

Observational Studies

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The influence of polymorphisms in cytokine genes on pain and response to palliative radiotherapy in multiple myeloma patients: prospective observational study

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Abstract

Objectives: The aim of this study was to assess the impact of polymorphisms in cytokine genes on pain severity and pain treatment with palliative radiotherapy.

Methods: 81 patients were enrolled. Pain severity and dose of analgesics were evaluated prior to radiotherapy and at 4, 12 and 24 weeks following treatment. The study analysed 12 gene polymorphisms of 6 cytokines (IL-6, IL-10, TNF α , IL-1 α , IL-1 β , IL-1RA) involved in the pathogenesis of pain syndrome.

Results: Association between severe pain and patients' variables and genotype groups of each cytokine gene studied were analysed. Karnofsky index $\geq 60\%$ and IL1RN rs2234677 polymorphism GG genotype were found to have significant impact on severe pain prior to radiation. Patients with IL-1 α encoding gene IL1A rs1800587 CC genotype and patients with IL-1 β encoding gene IL1B rs1143634 CC genotype had

significantly better response to radiotherapy. Patients with IL-1RA encoding gene IL1RN rs315952 CC genotype had a faster response to radiation.

Conclusions: Findings of this study emphasize the importance of gene polymorphisms which encode inflammatory interleukins in the severity of pain and response to palliative radiotherapy.

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Keywords: cytokine; single nucleotide polymorphisms; radiotherapy; multiple myeloma; pain

Introduction

Multiple myeloma (MM) is a malignant clonal plasma cell disorder characterized by anaemia, renal insufficiency, painful bone lesions and hypercalcaemia. Pain is the most common and debilitating clinical finding in MM patients. Pain in multiple myeloma can be divided into three main categories: bone pain caused by disease (osteolytic lesions, fractures; vertebral collapse, nerve compression), chemotherapy-induced neuropathic pain arising from commonly used anti-myeloma agents; and procedural pain resulting from invasive interventions performed to treat the disease. Furthermore, the molecular and cellular mechanisms underlying myeloma-associated bone pain remain poorly characterized. In preclinical multiple myeloma models both bone marrow denervation and pathological nerve sprouting within bone tissue have been reported; however, whether these findings accurately reflect the clinical situation is still unknown [1]. During the interaction with bone marrow stromal cells, MM cells stimulate emission of cytokines such as IL-6, IL-10, TNF α , IL-1 and others, which participate in proliferation of plasma cells and pathogenesis of bone destruction [2–6]. Circulating inflammatory cytokines are not only involved in the growth of malignant cells but are also

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related to pain, depressed mood, fatigue and sleep disturbances [7–11]. It is well known that the pain perception threshold, as well as response to analgesics and pain relief has great inter-patient variability [12]. Several studies have shown that variable pain sensations and response to analgesics during the course of oncologic disease are determined by distinct cytokine gene variants [13–20]. Secretion of cytokines is regulated genetically, therefore gene polymorphisms may impact cytokine secretion. Medical literature suggests that single nucleotide polymorphisms (SNPs) in certain cytokine gene promoter sequences determine their secretion and concentration in the blood [3, 5, 21–25]. Emission of substance P and irritant amino acids leads to increases of cytokines in the presynaptic neurons, thus sensitizing the peripheral nociceptors and causing increased pain sensation [26, 27]. This is the main hyperalgesia mechanism in patients with chronic diseases [28]. Several studies have evaluated the impact of polymorphisms in inflammatory cytokine genes on the perception of pain, depressed mood, sleep disturbances, fatigue, and dose and response to analgesics in pancreatic, lung and breast cancer [9, 12–21, 29]. Reyes-Gibby et al. found that polymorphisms TNFA rs1800629 and IL6 rs1800795 play a significant role in pain severity and opioid dose used in lung cancer patients [16]. A study of breast cancer patients confirmed that polymorphisms in IL-1R2 and IL-10 were related to preoperative breast pain [20]. Many other studies have demonstrated the impact of polymorphisms in inflammatory cytokine genes on pain and other cancer symptoms [9, 12–19, 21, 29]. This study examines this phenomenon in patients with the multiple myeloma. Based on studies conducted [9, 13–20] we evaluated a 12 SNP panel in 6 inflammatory cytokine genes. The aim of this study was to assess how the perception of pain is influenced not only by certain demographic and clinical factors, but also to evaluate the influence of SNPs on the perception of severe pain in cases of bone destruction due to MM prior to radiotherapy. And since radiotherapy has an analgesic effect, we also assessed the influence of SNPs of inflammatory cytokine genes impact on pain severity and analgesic intake to radiotherapy during the follow up period after radiation treatment. To date, this is the first study which evaluates the impact of gene polymorphisms of inflammatory cytokines in relation to response to radiotherapy in multiple myeloma patients.

Methods

Study design

A prospective observational study in a cohort of patients with painful bone lesions due to MM. The endpoint of this

study is to assess the impact of polymorphisms in cytokine genes on pain severity and pain treatment with palliative radiotherapy. The study sample was drawn from a previously described prospective randomized trial evaluating: single vs. multiple fraction regimens for palliative radiotherapy in treatment of MM [30].

Participants

Patients with diagnosed MM and painful bone destructions at Hematology department of Hospital of Lithuanian University of Health Sciences (LT) were invited to participate. Patients were selected for inclusion if they met the following criteria: age ≥ 18 years, diagnosis of MM, based on the International Myeloma Working Group's criteria [31], presence of painful bone lesions (VAS ≥ 1) or impending fracture verified by radiographs, Karnofsky index above 40 % ("Disable; requires special care and assistance"), written informed consent. Patients were excluded for the following reasons: presence of bone metastases from solid tumours, solitary plasmacytoma, prior receipt of radiotherapy requiring repeated irradiation at the same site, inability to complete quality of life questionnaires, patients that could not be monitored after radiotherapy.

The study protocol was prepared in accordance with the Helsinki Declaration and was approved by the Lithuanian Regional Research Ethics Committee, number BE-2-39. The participants provided informed consent.

Variables and data measurement

Pain severity was assessed using the visual analogue scale (VAS) [32, 33]. Pain was assessed using the VAS scale by asking patients to answer the question: "How much pain did you experience on a scale of 0–10 during the last week?" A graphical representation of the VAS scale was shown alongside this question. 0 was classified as no pain. A pain 1–4 was classified as mild, 5–7 as moderate and ≥ 8 as severe [34]. Analgesics were categorized into: opioid and non-opioid. Opioid doses were converted to and are reported as morphine-equivalent daily dose (MEDD) [35]. Demographic, clinical and laboratory data were collected prior to radiotherapy initiation. Pain severity and dose of analgesics utilized were collected before radiotherapy initiation and at 4, 12 and 24 weeks following treatment. The analgesic response rate was defined utilizing the International Consensus on Palliative Radiotherapy criteria [36].

This study evaluated 12 gene polymorphisms of in 6 cytokines (IL-6, IL-10, TNF α , IL-1 α , IL-1 β , IL-1RA) (Table 1).

SNPs chosen for analysis were based on published literature suggesting that they play a key role in MM bone disease pathogenesis and pain perception [37–41]. All mentioned interleukins' gene polymorphisms play a significant role in the development of bone metastasis by regulating inflammatory and bone resorption processes in such way affecting the severity of bone lesions, disease progression, and pain.

Genomic DNA was extracted from peripheral blood leukocytes using commercially available DNA extraction kit (GeneJet Genomic DNA Purification kit, Thermo Fisher Scientific). TNFA, IL1A, IL1B, IL1RN, IL-6 and IL-10 gene polymorphisms analyses were performed using a polymerase chain reaction – restriction fragment length polymorphism assay (PCR-RFLP).

Table 1: Incidence of polymorphisms in genes encoding cytokines.

Cytokines	Gene SNP	Allele frequency (%)	Distribution of genotypes N (%)
IL-6	rs1800795	C allele 47.5 G allele 52.5	GG genotype 23 (28.4) GC genotype 39 (48.1) CC genotype 19 (23.5)
IL-6	rs1800796	C allele 3.7 G allele 96.3	GG genotype 75 (92.6) GC genotype 6 (7.4)
IL-6	rs1800797	G allele 52.5 A allele 47.5	GG genotype 23 (28.4) GA genotype 39 (48.1) AA genotype 19 (23.5)
IL-10	rs1800896	G allele 46.9 A allele 53.1	GG genotype 17 (20.9) GA genotype 42 (51.9) AA genotype 22 (27.2)
IL-10	rs1800871	C allele 74.1 T allele 25.9	CC genotype 41 (50.6) CT genotype 38 (46.9) TT genotype 2 (2.5)
IL-10	rs1800872	C allele 77.2 A allele 22.8	CC genotype 46 (56.8) CA genotype 33 (40.7) AA genotype 2 (2.5)
TNFA	rs1800629	G allele 85.2 A allele 14.8	GG genotype 57 (70.4) GA genotype 24 (29.6)
IL-1α	rs1800587	C allele 62.9 T allele 37.1	CC genotype 28 (34.6) CT genotype 46 (56.8) TT genotype 7 (8.6)
IL-1β	rs1143634	C allele 64.2 T allele 35.8	CC genotype 30 (37.1) CT genotype 44 (54.3) TT genotype 7 (8.6)
IL-1RA	rs2234677	G allele 76.5 A allele 23.5	GG genotype 45 (55.5) GA genotype 34 (42) AA genotype 2 (2.5)
IL-1RA	rs315952	C allele 50.6 T allele 49.4	CC genotype 20 (24.7) CT genotype 42 (51.8) TT genotype 19 (23.5)
IL-1RA	rs2234663	1* allele 95.7 2* allele 3.7 3* allele 0.6	*1/*1 genotype 76 (93.8) *1/*2 genotype 2 (2.5) *2/*2 genotype 2 (2.5) *1/*3 genotype 1 (1.2)

The primer sequences and, annealing temperatures used in each case are provided in Table 2 along with the PCR-RFLP product sizes and restriction enzymes.

Statistical methods

Statistical data analysis was performed by using the IBM SPSS Statistics 23 for Windows (SPSS Inc., Chicago, IL, USA).

Uni-variate analysis utilizing Chi square test for the independence (homogeneity) (or Fisher's Exact test as appropriate) were performed. Odds ratios with 95 % confidence interval were used to analyse the influence of patient demographics, clinical, laboratory and genetic variables upon pain severity. In multivariate analysis of research data, a binary logistic regression model was used to draw conclusions about the influence of parameters to the probability of severe pain. Since quantitative values of pain severity and analgesics did not follow normal distribution, Kruskal-Wallis test, and its post hoc tests were used to compare changes in pain severity and in analgesics among three different groups. Differences were defined as statistically significant if the p-value <0.05.

Results

3.1. A total 81 patients with MM and painful bone destructions were enrolled, their characteristics are detailed in Table 3. The male gender 34.5 % (N 30), the median age 66.5 years (43–84), the median Karnofsky index 60 % (50–80), most of patients were III stage of disease 85.2 % (N 69) and IgG type of MM 64.2 % (N 52), radiation dose 8 vs. 30 Gy were 43.2 % (N 35) and 56.8 % (N 46) respectively, most common irradiate site was spinal vertebrae 58 % (N 47), most of patients were with concurrent chemotherapy 85.2 % (N 69) and without orthopaedic surgery 79.1 % (N 64), most commonly reported pain severity prior radiotherapy was 8–10 scores according VAS 53.1 % (N 43), median opioid dose (MEDD) at baseline was 60 mg/day (10–260).

Characteristics significant for presence of severe pain prior to radiotherapy

Univariate analysis was used to determined associations between baseline report of severe pain (defined as 8–10 score on Visual Analogue Scale (VAS)) and mild to moderate pain (i.e., VAS ≤7) and patient demographics (age, gender, Karnofsky index), clinical (stage of disease, type of MM, orthopaedic surgery) and laboratory finding (haemoglobin

Table 2: Genetic polymorphisms evaluated in the study including primer sequences, annealing temperatures, restriction enzymes and PCR and RFLP product sizes.

NCBI 1,000 genomes browser:	Primers (sense/antisense)	Polymorphism	Annealing temperature (°C)	Restriction enzyme	Fragment sizes after RFLP
rs1800629	5'-AGGCAATAGTTTTGAGGGCCAT-3' 5'-TCCTCCCTGCTCCGATTCCG-3'	TNFA -308G>A	63	<i>NcoI</i>	87 + 20 bp (G) 107 bp (A)
rs1800587	5'-ATCACACCTAGTTCATTTCTCTATTTA-3' 5'-GATTTTTACATATGAGCCTTCCATG-3'	<i>IL1A</i> c.-889C>T	60	<i>NcoI</i>	166 + 29 bp (C) 195 bp (T)
rs1143634	5'-CTCAGGTGCTCTCCAAGAAATCAAA-3' 5'-GCTTTTTTGCTGTGAGTCCCG-3'	<i>IL1B</i> c.3954C>T	63	<i>TaqI</i>	110 + 80 bp (C) 190 bp (T)
rs2234677	5'-GCATCAAGTCAGCCATCAGC-3' 5'-CCAGAGCCTGAAAGCATTG-3'	<i>IL1RN</i> 1812G>A	59	<i>AlwNI</i>	185 + 150 + 4 bp (G) 335 + 4 bp (A)
rs315952	5'-AGGGAGGCAGCACAGGACTT-3' 5'-AGTCCCTGCAGTCTTGCCA-3'	<i>IL1RN</i> c.11100T>C	66	<i>MspAI</i>	198 + 132 bp (C) 330 bp (T)
rs2234663	5'-CTCAGCAACTCTCTAT-3' 5'-TCCTGGTCTGCAGGTAA-3'	<i>IL1RN</i> (86bp)n	58		240 bp (2 repeats) 325 bp (3 repeats) 410 bp (4 repeats) 500 bp (5 repeats) 595 bp (6 repeats)
rs1800797	5'-GGAGACGCCTTGAAGTAACTGC - 3' 5'-GAGTTTCTCTGACTCCATC - 3'	<i>IL6</i> -597G>A	58	<i>FokI</i>	116 + 47 bp (A) 163 bp (G)
rs1800796	5'-GGAGACGCCTTGAAGTAACTGC - 3' 5'-GAGTTTCTCTGACTCCATC - 3'	<i>IL6</i> -572G>C	58	<i>MbiI</i>	101 + 62 bp (G) 163 bp (C)
rs1800795	5'-TTGTCAAGACATGCCAAAGTG-3' 5'-TCAGACATCTCCAGTCTATA-3'	<i>IL6</i> -174 C>G	59	<i>NlaIII</i>	135 + 111 + 54 bp (G) 246 + 54 bp (C)
rs1800896	5'-CTCGCTGCAACCAACTGGC-3' 5'-TCTTACTATCCCTACTTCC-3'	<i>IL10</i> -1082 A>G	54	<i>MnI</i>	106 + 33bp (G) 139 bp (A)
rs1800871	5'- TCATTCTATGTGCTGGAGATGG-3' 5'- TGGGGGAAGTGGGTAAGAGT-3'	<i>IL10</i> -819 T>C	58	<i>MaeIII</i>	125 + 84bp (C) 209 bp (T)
rs1800872	5'- GTGAGCACTACCTGACTAGC-3' 5'- CCTAGGTCACAGTGACGTGG-3'	<i>IL10</i> -592 A>C	63	<i>RsaI</i>	175 + 237 bp (A) 412 bp (C)

level in blood) variables. Results showed that only Karnofsky index <60 % (OR 2.97; 95 % CI 1.11–7.95; p=0.028) had a statistically significant influence on pain severity (i.e., 8–10 score on VAS). Other parameters did not show any difference between groups (Table 4).

Univariate statistical analysis was used to evaluate the relationship between severe pain before radiotherapy and genotype groups of each cytokine polymorphism. None of the genotypes analysed were found to be significant for severe pain before radiation treatment, only a borderline association was observed in patients with GG genotype of *IL1RN* rs2234677. This polymorphism was prevalent in patients with severe pain prior to radiotherapy as, compared to patients with GA and AA genotypes (OR 2.31; 95 % CI 0.94–5.65; p=0.065). The results are shown in Table 5.

Based on the results of the univariate analysis two variables: Karnofsky index <60 % and *IL1RN* rs2234677 were included in the binary logistic regression model for deeper analysis of their influence on severe pain. Both parameters,

showed statistically significant influence to determining the probability of the severe pain (Table 6).

Impact of polymorphism of genes encoding cytokines on pain relief

The Kruskal-Wallis test was used to measure the differences in pain severity before radiotherapy and during the monitored period (4, 12 and 24 weeks after radiotherapy), at the same time point among patients with different genotypes (Table 7 and Figure 1).

The analysis showed that patients with *IL-1α* encoding gene *IL1A* rs1800587 CC genotype responded significantly better to radiotherapy and experienced milder pain at 12 and 24 weeks as, compared to TT and CT genotypes. Additionally, patients with *IL-1β* encoding gene *IL1B* rs1143634 CC genotype reported milder pain after radiation treatment at 12 and 24 weeks, compared to TT and CT genotypes.

Table 3: Baseline demographics and disease characteristics.

Characteristics	N (%)
Gender:	
Male	30 (34.5)
Female	51 (65.5)
Age, years	66.5 (43–84)
Mean (range)	
Karnofsky Index, %	60 (50–80; 60.1)
Median (range; mean)	
Clinical stage:	
II	12 (14.8)
III	69 (85.2)
Paraprotein type:	
IgG	52 (64.2)
IgA	9 (11.1)
Light chains	18 (22.3)
IgM	1 (1.2)
Non-secretory	1 (1.2)
Radiation dose, Gy:	
8 × 1 fr	35 (43.2)
3 × 10 fr	46 (56.8)
Irradiated sites:	
Spinal vertebrae	47 (58)
Pelvic bone	20 (24.7)
Extremities	14 (17.3)
Orthopedic surgery:	
Yes	17 (20.9)
No	64 (79.1)
Concurrent chemotherapy at baseline:	
Chemotherapy	69 (85.2)
None	12 (14.8)
Pain severity prior to radiotherapy initiation:	
0–3	0 (0)
<4	13 (16)
5–7	25 (30.9)
8–10	43 (53.1)
Pain medication at baseline:	
Opioid	64 (79)
Non – opioid	17 (21)
Opioid dose at baseline, mg/day	60 (10–260; 69.39)
Median (range; mean)	

Patients with IL-1RA polymorphism IL1RN rs315952 CC genotype had a faster response to radiotherapy. Their pain severity significantly decreased after radiotherapy at 4 weeks, compared to patients with TT and CT genotypes. A borderline association was observed in patients who were homozygous for the G allele in IL-10 encoding gene IL10 rs1800896, they experienced greater pain at 4, 12 and 24 weeks after radiotherapy, compared to patients with AA and GA genotypes (p=0.061, p=0.09 and p=0.062 respectively).

Table 4: Univariate analysis of demographic and disease parameters are compared with each other in terms of severe pain.

Parameter	Severe pain N (%)	Mild and moderate pain N (%)	OR (95% CI)	p-Value
Gender:				
Male	14 (32.6)	16 (42.1)	0.66	0.375
Female ^a	29 (67.4)	22 (57.9)	(0.27–1.64)	
Age:				
≥65 years	26 (60.5)	25 (65.8)	0.79	0.620
<65 years ^a	17 (39.5)	13 (34.2)	(0.32–1.97)	
Clinical stage:				
III	37 (86.0)	32 (84.2)	1.16	0.816
II ^a	6 (14.0)	6 (15.8)	(0.34–3.94)	
Karnofsky index:				
<60 %	19 (44.2)	8 (21.1)	2.97	0.028
≥60 % ^a	24 (55.8)	30 (78.9)	(1.11–7.95)	
Paraprotein type:				
Others	18 (41.9)	12 (31.6)	1.56	0.339
IgG ^a	25 (58.1)	26 (68.4)	(0.63–3.89)	
Hemoglobin level, g/l:				
≤80	2 (4.7)	5 (13.2)	0.32	0.174
>80 ^a	41 (95.3)	33 (86.8)	(0.06–1.77)	
Orthopedic surgery:				
No	33 (76.7)	31 (81.6)	0.75	0.594
Yes ^a	10 (23.3)	7 (18.4)	(0.25–2.20)	

^aReference group. Statistically significant parameters are in bold.

Impact of polymorphism of genes encoding cytokines on analgesics intake

The Kruskal-Wallis test was used to compare differences in doses of analgesics before radiotherapy and during the monitored period (4, 12 and 24 weeks after radio-therapy), at the same time point among patients with different genotypes (Table 8 and Figure 2).

The analysis showed that patients with IL-1α encoding gene IL1A rs1800587 CC genotype had a significantly stronger response to radiotherapy and the dose of opioid analgesics significantly decreased at 12 and 24 weeks post-therapy, compared to patients with TT and CT genotypes. The same

Table 5: Genotype groups of each cytokine gene analyzed for assessment of severe pain before radiotherapy in univariate analysis. Genotypes are compared with each other in terms of severe pain.

Polymorphism	Genotype	Severe pain N (%)	Mild and moderate pain N (%)	OR (95 % CI)	p-Value
IL6 rs1800795	GG	11 (25.6)	10 (26.3)	0.96 (0.36–2.60)	0.940
	CC + GC ^a	32 (74.4)	28 (73.7)		
IL6 rs1800796	GG	40 (49.4)	35 (43.2)	0.875 (0.166–4.617)	1 ^b
	GC ^a	3 (3.7)	3 (3.7)		
IL6 rs1800797	GG	12 (27.9)	10 (26.3)	1.08 (0.41–2.89)	0.872
	GA + AA ^a	31 (72.1)	28 (73.7)		
IL10 rs1800896	AA	11 (25.6)	11 (28.9)	0.84 (0.32–2.25)	0.734
	GA + GG ^a	32 (74.4)	27 (71.1)		
IL10 rs1800871	CC	24 (55.8)	17 (44.7)	1.56 (0.65–3.76)	0.320
	CT + TT ^a	19 (44.2)	21 (55.3)		
IL10 rs1800872	CC	27 (62.8)	19 (50)	1.69 (0.69–4.09)	0.246
	CA + AA ^a	16 (37.2)	19 (50)		
TNFA rs1800629	GG	29 (67.4)	28 (73.7)	0.74 (0.28–1.34)	0.54
	GA ^a	14 (32.6)	10 (26.3)		
IL1A rs1800587	CC	17 (39.5)	11 (28.9)	1.61 (0.63–4.07)	0.317
	CT + TT ^a	26 (60.5)	27 (71.1)		
IL1B rs1143634	CC	18 (41.9)	12 (31.6)	1.56 (0.63–3.89)	0.34
	CT + TT ^a	25 (58.1)	26 (68.4)		
IL1RN rs2234677	GG	28 (65.1)	17 (44.7)	2.31 (0.94–5.65)	0.065
	GA + AA ^a	15 (39.9)	21 (55.3)		
IL1RN rs315952	TT	9 (20.1)	10 (26.3)	0.74 (0.27–2.08)	0.568
	CT + CC ^a	34 (79.9)	28 (73.7)		
IL1RN rs2234663	*1/*1	40 (93)	36 (94.7)	0.74 (0.12–4.69)	0.749
	Others ^a	3 (7)	2 (5.3)		

^aReference group. ^bFisher's Exact Test.

Table 6: Factors significant for presence of severe pain before radiotherapy in multivariate analysis.

Parameter		β coef. of model	p-Value	OR (95 % CI)
Karnofsky index	≥ 60 % vs. <60 % ^a	1.2	0.021	3.33 (1.196–9.296)
IL1RN rs2234677	GG genotype vs. GA and AA genotypes ^a	0.96	0.046	2.62 (1.02–6.72)

^aReference group.

trend was observed with patients expressing IL-1 β encoding gene IL1B rs1143634 CC genotype.

Patients with IL-1RA encoding gene IL1RN rs315952 CC genotype needed significantly lower doses of opioid analgesics after radiotherapy at 4 weeks, compared to patients with TT and CT genotypes. A borderline association was observed in patients who were homozygous by the G allele in IL-10 encoding gene IL10 rs1800896. They indicated a greater pain at 4, 12 and 24 weeks after radiotherapy and they used a larger dose of opioid analgesics, compared to patients with AA and GA genotypes (p=0.057, p=0.085 and p=0.071

respectively). Moreover, a borderline association was observed that patients with IL-1RA encoding gene IL1RN rs315952 CC genotype and IL-1RN encoding gene IL1RN rs2234663 *1/*1 genotype needed smaller doses of analgesics, compared to others (p=0.068 and p=0.062, respectively).

Discussion

Almost 70 % of all MM patients receive one or more radiation courses for treatment of painful bone lesions during their disease course [42]. After radiotherapy the pain severity can be reduced by 75–100 % from the previous level [42, 43]. Radiotherapy reduces pain by inhibiting inflammatory mediators in the irradiation site. It is well known that pain sensation, pain reduction and analgesic intake is highly individual [12]. Demographic characteristics and clinical variables may modify an individual's perception of pain and response to analgesics. Several mechanisms may be involved in pain perception and relief: drug metabolizing proteins, transporters, nociceptors, proinflammatory cytokines and their impact on genetic variability. The literature indicates that it is necessary to strive for personalized opioid analgesic

Table 7: Pain (VAS) before radiotherapy and change in pain severity among patients with different genotypes during the monitored period.

Cytokine gene SNP	Genotype	Pain assessment (VAS score)			
		Before RT, median (mean; min–max)	After 4 weeks, median (mean; min–max)	After 12 weeks, median (mean; min–max)	After 24 weeks, median (mean; min–max)
<i>IL1A</i> rs1800587	CT	7 (7.2; 2–10)	2 (3.3; 0–10)	0 (3.0; 0–10)a	0 (3.4; 0–10)b
	CC	8 (7.4; 2–10)	4 (3.8; 0–10)	0 (1.0; 0–5)	0 (0.4; 0–3)c
	TT	10 (8.7; 5–10)	6 (5.4; 0–9)	5 (4.6; 0–7)a	5 (4.0; 0–7)c, b
p-Value		0.259	0.282	0.013 (a 0.019)	0.006 (b 0.029, c 0.018)
<i>IL1B</i> rs1143634	CT	7 (6.9; 2–10)	2 (3.5; 0–10)	2 (3.3; 0–10)e	2 (3.5; 0–10)g
	CC	9 (7.8; 3–10)	3 (3.5; 0–10)	0 (0.8; 0–5)d	0 (0.4; 0–5)f
	TT	10 (8.7; 5–10)	6 (5.4; 0–9)	5 (4.6; 0–7)d, e	5 (4.0; 0–7)f, g
p value		0.096	0.323	0.002 (d 0.011, e 0.008)	0.002 (f 0.004, g 0.02)
<i>IL1RN</i> rs315952	CT	8 (7.8; 2–10)	4 (4.2; 0–10)	0 (2.8; 0–10)	0 (2.7; 0–10)
	CC	6 (6.4; 2–10)	0 (1.8; 0–9)h	0 (1.7; 0–9)	0 (1.5; 0–8)
	TT	7 (7.6; 3–10)	4 (4.5; 0–10)h	0 (2.8; 0–10)	0 (2.8; 0–10)
p value		0.156	0.023 (h 0.036)	0.505	0.591

Statistically significant parameters are in bold. a, b, s, d, e, f, g, h p-values of the post hoc analysis of Kruskal Wallis test.

prescriptions for cancer patients in order to effectively balance pain control with the prevention of abuse and related harm [44]. Identifying genotype-pain relief associations can significantly influence patient care by enabling more personalized, effective, and safer pain management strategies. Studies have demonstrated the impact of SNPs in genes encoding for proinflammatory cytokines on pain severity and pain relief in the treatment of other malignancies [9, 12–20, 29]. The current study analysed the influence of selected SNPs of IL-6, IL-10, TNF α , IL-1 α , IL-1 β and IL-1RA genes on pain severity and pain treatment with radiotherapy in patients with painful bone lesions due to MM. Our study gives the preliminary evidence that SNPs in cytokine genes are associated with pain perception and analgesic response to radiotherapy in patients with MM.

It is well known that increased levels of IL-6 and TNF- α in the serum correlate with greater pain in chronic inflammatory disorders. High levels of IL-6 in the serum correlates with advanced stage of myeloma, higher degree of bone destruction and it is associated with poor prognosis of the disease [4]. IL-6 is involved in the response to nociceptive irritants and could modulate the opioid analgesia pathway [45]. There is a strong link between the concentrations of the TNF- α and pain severity in patients with chronic disorders [28]. The rare A allele in the TNFA rs1800629 polymorphism influences a higher production of TNF- α in the serum and in such way increases inflammatory pain [46]. However, which SNP in the IL-6 encoding gene promoter alters the concentration of IL-6 in plasma is under debate [23, 25, 47].

Reyes-Gibby et al. evaluated the influence of genetic variability in cytokine genes on pain and response to analgesia in patients with non-small cell lung carcinoma

receiving supportive care [16, 18, 19]. These three clinical studies demonstrated that TNFA rs1800629 polymorphisms have a relation with the pain severity [16, 18, 19]. The authors identified that gender differences played a role in the association between genotype groups, pain and, opioid dose, specifically the TNFA rs1800629 polymorphism GA and AA genotypes in men and IL6 rs1800795 polymorphism GC and CC genotypes in women [16]. Patients with TNFA rs1800629 polymorphism GG and GA genotypes experienced a greater response to analgesic treatment [16]. A clinical study by Miaskowski et al. found that polymorphisms in interleukin-1 receptor 1 (IL1R1), IL6, and NFKB1 were associated with severity scores related to a group of treatment-related symptoms [29]. In contrast to their findings, we did not find a correlation between TNFA rs1800629 and IL6 rs1800795 polymorphisms and pain severity nor with analgesic response. This could be related to the smaller sample size in our study, as well as differences in populations (genetic background, ethnicity, or demographic characteristics of the patient population) may vary between studies, influencing the frequency of polymorphisms and their relationship with pain and analgesic response.

While it is logical that declining pain severity would be associated with decreased analgesic use, measuring both provides important additional insights: it helps evaluate how well the analgesic regimen is controlling pain over time, beyond just patient-reported pain levels; an increase in analgesic use despite stable or increasing pain scores could indicate tolerance or side effects; it offers a more nuanced, comprehensive picture of pain management progress and can inform more precise, patient-centered care. Several studies have examined the role of IL-1 in pain relief and opioids

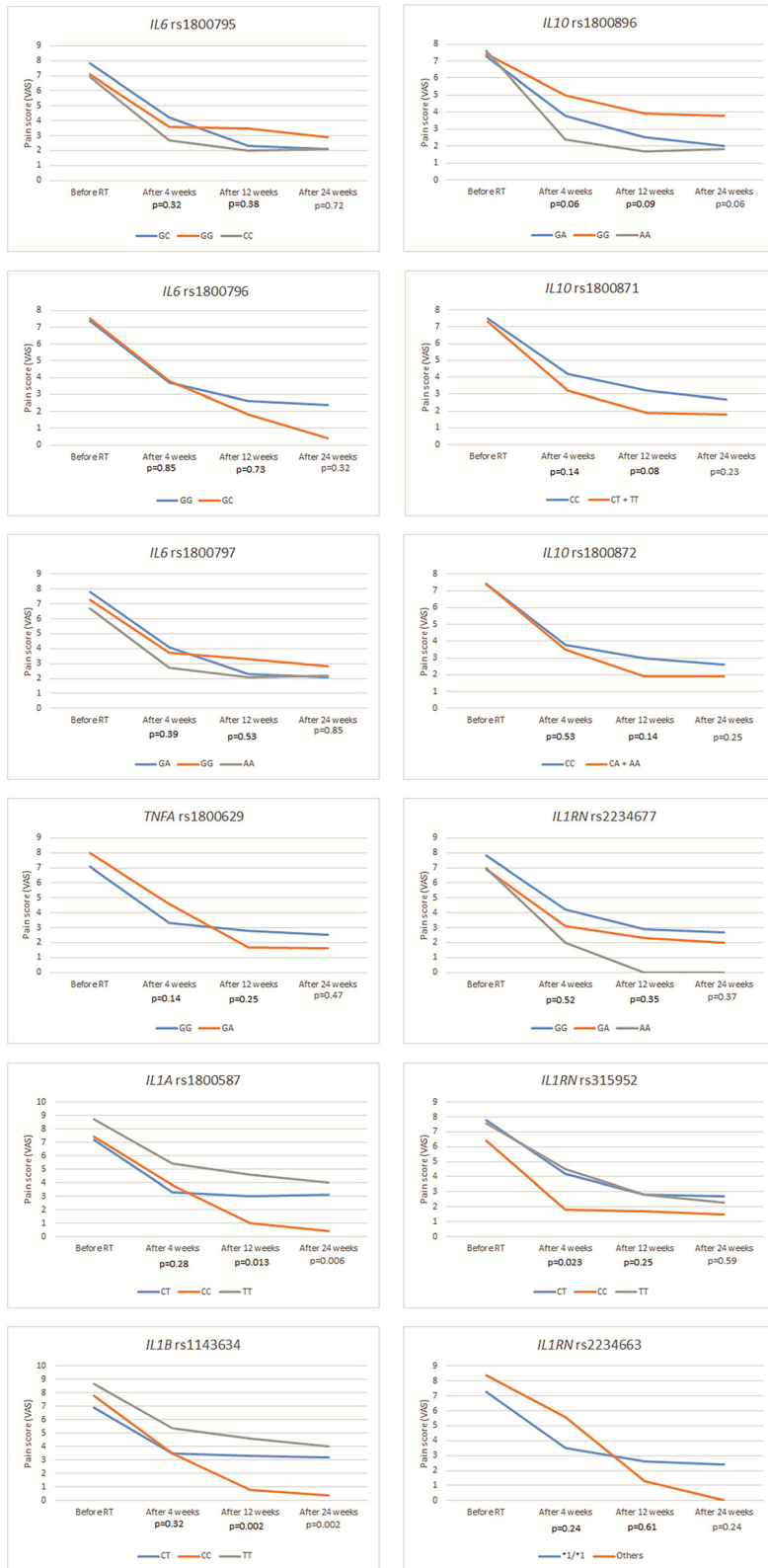


Figure 1: Pain severity before radiotherapy and during the monitored period (4, 12 and 24 weeks after radiotherapy), at the same time point among patients with different genotypes. VAS (visual analogue scale), RT (radiotherapy).

consumption [21, 48, 49]. The IL-1 family includes IL-1 β , IL-1 α and IL-1RA. Secretion of IL-1 β and IL-1 α induces inflammation and induce the expression of other proinflammatory genes

[48]. In contrast, IL-1RA inhibits the production of IL-1 β , IL-1 α . There is also evidence that IL1A rs1800587, IL1B rs1143634 and IL1RN rs2234663 polymorphisms correlate with the IL-1 and

Table 8: Morphine equivalent daily dose (mg/day) before radiotherapy and its reduction during the monitored period in patients with different genotypes.

Cytokine gene SNP	Genotype	Morphine equivalent daily dose (mg/day)			
		Before RT, median (mean; min–max)	After 4 weeks, median (mean; min–max)	After 12 weeks, median (mean; min–max)	After 24 weeks, median (mean; min–max)
<i>IL1A</i> rs1800587	CT	50 (58.8; 10–260)	0 (37.2; 0–270)	0 (31.2; 0–270)	0 (41.9; 0–240)
	CC	20 (56.5; 10–140)	0 (35.4; 0–180)	0 (16.1; 0–120)a	0 (5.2; 0–120) b
	TT	20 (47.1; 10–150)	30 (42.1; 0–135)	5 (32.9; 0–130)a	5 (22.9; 0–120)b
p value		0.998	0.401	0.007 (a 0.039)	0.008 (b 0.012)
<i>IL1B</i> rs1143634	CT	50 (59.1; 10–260)	0 (37.1; 0–270)	0 (29.7; 0–240)	0 (41.4; 0–240)
	CC	20 (56.2; 10–140)	0 (35.7; 0–180)	0 (11.9; 0–120)c	0 (7.5; 0–120)d
	TT	20 (47.1; 10–150)	30 (42.1; 0–135)	5 (32.9; 0–130)c	5 (22.9; 0–120)d
p value		0.969	0.401	0.039 (c 0.043)	0.022 (d 0.039)
<i>IL1RN</i> rs315952	CT	60 (58; 10–140)	7 (40.9; 0–180)	0 (26.5; 0–240)	0 (34.5; 0–240)
	CC	10 (38.2; 10–150)	0 (14.8; 0–135)e	0 (15.6; 0–130)	0 (15.9; 0–120)
	TT	60 (71.4; 10–260)	10 (51.6; 0–270)e	0 (38.2; 0–270)	0 (23.8; 0–180)
p value		0.068	0.032 (e 0.043)	0.304	0.505

Statistically significant parameters are in bold. a, b, c, d, e p-values of post hoc analysis of Kruskal-Wallis test.

IL-1RA production [21, 50, 51]. *IL1A* rs1800587 and *IL1B* rs1143634 T allele increase the IL-1 β and IL-1 α levels in plasma during the inflammation and exacerbate pain [52, 53]. Our findings provide further evidence and support and correlate with the results of these studies. Specifically, the *IL1RN* rs2234677 polymorphism GG genotype was associated with the severe pain in bone destructions before radiotherapy. Patients with *IL1A* rs1800587 CC genotype or with *IL1B* rs1143634 CC genotype had a significantly better response to radiotherapy. Lastly, patients with the *IL1RN* rs315952 CC genotype had a faster response; and pain severity and analgesic intake were lower at 4 weeks after radiation compared to patients with TT and CT genotypes. Our study showed that patients with these genotypes may benefit more from radiotherapy for pain relief. By identifying such patients, clinicians can decide which of them will have better pain relief options.

The influence of *IL1B* polymorphism was found in another study looking at patients with pancreatic carcinoma [17]. The authors observed that women, African Americans, advanced stage of disease, depressed mood, TC and CC genotypes for *IL1B* rs1143627, TT and TA genotypes for *IL8* rs4073 are significant predictors of severe pain [17].

IL-10 plays anti-inflammatory role by suppressing the secretion of IL-1, IL-6, TNF- α [54]. Increased serum levels of IL-6 and IL-10 are observed in MM patients and correlate with progressive MM disease [25]. Promoter polymorphisms rs1800896 A allele, rs1800871 T allele, rs1800872 A allele were reported to be associated with decreased secretion of IL-10 whereas polymorphisms of rs1800872 C allele are associated with increased levels of IL-10 [55]. In our study we found a borderline association in patients homozygous for the G allele in IL-10 encoding gene *IL10* rs1800896 indicating

greater pain sensation 4, 12 and 24 weeks after radiotherapy. These patients had a weaker response to radiotherapy and needed larger doses of opioids, as compared to patients with AA and GA genotypes. Rausch et al. analysis of lung cancer patients supports our findings where they found an association between pain symptoms and polymorphisms in *IL10* rs1800871 [15]. In this way, testing the interleukins polymorphisms for oncological patients diagnosed with pain syndrome due to metastatic disease would allow us to predict the benefits they will derive from analgesic treatment and plan it accordingly.

Both genetic and nongenetic factors can influence pain severity in oncology patients [9, 11, 12, 14, 17–21, 29]. The advanced stage of disease, younger age, gender, depressed mood, fatigue together with cytokines polymorphisms correlate with pain severity. In our study we found that clinical factor (Karnofsky index >60 %) and genetic factor (and *IL1RN* rs2234677 polymorphism GG genotype) can influence severe pain before radiotherapy. Our study contributes additional data suggesting the influence of cytokine gene polymorphisms on pain perception and analgesic response to radiotherapy in MM patients. There is still debate about which radiotherapy treatment regimen is more effective, but to date there is no evidence that multiple-fraction radiotherapy is more effective than single-fraction. In this study, patients were treated with single and multiple fractions in equal proportions and no treatment regimen was found to be superior in terms in pain relief, which is supported by other studies too [30, 33, 56, 57].

Our study is, to our knowledge, the first to analyze the role of selected cytokine gene SNPs (*IL-6*, *IL-10*, *TNFA*, *IL-1 α* , *IL-1 β* , and *IL-1RA*) in modulating pain severity and

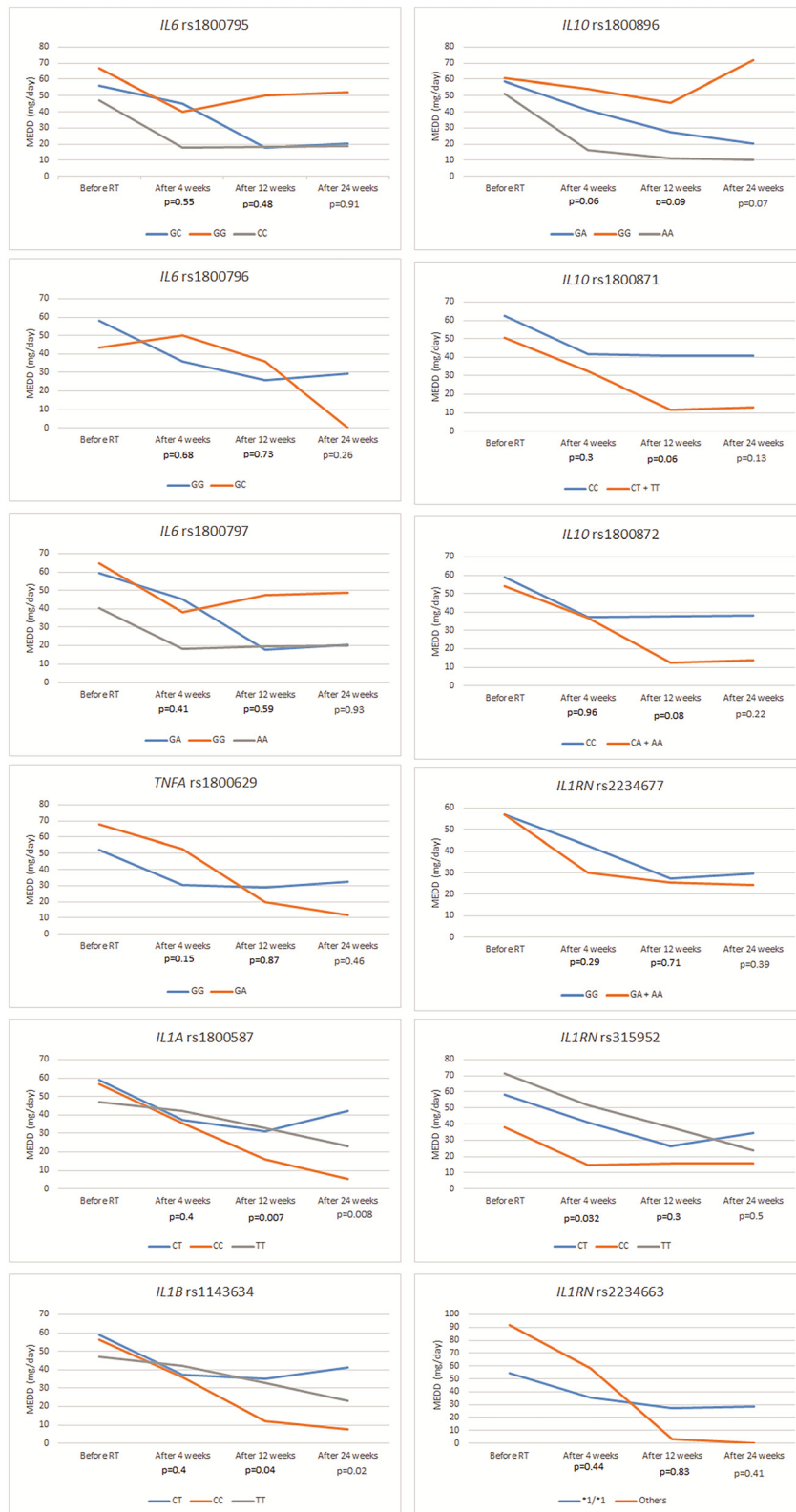


Figure 2: Doses of analgesics before radiotherapy and during the monitored period (4, 12 and 24 weeks after radio-therapy), at the same time point among patients with different genotypes. MEDD (morphine-equivalent daily dose), RT (radiotherapy).

therapeutic response to radiotherapy in patients with bone pain due to multiple myeloma. Preliminary findings indicate that certain polymorphisms within these genes may

contribute to interindividual variability in pain sensitivity and radiotherapy-induced analgesia. Understanding the association between cytokine gene polymorphisms and pain

response to radiotherapy may help identify patients who are more or less likely to benefit from this treatment. Such knowledge could enable more personalized pain management strategies, improving both the efficacy of analgesic therapy and patients' quality of life.

There are some limitations in this study. The number of patients in the study is limited and we assessed only 12 gene polymorphisms of 6 cytokines however the pain and response to analgesic treatment is an integrated process with other numerous genes. Further studies with more patients and combination of multiple cytokines polymorphisms are needed to explain the predictors of pain and response to palliative radiotherapy.

In conclusion, this study gives preliminary results that interleukins polymorphisms – pain relief associations can significantly impact patient care, particularly in the treatment of painful bone lesions in MM patients undergoing radiotherapy. The findings highlight that cytokine gene SNPs can influence pain severity and analgesic response. Specific genotypes were associated with either higher pain intensity or a better response to radiotherapy, allowing for more precise predictions of how patients will respond to treatment.

The application of genetic testing could enhance pain management strategies, enabling more personalized treatment and minimizing adverse effects. While these results are promising, further studies with larger patient cohorts and more comprehensive genetic analyses are needed to refine pain prediction models. Ultimately, genotyping could become an essential tool in oncological pain management, helping clinicians customize treatment based on a patient's genetic profile, leading to better pain relief outcomes and improved quality of life.

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Research ethics: The protocol of this clinical study was approved by the regional research ethical committee (BE-2-39) and the study was conducted strictly following the Good Clinical Practice guidelines and Helsinki declaration. The study was registered with clinicaltrials.gov (NCT02024815).

Informed consent: All participants provided written informed consent prior to enrolment.

Author contributions: MR, AI, RG conceived the idea and designed the study, MR, RD, VR collected data, RU, MK performed the genotyping of interleukins, MR, EJ, RD, DV, VR

analysed the data and revised the manuscript, RP prepared the statistical analysis of the data, MR and VR drafted the manuscript. All authors read and approved the final manuscript.

Use of Large Language Models, AI and Machine Learning

Tools: Artificial intelligence/ Machine learning tools were not used in the clinical study or in the preparation of manuscript.

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Data availability: The raw data can be obtained on request from the corresponding author.

References

1. delCastillo MD, Andrews RE, Mandal A, Andersen TL, CDA, Heegaard AM. Bone pain in multiple myeloma (BPMM)-A protocol for a prospective, longitudinal, observational study. *Cancers* 2021;13:1596.
2. DuVillard L, Guiguet M, Casasnovas RO, Caillot D, Monnier-Zeller V, Bernard A, et al. Diagnostic value of serum IL-6 level in monoclonal gammopathies. *Br J Haematol* 1995;89:243–9.
3. Lauta VM. A review of the cytokine network in multiple myeloma: diagnostic, prognostic, and therapeutic implications. *Cancer* 2003;97:2440–52.
4. Lauta VM. Interleukin-6 and the network of several cytokines in multiple myeloma: an overview of clinical and experimental data. *Cytokine* 2001;16:79–86.
5. Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, Björkholm M, et al. Interleukin 6, tumour necrosis factor alpha, interleukin 1 beta and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. *Br J Haematol* 2008;109:39–45.
6. Serin I, Oyaci Y, Pehlivan M, Pehlivan S. Role of cytokines in multiple myeloma: IL-1RN and IL-4 VNTR polymorphisms. *Cytokine* 2022;153:155851.
7. Zajączkowska R, Kocot-Kępska M, Leppert W, Wordliczek J. Bone pain in cancer patients: mechanisms and current treatment. *Int J Mol Sci* 2019;20:6047.
8. Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation* 2004;11:279–92.
9. Reyes-Gibby CC, Wang J, Spitz M, Wu X, Yennurajalingam S, Shete S. Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. *J Pain Symptom Manag* 2013;46:161–72.
10. Reyes-Gibby CC, Wu X, Spitz M, Kurzrock R, Fisch M, Bruera E, et al. Molecular epidemiology, cancer-related symptoms, and cytokines pathway. *Lancet Oncol* 2008;9:777–85.
11. Cameron B, Webber K, Li H, Bennett BK, Boyle F, de Souza P, et al. Genetic associations of fatigue and other symptoms following breast cancer treatment: a prospective study. *Brain Behav Immun Health* 2020;10:100189.

12. Yennurajalingam S, Astolfi A, Indio V, Beccaro M, Schipani A, Yu R, et al. Genetic factors associated with pain severity, daily opioid dose requirement, and pain response among advanced cancer patients receiving supportive care. *J Pain Symptom Manag* 2021;62:785–95.
13. Illi J, Miaskowski C, Cooper B, Levine JD, Dunn L, West C, et al. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. *Cytokine* 2012;58:437–47.
14. McCann B, Miaskowski C, Koetters T, Baggott C, West C, Levine JD, et al. Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. *J Pain* 2012;13:425–37.
15. Rausch SM, Clark MM, Patten C, Liu H, Felten S, Li Y, et al. Relationship between cytokine gene single nucleotide polymorphism and symptom burden and quality of life in lung cancer survivors. *Cancer* 2010;116:4103–13.
16. Reyes-Gibby CC, El Osta B, Spitz MR, Parsons H, Kurzrock R, Wu X, et al. The influence of tumor necrosis factor-alpha -308 G/A and IL-6-174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiol Biomarkers Prev* 2008;17:3262–7.
17. Reyes-Gibby CC, Shete S, Yennurajalingam S, Frazier M, Bruera E, Kurzrock R, et al. Genetic and non genetic covariates of pain severity in patients with adenocarcinoma of the pancreas: assessing the influence of cytokine genes. *J Pain Symptom Manag* 2009;38:894–902.
18. Reyes-Gibby CC, Spitz M, Wu X, Merriman K, Etzel C, Bruera E, et al. Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-alpha-308 G/A IL6-174G/C and IL8-251T/A. *Cancer Epidemiol Biomarkers Prev* 2007;16:2745–51.
19. Reyes-Gibby CC, Spitz MR, Yennurajalingam S, Swartz M, Gu J, Wu X, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. *Cancer Epidemiol Biomarkers Prev* 2009;18:2636–42.
20. Stephens K, Cooper BA, West C, Paul SM, Baggott CR, Merriman JD, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *J Pain* 2014;15:169–80.
21. Oliveira A, Dinis-Oliveira RJ, Nogueira A, Gonçalves F, Silva P, Vieira C, et al. Interleukin-1 β genotype and circulating levels in cancer patients: metastatic status and pain perception. *Clin Biochem* 2014;47:1209–13.
22. Sen A, Paine SK, Chowdhury IH, Mukherjee A, Choudhuri S, Saha A, et al. Impact of interleukin-6 promoter polymorphism and serum interleukin-6 level on the acute inflammation and neovascularization stages of patients with eales' disease. *Mol Vis* 2011;17:2552–63.
23. Bennermo M, Held C, Stemme S, Ericsson CG, Silveira A, Green F, et al. Genetic predisposition of the interleukin-6 response to inflammation: implications for a variety of major diseases? *Clin Chem* 2004;50:2136–40.
24. Endler G, Marsik C, Joukhadar C, Marculescu R, Mayr F, Mannhalter C, et al. The interleukin-6 G(-174)C promoter polymorphism does not determine plasma interleukin-6 concentrations in experimental endotoxemia in humans. *Clin Chem* 2004;50:195–200.
25. Zheng C, Huang D, Liu L, Wu R, Bergenbrant Glas S, Osterborg A, et al. Interleukin-10 gene promoter polymorphisms in multiple myeloma. *Int J Cancer* 2001;95:184–8.
26. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. *Pain* 1995;63:289–302.
27. Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. *J Intern Med* 2005;257:139–55.
28. Junger H, Sorkin LS. Nociceptive and inflammatory effects of subcutaneous TNF alpha. *Pain* 2000;85:145–51.
29. Miaskowski C, Conley YP, Mastick J, Paul SM, Cooper BA, Levine JD, et al. Cytokine gene polymorphisms associated with symptom clusters in oncology patients undergoing radiation therapy. *J Pain Symptom Manag* 2017;54:305–16.e3.
30. Rudzianskiene M, Inciura A, Gerbutavicius R, Rudzianskas V, Macas A, Simoliuniene R, et al. Single vs. multiple fraction regimens for palliative radiotherapy treatment of multiple myeloma: a prospective randomized study. *Strahlenther Onkol* 2017;193:742–9.
31. Rajkumar SV. Updated diagnostic criteria and staging system for multiple myeloma. *Am Soc Clin Oncol Educ Book* 2016;35:e418–23.
32. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27:117–26.
33. Chow R, Hoskin P, Schild PE, Raman S, Im J, Zhang D, et al. Single vs multiple fraction palliative radiation therapy for bone metastases: cumulative meta-analysis. *Radiother Oncol* 2019;141:56–61.
34. Chow E, Doyle M, Li K, Bradley N, Harris K, Hruba G, et al. Mild, moderate or severe pain categorized by patients with cancer with bone metastases. *J of Pall Medicine* 2006;9:850–4.
35. Selby & York Palliative Care Team & Pharmacy Group. Palliative care analgesic dose conversion chart. 03/2006 review date 01/2011. Available from: http://www.drjcope.com/uploads/1/3/1/4/13140168/palliative_care_drug_converter_1.pdf.
36. Chow E, Hoskin P, Mitera G, Zeng L, Lutz S, Roos D, et al. International bone metastases consensus working party. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys* 2012;82:1730–7.
37. Harmer D, Falank C, Reagan MR. Interleukin-6 interweaves the bone marrow microenvironment, bone loss, and multiple myeloma. *Front Endocrinol* 2019;9:788.
38. Lafrenie R, Bewick M, Buckner C, Conlon M. Plasma cytokine levels and cytokine genetic polymorphisms in patients with metastatic breast cancer receiving high-dose chemotherapy. *Immuno* 2023;3:16–34.
39. Fu SC, Wang P, Ming-Xing Q, Peng J-P, Lin X-Q, Zhang C-Y, et al. The associations of TNF-alpha gene polymorphisms with bone mineral density and risk of osteoporosis: a meta-analysis. *Int J Rheum Dis* 2019;22:1619–29.
40. Duch CR, Figueiredo MS, Ribas C, Almeida MS, Colleoni GW, Bordin JO. Analysis of polymorphism at site -174 G/C of interleukin-6 promoter region in multiple myeloma. *Braz J Med Biol Res* 2007;40:265–7.
41. Kong F, Liu J, Liu Y, Song B, Wang H, Liu W. Association of interleukin-10 gene polymorphisms with breast cancer in a Chinese population. *J Exp Clin Cancer Res* 2010;29:72.
42. Stolting T, Knauerhase H, Klautke G, Kundt G, Fietkau R. Total and single doses influence the effectiveness of radiotherapy in palliative treatment of plasmacytoma. *Strahlenther Onkol* 2008;184:465–72.
43. Balducci M, Chiesa S, Manfrida S, Rossi E, Za T, Frascino V, et al. Impact of radiotherapy on pain relief and recalcification in plasma cell neoplasms: long-term experience. *Strahlenther Onkol* 2011;187:114–9.
44. Dalal S, Bruera E. Pain management for patients with advanced cancer in opioid epidemic era. In: *American society of clinical oncology educational book*. Alexandria, VA: American Society of Clinical Oncology; 2019:24–35 pp.

45. De Jongh RF, Vissers KC, Meert TF, Booij LH, De Deyne CS, Heylen RJ. The role of Interleukin-6 in nociception and pain. *Anesth Analg* 2003;96: 1096–103.
46. Wilson AG, Symons JA, McDowell TL, McDewitt HO, Duff GW. Effects of polymorphism in the human tumor necrosis factor α promoter on transcriptional activation. *Proc Natl Acad Sci* 1997;94:3295–9.
47. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Nickerson P, et al. Cytokine genotypes correlate with pain and radiologically defined joint damage in patients with juvenile rheumatoid arthritis. *Rheumatology* 2005;44:1115–21.
48. Neeb L, Hellen P, Boehnke C, Hoffmann J, Schuh-Hofer S, Dirnagl U, et al. IL-1 β stimulates COX-2 dependent PGE₂ synthesis and CGRP release in rat trigeminal ganglia cells. *PLoS One* 2011;6: e17360.
49. Martucci C, Trovato AE, Costa B, Borsani E, Franchi S, Magnaghi V, et al. The purinergic antagonist PPADS reduces pain related behaviours and interleukin-1 beta, interleukin-6, iNOS and nNOS overproduction in central and peripheral nervous system after peripheral neuropathy in mice. *Pain* 2008;137:81–95.
50. Kamenarska Z, Dzhebir G, Hristova M, Savov A, Vinkov A, Kaneva R, et al. IL-1RN VNTR polymorphism in adult dermatomyositis and systemic lupus erythematosus. *Dermatol Res Pract* 2014;2014:953597.
51. Magyari L, Varszegi D, Kovessi E, Sarlos P, Farago B, Javorhazy A, et al. Interleukins and interleukin receptors in rheumatoid arthritis: research, diagnostics and clinical implications. *World J Orthop* 2014;5:516–36.
52. Hulkkonen J, Laippala P, Hurme M. A rare allele combination of the interleukin-1 gene complex is associated with high interleukin-1 beta plasma levels in healthy individuals. *Eur Cytokine Netw* 2000;11: 251–5.
53. Berger P, McConnell JP, Nunn M, Kornman KS, Sorrell J, Stephenson K, et al. C reactive protein levels are influenced by common IL-1 gene variations. *Cytokine* 2002;17:171–4.
54. Shen KF, Zhu HQ, Wei XH, Wang J, Li YY, Pang RP, et al. Interleukin-10 down-regulates voltage gated sodium channels in rat dorsal root ganglion neurons. *Exp Neurol* 2013;247:466–75.
55. Howell WM, Rose-Zerilli MJ. Cytokine gene polymorphisms, cancer susceptibility, and prognosis. *J Nutr* 2007;137:1945–1995.
56. Piny PA, Le Fèvre C, Antoni D, Blondet C, Noël G, Noël G. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. *Crit Rev Oncol Hematol* 2018;123:132–7.
57. Fabian A, Domschikowski J, Letsch A, Schmalz C, Freitag-Wolf S, Dunst J, et al. Use and reporting of patient-reported outcomes in trials of palliative radiotherapy: a systematic review. *JAMA Netw Open* 2022;5: e2231930.