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Identifying the Effects of Montelukast in Head and Neck Cancer Cells

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Abstract

Objective: Head and neck squamous cell carcinoma (HNSCCs) are one of the most common cancer types worldwide. There are different treatment approaches including drug repurposing against HNSCCs. In this study, we aim to evaluate montelukast effect on HNSCC cell lines by proliferative capacity, self-renewal potential, and cell cycle dynamics.

Methods: In the study, UM-SCC-47 and HSC-3 cell lines were cultured and treated with 10 uM montelukast. Control and treated cells investigated by colony formation assay, sphere formation assay. Stemness-related markers were detected via qRT-PCR and cell cycle analysis was performed with flow cytometry.

Results: The sphere formation assay demonstrated that the montelukast treated group was smaller and organized compared to the control. NANOG and SOX2 mRNA levels were reduced whereas KLF4 and OCT3/4 increased. Colony formation was reduced in the montelukast treated group. Cell cycle was arrested in the S phase in montelukast-treated HNSCC groups.

Conclusion: Montelukast treatment at a concentration of 10 µM impacted several functional properties of head and neck cancer cells, highlighting its potential effects in this context. Future studies should explore a broader range of concentrations to better understand its therapeutic potential and dose-dependent effects.

Keywords: Head and Neck Cancer, Antihistamine, Montelukast, Inhibitor of cysteinyl leukotriene receptors, Antitumor Effect

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Montelukast'ın Baş ve Boyun Kanseri Hücreleri Üzerindeki Etkilerinin Belirlenmesi

Öz

Amaç: Baş ve boyun skuamöz hücreli karsinomu (BBSHK) dünya çapında en yaygın kanser türlerinden biridir. BBSHK'lere karşı ilaç yeniden kullanımı da dahil olmak üzere farklı tedavi yaklaşımları vardır. Bu çalışmada, montelukastın BBSHK hücre hatları üzerindeki etkisini proliferatif kapasite, kendini yenileme potansiyeli ve hücre döngüsü dinamikleri açısından değerlendirmeyi amaçlıyoruz.

Yöntemler: Çalışmada, UM-SCC-47 ve HSC-3 hücre hatları 10 uM montelukast ile muamele edildi. Kontrol ve muamele edilen hücreler koloni oluşumu testi, küre oluşumu testi, qRT-PCR ve hücre döngüsü analizi ile incelendi.

Bulgular: Küre oluşumu testi, montelukast ile tedavi edilen grubun kontrole kıyasla daha küçük ve organize olduğunu gösterdi. NANOG ve SOX2 mRNA seviyeleri azalırken KLF4 ve OCT3/4 arttı. Koloni oluşumu montelukast ile tedavi edilen grupta azaldı. Kök hücre belirteçleri qRT-PCR ile saptandı ve hücre döngüsü analizi akış sitometrisi ile gerçekleştirildi.

Sonuç: Montelukast'ın 10 μM konsantrasyonda tedavisi baş ve boyun kanseri hücrelerinin çeşitli işlevsel özelliklerini etkileyerek bu bağlamdaki potansiyel etkilerini vurguladı. Gelecekteki çalışmalarda, terapötik potansiyelini ve doza bağlı etkilerini daha iyi anlamak için geniş bir konsantrasyon aralığını araştırmalıdır.

Anahtar kelimeler: Baş ve Boyun Kanseri, Antihistaminik, Montelukast, Sisteinil lökotrien reseptörlerinin inhibitörü, Antitümör Etkisi.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCCs) are heterogeneous malignancies groups that usually originate in the squamous epithelium of mucosal surfaces of the head and neck. These cancers are often associated with tobacco & paan use, alcohol consumption, radiation exposure, occupational exposure, Epstein-Barr virus infection, and human papillomavirus (HPV) infection[1]. According to the 2024 data, more than 70.000 HNSCC cases occur annually. This accounted for four percent of all cases of cancer[2]. The standard treatment approach for HNSCCs typically involves surgery, followed by adjuvant radiation therapy. However, treatment strategies vary depending on the cancer's location and the extent of metastasis. In advanced or metastatic stages, chemotherapy and targeted therapies, including immunotherapy, may be effective alternatives[3]. Despite advanced studies in HNSCC to the diagnostic and treatment approaches, its prognosis is still poor due to the aggressive behavior and treatment resistance[4]. It shows an urgent need for novel therapeutic strategies to overcome therapy limitations.

Drug repurposing is the therapeutic re-evaluation of existing drugs for new targets. This approach accelerates drug development processes and reduces costs, as the safety and pharmacokinetic profiles of the drugs are already established and approved by the FDA[5]. In this context, antihistamines have emerged as notable candidates for drug repurposing in recent years. Antihistamines are generally used for allergic reactions and reduce their symptoms by inhibiting the histamines that produce against allergens in the body[6]. In the last decade, antihistamines have been investigated for some cancers, including glioma, ovarian cancer, and hepatocellular carcinoma, and reported reduced risk of them. Moreover, antihistamines may modulate tumor-associated processes such as inflammation, angiogenesis, and immune response[7]. These findings raise the possibility of repurposing antihistamines as adjuvant therapies in cancer treatment.

Montelukast, a leukotriene receptor antagonist mainly used in treating asthma and allergic rhinitis, has received increasing attention for its potential anti-tumor properties. Montelukast

can regulate inflammatory responses, suppress tumor-promoting signaling pathways, and induce apoptosis in cancer cells by inhibiting cysteinyl leukotriene receptors (CysLT1R)[8]. The pharmacological effects of the compound highlight its potential to regulate cancer-linked inflammation and make it a candidate for repurposing as a new treatment in cancer care, providing a promising direction for further clinical investigation.

Furthermore, montelukast has been shown to regulate the cell cycle in cancer cells, inhibiting cell proliferation and potentially reducing the metastatic characteristics of these cells[9]. Additionally, its anticancer effects may be linked to the attenuation of oxidative stress by reducing intracellular reactive oxygen species[10]. Recent studies have suggested combining montelukast with other chemotherapy agents could enhance its therapeutic efficacy, positioning it as a promising candidate for combination therapies in cancer treatment[11–13]. These findings pave the way for novel therapeutic strategies and underscore the need for further investigation into the clinical potential of montelukast within comprehensive cancer treatment protocols.

In this study, we aimed to use montelukast on HNSCC in-vitro to evaluate its therapeutic potential by investigating its effect on proliferative capacity, self-renewal potential, and cell cycle dynamics to improve HNSCC treatment strategies.

METHODS

Cell Culture and Chemicals

Head and Neck Cancer Cell lines, tongue derived, primary HPV (+) UM-SCC-47 and metastatic HSC-3, were cultured in Dulbecco's modified Eagle medium (DMEM) containing 4500 mg/L glucose, and 10% fetal bovine serum (Sigma-Aldrich), streptomycin (100 µg/ml) (Invitrogen) and 2 mM L-glutamine, penicillin (100 U/ml). Cells were placed in the incubator for at 37°C in 5% CO2. Cells were proved to be mycoplasma free. Montelukast was freshly prepared for each experiment and administered to the cells every two days in the media. 10 uM Montelukast was applied considering the previous studies[11,14-17]. Control groups were treated with the carrier solvent (0.1% DMSO). Montelukast (608,2 g/mol) was dissolved in dimethyl sulfoxide (DMSO) (Sigma Chemical Co., St. Louis, MO, USA).

Cell Cycle Analysis

The cell cycle profile of the cells and DNA damage ratio were determined, following a previously established protocol by using the BD FACS Aria III device[18]. Shortly, the cells were incubated at 37 °C for 30 minutes with a solution containing 5 µg/ml PI and RNase at a 1:10 ratio. The measurement was applied after 48 hours of 10 uM montelukast treatment. The results were analyzed by using the ModFit LT programme.

Sphere Formation

A total of 15000 UM-SCC-47 and HSC-3 cells were seeded in DMEM-High medium supplemented with 10 ng/mL EGF (GIBCO, USA), 10 ng/mL bFGF (GIBCO, USA), 2% B27 (GIBCO, USA), 1% N2 (GIBCO, USA), and 1% penicillin-streptomycin. Cells were cultured in an ultra-low attachment 24-well plate (Corning Inc., Corning, NY, USA). Sphere medium, including 10 uM montelukast, was added on the third day. Spheres were counted after 6 days, with microscopic images recorded daily. All experiments were performed in triplicate.

RNA Isolation and qRT-PCR Analysis

Total RNA was extracted from spheres with the TRIzol Reagent (Thermo Fisher, USA). The high-capacity cDNA Reverse Transcription (Invitrogen, Carlsbad, CA) was used to produce cDNA, according to the manufacturer's instructions. Quantitative reverse transcription polymerase chain reaction was performed using a Step One Plus instrument (Applied Biosystems, Foster City, Calif, USA). The expressions of target genes (KLF4, OCT3/4, NANOG, SOX2), were normalized against those of housekeeping genes β-actin gene (ACTB).

The 2−ΔΔCT method was used to calculate fold change. The experiments were carried out in triplicate.

Colony Formation Assay

1000 cells per well were seeded in 6-well plates. After a two-week incubation period, the cells were stained with a 0.5% crystal violet solution (Sigma-Aldrich Corp.) 30-50 cells were counted as a colony. The average number of colonies was then calculated.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism 8 (GraphPad Software, La Jolla, CA), and comparisons were made using applicable two-way analysis of variance (ANOVA). A p-value of < 0.05 was considered statistically significant.

RESULTS

The Effect of Montelukast on Stemness in HNSCC

The sphere formation assay was applied for both control and treatment groups. The spheres were observed as larger, well-organized spheres in control groups, whereas smaller and less organized spheres were observed in the montelukast-treated group. Considering the morphological properties of HSC-3 spheres, the montelukast-treated group lacked a black line out of the sphere compared to the control (Figure 1).

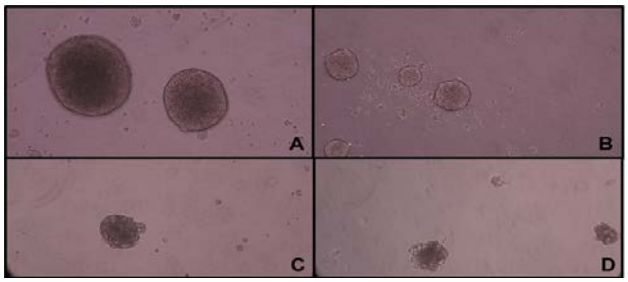

Figure 1. Microscopic Images of Sphere Formation in HNSCC Cells: **(A)** UM-SCC-47 Control, **(B)** UM-SCC-47 Treated with Montelukast, **(C)** HSC-3 Control, and **(D)** HSC-3 Treated with Montelukast. All photos were taken at 10X magnification. Control groups treated with complete media include DMSO. Statistical analysis was conducted using GraphPad Prism 8, with comparisons performed via two-way ANOVA. Significance was set at $p < 0.05$.

Stemness-related markers (KLF4, OCT3/4, NANOG, SOX2) expressions were investigated by qRT-PCR. The control and montelukast-treated sphere samples were evaluated via 2−ΔΔCT ratio. Interestingly, KLF4 (1,315 ±0,3150) and OCT3/4 (1,320 ±0,3200) expression levels increased in UM-SCC-47 spheres treated with 10 uM montelukast whereas SOX2 and NANOG expression were decreased (0,6850 ±0,3150) (Figure 2). However, there was no statistically significant difference in expression levels.

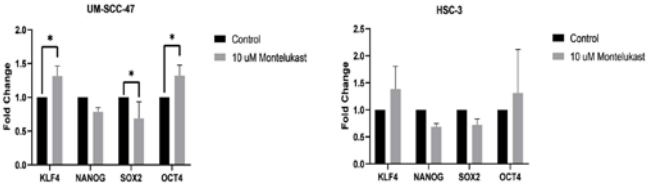

Figure 2. qRT-PCR bar graphs showing the fold change in the gene expression after treatment with montelukast. Control groups treated with complete media include DMSO. Statistical analysis was conducted using GraphPad Prism 8, with comparisons performed via two-way ANOVA. Significance was set at $p < 0.05$.

The Effect of Montelukast on Clonogenicity in HNSCC

Results showed a decrease in colony formation in both cell lines that were exposed to 10 μM of montelukast when compared to the untreated control group. However, the decrease was not significant statistically (Figure 3).

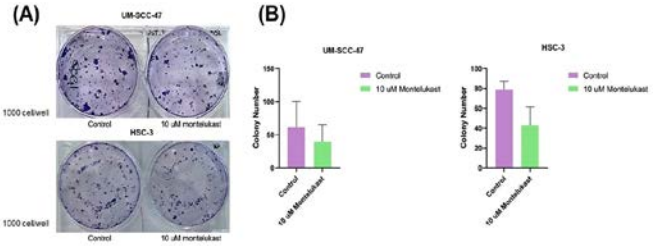

Figure 3. Colony formation assay on UM-SCC-47 and HSC-3 cells with and without 10 uM montelukast treatment: **(A)** Photos of colonies, **(B)** Colony number analysis. Control groups treated with complete media include DMSO. Statistical analysis was conducted using GraphPad Prism 8, with comparisons performed via two-way ANOVA. Significance was set at $p < 0.05$.

The Effect of Montelukast on Cell Cycle in HNSCC

The effects of montelukast treatment were also investigated via cell cycle and genetic stability in both UM-SCC-47 and HSC-3 cell lines. Minor changes were observed within the G1, S, and G2 phases in both cell lines However, no significant effect was observed (Figure 4). In addition, the percentage of damaged DNA slightly decreased with montelukast treatment in HNSCC (Figures 4C and 4F).

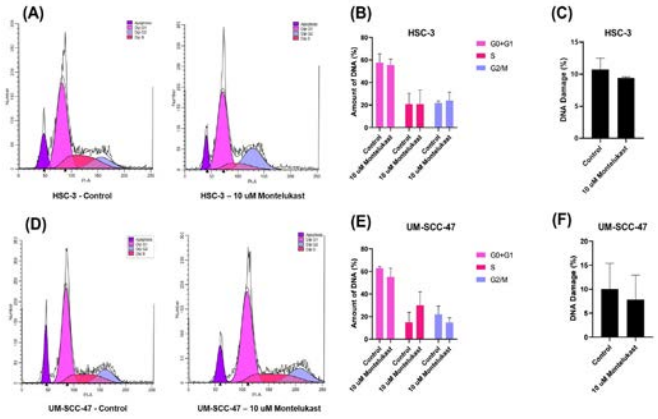

Figure 4. (A) Effect of montelukast on the cell cycle of HSC-3 cells by flow cytometry. **(B)** Histogram of cell cycle of HSC-3 cells. **(C)** The percentage of damaged DNA on HSC-3 cells. **(D)** Effect of montelukast on the cell cycle of UM-SCC-47 cells by flow cytometry. **(E)** Histogram of cell cycle of UM-SCC-47 cells. **(F)** The percentage of damaged DNA on UM-SCC-47 cells. Control groups treated with complete media include DMSO. Statistical analysis was conducted using GraphPad Prism 8, with comparisons performed via two-way ANOVA. Significance was set at $p < 0.05$.

DISCUSSION

In this study, the anti-cancer potential of montelukast, a leukotriene receptor antagonist, was investigated in vitro on two different HNSCC cell lines by treatment of these lines with 10 uM of Montelukast concentration.

Several studies have explored the effects of montelukast across various cancer types and cell lines, utilizing a range of concentrations. For instance, Tsai, MJ et al. demonstrated the use of 60 µM montelukast in lung cancer research, showcasing its potential therapeutic effects[14]. Similarly, Gelzinis, JA et al. investigated the impact of montelukast at concentrations of 30 µM and 100 µM on ovarian cancer cell lines, highlighting its influence on cellular processes[15]. In another study, Bellamkonda, K. et al. utilized 5–10 µM montelukast on human colon adenocarcinoma-derived cell lines HT-29 (HTB-38) and SW-480 (CCL228), observing its anti-cancer activity[16]. Beyond its application in cancer research, Fei, Z., and colleagues examined the protective effects of montelukast against pemetrexed (PMX)-induced hepatotoxicity by treating primary human LO-2 hepatocytes with 5–10 µM concentrations, revealing its hepatoprotective potential[17]. Furthermore, Arai, J. et al. conducted studies on montelukast in HEPG2 cells, a human liver cancer cell line, using doses ranging from 10 µM to 50 µM. Interestingly, even at the lowest dose of 10 µM, montelukast significantly reduced cell viability, indicating its potent effects[11]. Research on montelukast suggests that it exerts an antitumor effect in a dose-dependent manner. Based on previous literature, a dose of 10 µM montelukast was selected to evaluate its potential anti-tumorigenic effects in HNSCC. While this concentration may exhibit limited efficacy in HNSCC cells, it was sufficient to observe its inhibitory effects on colony formation, sphere size, and cell cycle.

The sphere-forming potential of the cells was assessed in 10 µM Montelukast-treated cells compared to the control group by evaluating morphological characteristics and mRNA expression levels of SOX2, KLF4, OCT3/4, and NANOG genes. Sphere formation experiments are commonly used to demonstrate the association with stemness, and the four genes involved, known as the Yamanaka factors, are highly expressed in reprogrammed stem cells[19,20]. While no significant differences were observed in the number of spheres in either cell line, spheres formed in the montelukast-treated groups were smaller and less organized than

the control group (Figure 1 and Figure 2). In a study by Chen, W. et al., WNK1 kinase and related proteins, such as Akt, were shown to promote 3D macro-sphere formation in glioblastoma[21]. Furthermore, montelukast has been reported to reduce the phosphorylation of several proteins, including extracellular signal-regulated kinase 1/2 (Erk1/2), protein kinase B (Akt), WNK1, MAPK/Erk kinase (MEK), and proline-rich Akt substrate of 40-kDa (PRAS40)[14]. On the other hand, Xie et al. highlighted that the Wnt/β-catenin signaling pathway, activated by CysLT1R, induces sphere formation[22]. These findings suggest that montelukast may exert a dual effect on sphere formation, as supported by the literature. The response variability may also be attributed to tumor heterogeneity[23]. Consequently, changes in the mRNA expression levels of specific genes in the cell lines may contribute to alterations in sphere morphology and molecular profiles. In light of these observations, further comprehensive studies are warranted to evaluate tumor-sphere responses to montelukast and other therapeutic agents in combination.

Although a dramatic decrease in colony numbers was observed in both cell lines following treatment with 10 μM Montelukast, this decrease was not statistically significant. This may be due to the cell dynamics that influences different attachment properties because of settling and the interaction between cells and drugs. Many studies have shown that CysLTR1 antagonists such as montelukast reduce colony formation and proliferation in cancer cells[11,14–17,23,24]. In relation to the cell cycle, montelukast was previously shown to reduce the proliferation and colony formation ability of cells via the apoptotic pathway[25,26]. Supporting this, the study by Tsai, MJ, et al. showed that montelukast can cause apoptotic death in lung cancer cells. It highlights the activation of apoptotic pathways, particularly the downregulation of Bcl-2 and the nuclear translocation of AIF, as well as the inhibition of cell proliferation and colony formation. In accordance with previous data in the literature our results also showed a decrease in colony formation.

Furthermore, the decreased phosphorylation of signaling pathways such as WNK1, Akt, Erk1/2, MEK, and PRAS40 indicates that montelukast induces cell death through multiple mechanisms[14]. Zovko, A. et al. demonstrated a similar apoptosis mechanism in chronic myeloid leukemia (CML) involving BCL2 and WNT/β-catenin pathway[26]. Moreover, the effects of montelukast on cancer cells have been reported in various cancer types, including its role in inducing apoptosis, inhibiting metastasis, and suppressing proliferation[9,26-28]. In this study, even though cell lines did not show any statistically significant difference in cell cycle phases, a slight increase in UM-SCC-47 cells arrested in the S phase when treated with montelukast (Figure 4E). Despite this, minor elevation in G2/M phase was shown in HSC-3 cells (Figure 4B). Contrary to the finding in previous literature[26,27], in this current study DNA damage ratios were not significantly changed (Figure 4C ve Figure 4F) between the treatment and control groups. Piromkraipak, P. et al. investigated the effects of montelukast and zafirlukast, another leukotriene receptor antagonist, on glioblastoma and reported that zafirlukast was more effective at inducing apoptosis than montelukast. According to that study, zafirlukast demonstrated a greater antiproliferative effect and induced G0/G1 cell cycle arrest, consistent with our findings[27]. Similarly, Tong, Jia et al. demonstrated that montelukast treatment induced cell cycle arrest in the G0/G1 phase in multiple myeloma (MM) cells, except for RPMI 8226 cells, which exhibited arrest in the G2/M phase[25].

The findings from previous research studies provide a substantial base for understanding

the therapeutic advantages of medications such as montelukast in the context of cancer, specifically head and neck cancer. However, we emphasize that the anti-cancer effects of montelukast may vary depending on the cell type, dose, and treatment duration. We also conclude that more in-depth analyses are needed beyond this study. This study is expected to provide a framework for further in vitro and in vivo research, to clarify the therapeutic potential of montelukast on Head and Neck Cancer, and facilitate the development of new treatment approaches.

CONCLUSION

This study investigated the anticancer potential of montelukast, a leukotriene receptor antagonist, in two different HNSCC cell lines. Highlights the potential therapeutic benefits of montelukast in cancer, particularly head and neck cancer, while acknowledging that its anti-cancer effects depend on factors such as cell type, dose, and treatment duration. These findings emphasize the therapeutic potential of montelukast and similar antihistamines in cancer treatment while highlighting the critical importance of optimizing dosage and treatment protocols. Further studies are warranted to explore the molecular mechanisms underlying these effects and evaluate montelukast's clinical relevance as a potential adjunct therapy in head and neck cancer.

Ethical Approval: Due to the use of commercial cell lines, no need to provide ethical approval for the study.

Conflict of Interest: The author declares no conflicts of interest.

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