

Introduction

Multiple myeloma (MM) is more common in elderly individuals and constitutes approximately 10% of all hematological malignancies [1]. With a recent perspective of aging and frailty, treatment of MM has become more individualized. In newly diagnosed fit patients, mainstream of treatment is consisted of a proteosome inhibitor-immunomodulatory drug and dexamethazone followed by autologous stem cell transplantation (ASCT). Maintenance or even consolidation is recommended until progression. Maintenance with lenalidomide is demonstrated to be related with an improved overall survival though there is an ongoing concern about treatment related toxicities (TrT) including cytopenias and secondary malignancies.

Clonal hematopoiesis of indeterminate potential (CHIP) has been associated with a risk of progression to myeloid clonal disorders including myelodysplastic syndrome and acute myeloid leukemia and also interestingly with cardiovascular diseases. Besides the relation with aging, CHIP was observed to be related with previous exposure to cytotoxic treatments and radiation. In our study, we aimed to detect concomitant somatic mutations, dysplasias and the presence of CHIP in MM patients and to evaluate the TrTs of patients in the presence of CHIP accompanying MM.

Materials & Methods

The data of 45 MM patients who underwent bone marrow biopsy and aspiration studied NGS at Trakya University Hospital between February 2020 and January 2021 were retrospectively re-evaluated. Patients were diagnosed with MM using the WHO 2016 Classification of Myeloid Neoplasm. Somatic mutation results were analyzed by the QIAact Myeloid DNA NGS Panel

molecular analysis. Bone marrow aspiration-biopsies of all patients were evaluated for dysplasia using the WHO 2016 Classification of Myeloid Neoplasm. Hematologic TrTs National Cancer Institute's common nomenclature criteria were used for adverse events.

Results

Data of 45 MM patients were analyzed and mean age of patients were 63,67 years (29-84) is observed. 24 patients were female while 21 were male (53,3%/46,7%). 25 patients had at least one lineage dysplasia (55,6%) and CHIP was detected in 35 patients. Mutational profile showed DNMT3A mutation in 11 patients, TET2 in 13 patients, RAS in 10 patients and other mutations including ASXL1, CSFR3R or RUNX1 in 11 patients. Dual DNMT3A and TET2 positivity was observed in 2 patients and in 10 patients, no mutation was observed. Though anemia is an end organ damage of MM, DNMT3A positivity was related with initial presentation of anemia (p=0.043). Thrombocytopenia was observed at the time of diagnosis in two patients with positive RAS (p=0.006).

Treatment was homogenous in all patients starting with VCD (bortezomib, cyclophosphamide and dexamethazone) for 4 cycles with an intention to proceed with ASCT. ASCT was able to be performed in 26 patients and 19 patients received maintenance treatment after remission. Anemia was observed in 32 patients after treatment, and 27 of these patients (10 DNMT3A, 11 TET2 and 8 RAS mutations) had CHIP (p=0.009). We found that patients using maintenance lenalidomide or bortezomib after ASCT were associated with the development of anemia in DNMT3A positive patients, but not with the development of anemia in TET2 positive patients. Neutropenia was observed in 22 patients after treatment, and 20 of these patients (8 DNMT3A, 8 TET2 and 6 RAS

mutations) had CHIP (p=0.039). Thrombocytopenia was observed in 17 patients after treatment, and 14 of these patients (6 DNMT3A, 4 TET2, and 6 RAS mutations) had CHIP (p=0.575). Cytopenia after treatment is in table 1. These cytopenias were recognized after 100 days of ASCT in patients undergoing ASCT. The mean survival of the patients was 28.1 months, and 8 patients died during their follow-up.

Cytopenia after treatment is in table 1.

Cytopenia after treatment		Number of patients (%)
Anemia	Grade 1	15 (33,3%)
	Grade 2	12 (26,7%)
	Grade 3	5 (11,1%)
Neutropenia	Grade 1	13 (28,9%)
	Grade 2	6 (13,3%)
	Grade 3	3 (6,7%)
Thrombocytopenia	Grade 1	9 (20%)
	Grade 2	4 (8,9%)
	Grade 3	4 (8,9%)

Discussion

A number of recent studies have shown that recurrent somatic mutations in the blood of healthy adults, a condition referred to as CHIP [2]. It has been reported that the prevalence of CHIP increases with age, approximately 1% in individuals under 50 years of age, and 10-15% in those older than 70 years [3-5]. The most common mutated genes in patients with CHIP are DNMT3A, TET2, TP53, and ASXL1. In our study, the most common TET2 mutation was detected, and this was found to be DNMT3A, RAS, ASXL1, RUNX1, respectively.

CHIP mutations are common in plasma cell neoplasms. A study at the Mayo Clinic found that 30 out of 101 MM patients had CHIP mutations when evaluated by retrospective NGS testing [6]. In our study, CHIP was detected in 35 (77.8%) of

45 Multiple Myeloma patients.

It is possible that patients with CHIP are more prone to the development of cytopenias and other toxicity from therapy, thus increasing the frequency of treatment delays or dose reductions and limiting their ability to receive optimal myeloma directed therapy [1]. TrTs (anemia, thrombocytopenia and neutropenia) were frequently observed in our patients with CHIP. The development of neutropenia (p: 0.041) was found to be associated with CHIP. We also found that patients receiving maintenance lenalidomide or bortezomib after ASCT were associated with the development of anemia in DNMT3A positive patients.

Patients with CHIP are more prone to develop cytopenia and other toxicities with treatment. Patients do not receive optimal myeloma treatment with treatment delays or dose reductions. Determining the presence of CHIP with the NGS method, which is now used, is necessary in order to reduce the complications that patients may experience due to cytopenias and to regulate the treatment. Investigation of CHIP in MM patients is essential in treatment planning and follow-up.

References

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