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Cytokine Gene Polymorphisms and Chromosome 13 Deletion in Multiple Myeloma Patients

Multiple Myeloma Hastalarında Sitokin Gen Polimorfizmleri ve Kromozom 13 Delesyonu

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ABSTRACT

Objective: Multiple myeloma (MM) is a clonal enlargement of plasma cells. The most common cytogenetic anomaly in MM is monosomy 13 and appears approximately 40%–50% in multiple myeloma. Studies have shown that in the majority of patients, 80%–90% of chromosomal anomalies are monosomy 13, and 10%–20% are regional deletions. Monosomy 13 is the most powerful predictor of survival in MM. Cytokines are proteins that regulate many functions of these cells and are secreted by cells of the immune system. Plasma cell stimulates angiogenesis by increasing the release of cytokines such as IL-1β, IL-6, and IL-10. Single nucleotide polymorphisms (SNP) of cytokine genes can affect their secretion rate or biological activity. Two of the important factors for MM disease are cytokines and chromosome 13 deletion (del13). We investigate chromosome 13 deletion and cytokine gene polymorphisms (IFN-γ, TGF-β, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12, IL-1R, IL-1Rα, IL-4Rα) in patients with MM.

Materials and Methods: EDTA blood was collected from 38 patients with MM included in the study, and DNA was isolated. PCR-SSP method was used for cytokine gene polymorphism typing (Protrans). FISH method was applied using LSI D13S25 SO DNA probe for deletion 13.

Results: 13q deletion was detected in 15 of the 38 of the patients. Statistical analysis of 13q deletion and cytokine gene polymorphisms was not statistically significant ($p>0.05$) by patient age, sex, disease stage, and β2-microglobulin levels. There is a statistical significance between level of LDH and TGF-β TG/TG haplotype ($p=0.002$). No significant results were obtained in the relationship between cytokine polymorphisms and del13 ($p>0.05$).

Conclusion: Cytokines, which are associated with the function and viability of plasma cells, have a major role in the etiology and prognosis of the disease. Moreover, similar effects were observed with the 13q deletion. In our study, we did not find a statistical significance between cytokine gene polymorphisms and 13q deletion. Although both parameters independently have great importance on the effects of the disease, combining them together does not yield the same effect.

Keywords: Cytokine, polymorphism, multiple myeloma, chromosome 13, deletion

ÖZ

Amaç: Multiple myeloma (MM), plazma hücrelerinin kemik iliği, lenfoid dokular ve çevre kanında birikmesidir. MM'de görülen en sık anomalilerden biri 13/13q delesyonudur ve yaklaşık %40-50 oranında görülür. Yapılan çalışmalar, hastaların çoğunda kromozom anomalisinin %80-90'ının monozomi 13 şeklinde iken %10-20'sinin bölgesel delesyonlar şeklinde olduğunu göstermiştir. Monozomi 13, sağkalımı belirleyen en önemli belirteçlerden biridir. Sitokinler, immün sistem hücrelerince salınan ve bu hücrelerin birçok fonksiyonunu düzenleyen proteinlerdir. Plazma hücresi, immünglobin üretiminde IL-1β, IL-6, IL-10 ve TNF-α gibi sitokinleri üretirler. Tek nükleotid polimorfizmleri de tek amino asit değişikliği ile sitokin fonksiyonunda ve üretiminde farklılıklar oluştururlar. Sitokinler ve kromozom 13 delesyonu (del13), MM hastalığı için önemli olan faktörlerden ikisidir. Biz de çalışmamızda MM ile del13 ve 10 sitokin (IL-1α, IL-1β, IL-12, IFN-γ, TGF-β, TNF-α, IL-2, IL-4, IL-6, IL-10), 2 reseptör (IL-1R, IL-4Rα) ve 1 reseptör antagonistinin (IL-1RA) gen polimorfizmleri arasındaki ilişkiyi incelemeyi amaçladık.

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Gereç ve Yöntem: Çalışmaya multiple myeloma tanısı konmuş 38 hasta dahil edildi. Sitokin gen polimorfizm tiplemesi için PCR-SSP yöntemi kullanıldı (Protrans). Delesyon 13 için LSI D13S25 SO DNA probu kullanılarak FISH yöntemi uygulandı.
Bulgular: Hastaların %40'ında del 13 saptandı. 13q delesyonu ve sitokin gen polimorfizmlerinin ayrı ayrı hasta yaşı, cinsiyeti, hastalık evresi ve β2-mikroglobulin seviyeleri ile istatistiksel analizi sonucu anlamlı bir değer gözlenmedi. LDH düzeyi ile TGF-β TG/TG haplotipi arasında istatistiksel anlamlılık saptandı (p:0.002). Sitokin polimorfizmleri ve del13 arasındaki ilişkiye bakıldığında anlamlı bir sonuç elde edilmedi (p>0.05).
Sonuç: Sitokin polimorfizmi ve del13 varlığının hastalığın prognozu üzerine ayrı ayrı etkisi olsa da iki parametrenin birlikte prognoz üzerine etkisi saptanamadı.
Anahtar Kelimeler: Sitokin, polimorfizm, multiple myeloma, kromozom 13, delesyon

INTRODUCTION

Multiple myeloma (MM) is a clonal enlargement of plasma cells. This characteristic feature is observed in the bone marrow, lymphoid tissues, and peripheral blood (1). MM is responsible for 15% of hematological malignancies (2). Factors such as genetic factors, inflammation, and oxidative stress play a role in MM etiology (3).

MM cells are predominantly localized in the bone marrow (BM), and their interaction with bone marrow stromal cells (BMSCs) stimulates the transcription and secretion of cytokines from BMSCs. Although cytokines have a negative effect on MM cells, it is effective as a treatment when applied (4).

Plasma cells increase the release of cytokines such as IL-1β, IL-6, and IL-10 (5). IL-6 supports the growth and survival of normal and myeloma plasma cells. IL-10 is a growth factor of malignant plasma cells (4). TGF-1β is an important cytokine in immune regulation (6). Genes of cytokines and their receptors are highly polymorphic. Single nucleotide polymorphisms (SNPs) can affect the expression and/or biological activity of the protein occurring in the gene (4,7,8).

Monosomy 13 is the most common cytogenetic abnormality (approximately 40%–50%) observed in MM (9–14).

Therefore, cytokines and chromosome 13 deletion (del13) are important prognostic factors for MM. We investigate chromosome 13 deletion and cytokine gene polymorphism in patients with MM.

MATERIALS AND METHODS

Thirty-eight patients (F/M: 17/21) with MM from İstanbul Faculty of Medicine Hematology were included in the study. Mean age of the patient was 57 years (min:max: 40:78). Analysis of cytokine gene polymorphisms and chromosome 13 abnormality was performed in İstanbul Faculty of Medicine, Department of Medical Biology.

Cytokine gene polymorphism genotyping

DNA was extracted from the whole peripheral blood with EDTA (15). Cytokine genotyping was performed using the PCR-SSP method (16) with Protrans kit that was designed to detect polymorphisms of thirteen cytokine genes (IL-1α, IL-1β, IL-1R, IL-1RA, IL2, IL-4, IL-6, IL-10, IL-12, TNF-α, INF-γ, TGF-β and IL-4Ra).

Detection chromosome 13 deletion

Following the FISH procedure, BM or peripheral blood samples were studied. Target DNA was attached to glass slides. The slide containing DNA and probe was denatured in 70% formamide (pH 7.0) for 5 minutes at 73°C. The slides were passed through a cold ethanol batch and allowed to dry. The denatured probe was placed on the target DNA, and the slides were incubated at 37°C overnight. After hybridization, it was washed for 2 minutes at 0.5XSSC at 72°C and twice for 3 minutes in phosphate buffered detergent at room temperature. Finally, the slides were stained with DAPI. Thereafter, the slides were viewed with a fluorescence microscope (Nikon E800) with the appropriate set of filters (17).

RESULTS

Fifteen (40%) of the 38 patients were detected with chromosome 13q deletion. No statistical significance between chromosome 13q deletion and age, gender, stage of disease, level of LDH, and β_2-microglobulin (p>0.005) was found.

There was a statistical significance between level of LDH and TGF-β TG/TG haplotype (p=0.002). No statistical significance between cytokine gene polymorphisms and age, gender, stage of disease, and level of β_2-microglobulin (p>0.005) was found.

Patients' cytokine gene polymorphisms and chromosome 13q deletion results are shown in Table 1. There was no statistical significance between cytokine gene polymorphisms and 13q deletion (p>0.05).

DISCUSSION

MM is a malignancy of the plasma cell. The chromosomal abnormalities of MM were detected such as del13 (40%–50%) and the *t* (11; 14) (9). Deletion of chromosome 13 has been associated with a poor prognosis in MM (18). In this study, we detected

Table 1. Results of the cytokine gene polymorphisms and 13q deletion

	13q del	IL-1α	IL-1β	IL-1R	IL-1RA	IL-4RA	IL-12	IFN-γ	TGF-β1	TNF-α	IL-2	IL-4	IL-6	IL-10
1	del-	C-C	C-T / C-C	C-C	T-C	A-A	A-A	A-T	TG-CG	AG-GG	GG-GG	TC-C-TCC	GG-GG	ATA-ACC
2	del-	C-C	C-C / T-C	C-T	T-C	A-A	A-A	T-T	TG-CG	GG-GG	GG-TG	TC-C-TCC	CA-CA	GC-C-GCC
3	del-	C-C	C-C / C-C	C-C	T-T	G-A	C-A	A-A	TG-CG	AG-GG	GG-GG	GC-C-TCC	CG-GG	GC-C-ACC
4	del-	C-C	T-T / C-C	C-C	T-T	G-A	C-C	T-T	CG-CC	GG-AA	GG-TT	TC-C-TTC	CA-GG	GC-C-GCC
5	del-	C-C	C-T / C-C	C-T	T-T	A-A	A-A	A-T	CG-CC	AG-AA	GG-TG	GC-C-TCC	GG-GG	GC-C-ACC
6	del+	T-C	C-T / C-C	C-C	T-C	A-A	A-A	A-A	TG-CC	GA-GG	GG-TG	TC-C-TTT	GG-GG	AC-C-ACC
7	del+	C-C	C-C / C-C	C-T	T-T	A-A	A-A	A-A	CG-CC	AG-AA	TG-TG	TC-C-TTT	GG-GG	GC-C-ACC
8	del-	T-T	C-C / T-C	C-T	T-C	G-A	A-A	A-T	CG-CC	GG-GG	TG-TT	GC-C-TCC	GG-GG	ATA-A-TA
9	del-	C-C	T-T / C-C	C-C	T-C	A-A	C-A	A-T	CG-CC	AG-AA	TT-GT	TC-C-TTT	CG-GG	ATA-GCC
10	del-	T-C	C-T / C-C	C-C	T-C	A-A	C-A	T-T	CG-CG	AG-AA	GG-TT	TC-C-TCT	CA-GG	ATA-ACC
11	del+	T-C	C-T / C-C	T-T	T-C	A-A	C-A	T-T	TG-CG	AG-GG	GG-TG	TC-C-TCC	CA-GG	GC-C-ACC
12	del+	C-C	C-T / C-C	C-T	T-T	A-A	C-A	A-T	TG-CC	AG-GG	TG-TG	TC-C-TCC	CA-GG	GC-C-GCC
13	del+	C-C	C-C / C-C	C-T	T-T	A-A	C-A	A-T	CG-CC	AG-AA	TT-TT	GC-C-TCC	GG-GG	ATA-GCC
14	del-	C-C	C-T / C-C	C-T	T-T	G-A	A-A	A-T	TG-CG	GG-GG	GG-GG	TC-C-TCC	CA-GG	GC-C-ACC
15	del-	T-C	C-T / T-C	C-C	T-C	A-A	A-A	T-T	TG-CC	GA-GG	TG-TT	TC-C-TTT	GG-GG	ATA-GCC
16	del+	C-C	C-T / C-C	C-C	T-T	A-A	C-A	T-T	CG-CG	GG-GG	TG-TT	TC-C-TCC	CA-GG	ATA-GCC
17	del-	T-C	C-T/ C-C	C-T	T-T	A-A	C-A	A-T	CG-CC	AG-AA	GG-TG	GC-C-TCC	CA-GG	GC-C-GCC
18	del+	C-C	C-C / C-C	C-T	T-T	A-A	C-A	A-T	TG-CG	AG-GG	GG-GG	GC-C-GCC	GG-GG	ATA-GCC
19	del+	T-C	C-C / T-C	T-T	T-T	G-A	C-A	A-T	CG-CG	AG-GG	GG-TG	TC-C-TCC	CA-GG	ATA-GCC
20	del-	C-C	C-C / C-C	C-T	T-T	A-A	C-A	A-T	TG-TG	GG-GG	GG-TG	TC-C-TCC	CA-GG	ATA-GCC
21	del+	C-C	C-T / C-C	C-C	T-T	A-A	C-A	A-T	TG-CG	GG-GG	GG-GG	GC-C-TCC	GG-GG	AC-C-ACC
22	del-	C-C	C-T / C-C	C-T	T-T	A-A	A-A	A-T	CC-CC	AG-AA	TG-TG	TTT-GTT	CA-GG	ATA-ACC
23	del-	C-C	T-T / C-C	C-C	T-T	A-A	A-A	A-A	TG-CG	GG-GG	GG-GG	TC-C-TCC	CA-CA	ATA-ACC
24	del-	T-C	C-T / C-C	C-C	T-T	A-A	A-A	A-A	TG-CG	GA-GG	GG-TT	GC-C-TCC	CA-GG	ATA-ACC
25	del+	C-C	C-C/ C-C	C-T	T-T	G-A	C-C	A-T	TG-CG	GG-GG	GG-TG	TC-C-TCC	CA-GG	ATA-GCC
26	del-	T-C	C-C/ C-C	C-C	T-T	A-A	C-A	A-T	CG-CC	AG-AA	TG-TG	TC-C-TTT	GG-GG	GC-C-ACC
27	del+	T-T	C-C/ T-C	C-T	T-C	G-A	C-A	A-A	CG-CC	AG-AA	GG-TT	GC-C-TCC	CA-GG	ATA-A-TA

Table 1. Continued

28	del-	T-C	C-T / T-C	C-C	T-C	A-A	A-A	A-T	CG-CG	GG-GG	GG-GG	TC-C-TCC	CA-GG	GC-C-GCC
29	del-	T-C	C-T / T-C	C-T	T-T	G-A	C-A	T-T	TG-CG	GG-GG	GG-TG	TC-C-TCC	CA-GG	ATA-GCC
30	del-	C-C	T-T / C-C	C-T	T-T	A-A	C-A	T-T	TG-CG	GG-GG	TG-TG	TC-C-TCC	GG-GG	GC-C-ACC
31	del+	T-C	C-T / C-C	C-C	T-C	A-A	A-A	A-T	TG-CG	AG-GG	TG-TG	GC-C-GCC	CA-CA	GC-C-GCC
32	del-	C-C	T-T / C-C	C-C	T-T	A-A	A-A	A-A	CG-CG	GA-GG	GG-TG	GC-C-TTT	CG-GG	ATA-ACC
33	del+	C-C	C-T / C-C	C-C	T-T	G-A	C-A	T-T	CG-CC	GG-GG	GG-TT	TC-C-GCT	CG-GG	ATA-GCC
34	del-	C-C	T-T / C-C	C-C	C-C	A-A	A-A	A-A	CG-CC	AG-AA	GG-TG	GC-C-TCC	GG-GG	ATA-ACC
35	del-	T-C	C-T/ C-C	T-T	T-C	A-A	A-A	A-T	TG-CG	GG-GG	GG-GG	GC-C-TCC	CG-GG	GC-C-ACC
36	del+	C-C	C-C/ C-C	T-T	C-C	A-A	C-A	T-T	CG-CC	AG-AA	GG-GG	GC-C-TCC	CA-GG	GC-C-ACC
37	del-	T-C	C-T / T-C	C-C	C-C	G-A	A-A	A-T	TG-TG	GG-GG	GG-TG	TC-C-TTT	CA-GG	GC-C-ACC
38	del+	T-C	C-T/ C-C	C-T	T-C	G-A	A-A	A-A	CG-CC	AG-AA	TG-TT	GC-C-TCC	CG-GG	GC-C-GCC

chromosome 13 deletion rate at 40%, which did not demonstrate statistical significance between chromosome 13q deletion and age, gender, stage of disease, level of LDH, and β_2-microglobulin.

Cytokines are crucial in the regulation of key pathways of immunity. SNPs alter the expression or function of the gene product. Some studies have shown an association between polymorphisms in cytokine genes and MM (4,5,19); however, other studies have not detected it (6,20,21). No statistical significance was found between cytokine gene polymorphisms and age, gender, stage of disease, and level of β_2-microglobulin. However, a statistical significance was observed between high levels of LDH, which is the indicator of a poor prognosis and TGF-β TG/TG haplotype. Furthermore, TG/TG haplotype associates with high level production of TGF-β. We considered that TGF-β triggers conversion to plasma cells from B cells by elevating LDH levels, and therefore, cause to a poor prognosis for the disease.

Cytokines, which is related the function and survive of plasma cells and 13q deletion, have a major role in the etiology and prognosis of diseases. In our study, a statistical significance between cytokine gene polymorphisms and 13q deletion was observed. Although both parameters independently have great importance on the effects of the disease, it seems that combining them together is not favorable.

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