiogenic agents like thalidomide and lenalidomide. Additionally, microparticle related tissue factor activity has been associated with TE in MM as well as nonhematological malignancies [12]. Besides the pathogenetic mechanisms, patient related factors and frailty are trend topics of consideration. Treatment of the cancer is not the single goal; improving the quality of life, integrating treatment into daily life are important, especially in cancer types such as MM, where almost always, a cure is unattainable. Despite the knowledge regarding thromboprophylaxis in the treatment course of MM, TE is still frequent, as in our patient group, 22.4%. All patients have been either on acetylsalicylic acid or on LMWH. Our endeavors to comprehend this proclivity towards thromboembolism, we aimed to start from basics. Starting from age, and how to save younger patients from TE, we divided our patients as <65 and ≥ 65 years old. The major finding of general TE risks for ages was polypharmacy, radiotherapy, and anticoagulants use such as antiviral, antifungal and antineuromyocystis prophagaxy during TE episode, fracture, pneumonia, LDH elevation and bedrest. In conclusion, particularly in younger patients, performance status assessment should be the backbone of VTE risk assessment with ECOG, Karnofsky and even more thorough frailty evaluation systems and patients with poor performance should be identified and protected with prophylactic treatments.

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**References**


