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Review

Chemotherapy-ınduced cellular senescence: a comprehensive review of clinical methodologies and treatment outcomes

Kemoterapi ile indüklenen hücresel senesens: klinik yöntemler ve tedavi sonuçlarının kapsamlı bir incelemesi

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Abstract

The phenomenon of cellular senescence, which inevitably occurs as a result of chemotherapy, which is the basis of today's cancer treatment, has been a subject of increasing interest in recent years. This article aims to methodologically examine how cellular senescence is induced by chemotherapeutic agents and how this condition is detected in patients who are receiving or have received treatment. How senescent cells induced by chemotherapy during cancer treatment are determined, which biomarkers are used to detect senescence, and the methods used to detect these markers are discussed. In addition, the effects of senescent cells on the tumor microenvironment and the important clinical outcomes that may occur in patients with treatment are examined. In conclusion, in this review, we aimed to examine the clinical importance of cellular senescence induced by chemotherapy in cancer patients, how it may affect the response to chemotherapy, the side effects and long-term clinical outcomes it may cause in patients and possible new treatment methods to prevent potential adverse consequences.

Keywords: senescence, cancer, chemotherapy, biomarker, clinic, tumor

Öz

Günümüz kanser tedavisinin temelini oluşturan kemoterapinin kaçınılmaz bir sonucu olarak ortaya çıkan hücresel senesens olgusu, son yıllarda artan bir ilgiyle araştırılmaktadır. Bu makalede, kemoterapötik ajanlar tarafından hücresel senesens'in nasıl indüklendiği ve bu durumun tedavi almakta olan ya da tedavi almış hastalarda nasıl tespit edildiği yöntemsel olarak incelenmiştir. Kanser tedavisi sırasında kemoterapiye bağlı olarak gelişen senesens hücrelerin nasıl belirlendiği, senesens'in tespitinde kullanılan biyobelirteçler ve bu belirteçleri saptamada kullanılan yöntemler tartışılmıştır. Ayrıca, senesens hücrelerin tümör mikroçevresi üzerindeki etkileri ve tedavi gören hastalarda ortaya çıkabilecek önemli klinik sonuçlar değerlendirilmiştir. Sonuç olarak, bu derlemede kemoterapiye bağlı olarak gelişen hücresel senesens'in kanser hastalarındaki klinik önemini, kemoterapiye yanıtı nasıl etkileyebileceğini, hastalarda oluşturabileceği yan etkiler ile uzun vadeli klinik sonuçlarını ve potansiyel olumsuz sonuçları önlemeye yönelik yeni tedavi yöntemlerini incelemeyi amaçladık.

Anahtar Kelimeler: senesens, kanser, kemoterapi, biyobelirteç, klinik, tümör

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Introduction

Cellular senescence was first discovered by Hayflick in 1961 and was defined as the permanent exit of cells from the cell cycle as a result of cells losing their ability to divide [1]. Healthy cells have a certain capacity to divide (50-55 divisions, Hayflick Limit), and the main reason for this limitation is that with each cell division, DNA sequences called telomeres at the ends of chromosomes are lost. Shortening of telomeres and decreased telomerase activity cause cells to permanently exit the cell cycle after a certain number of divisions and lose their ability to reproduce. This permanent growth arrest is called replicative senescence [1, 2].

In addition to telomere shortening, DNA damage, oxidative stress, mitochondrial dysfunction, oncogene activation, ionizing radiation, epigenetic changes, genotoxic agents, and chemotherapeutic drugs have also been shown to be effective in the occurrence of cellular senescence (Fig.1) [3-5].

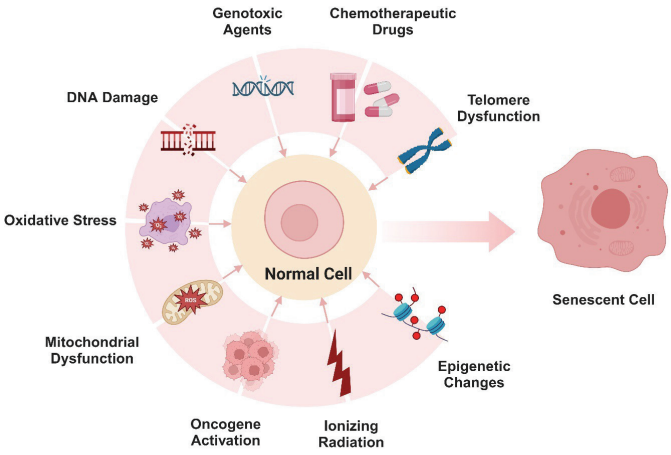

Figure 1. The Causes of Senescence Cellular senescence can be triggered by a variety of intrinsic and extrinsic factors, including telomere shortening, DNA damage, oxidative stress, mitochondrial dysfunction, oncogene activation, ionizing radiation, epigenetic changes, genotoxic agents, and chemotherapeutic drugs. These factors cause cells to irreversibly exit the cell cycle and lose their ability to proliferate. The figure shows the basic molecular and environmental drivers of senescence and their role in cellular processes. This figure was created using BioRender.

While replicative senescence in normal cells results in cell cycle arrest, cancer cells have unlimited proliferation capacity due to the telomerase reverse transcriptase enzyme (TERT), and this enzyme, which has a critical role in telomere synthesis, has been found to be overexpressed in many tumors and tumor cell lines [6]. Based on this information, it is thought that cellular senescence may have a positive role in preventing cancer and that permanent cessation of cell proliferation as a result of senescence will suppress the tumor [7, 8].

Treatment with chemotherapeutic drugs is a frequently used method in the treatment of cancer patients, and cellular senescence, which inevitably occurs during chemotherapy, can be considered a promising treatment approach in the suppression of cancer because it irreversibly stops the cell cycle. However, senescent cells formed by cellular senescence, which is considered an endogenous tumor suppressor mechanism, are alive and metabolically active, although they have lost their proliferation ability. These cells typically have an expanded and flattened morphology, multinucleated, and a vacuole-rich cytoplasm [9]. Although these cells have exited the cell cycle, they secrete many proinflammatory cytokines and chemokines, growth factors, survival molecules, and damage-associated molecular patterns, which have been described as a senescence-associated secretory phenotype (SASP) [10, 11].

While senescence appears as an effective mechanism in tumor suppression, SASP paradoxically creates various negative effects on both other cancer cells and non-cancerous cells in the cancer microenvironment. These effects occur in different ways, from proliferation, migration induction, and immune system suppression of other cancer cells to drug resistance; it can protect malignant cells from immune clearance and affect the tumor microenvironment (TME), ultimately causing cancer recurrence and metastasis [5, 12, 13]. Therefore, it is quite difficult to predict the effect of cellular senescence in cancer treatment. It is suggested that the presence of senescent cells during chemotherapy may affect the response of tumors to chemotherapy, and it is emphasized that the role of senescent cells and SASP should be better understood in order to increase the effectiveness of chemotherapeutic agents in cancer treatment.

Determination of Cellular Senescence in the Clinical Setting

The identification of biomarkers for the detection of senescent cells in cancer research is of great importance [14]. Cellular senescence can be relatively easily identified in vitro by detecting various senescence-associated biomarkers, as well as by the changing phenotypic signs of senescent cells [15]. However, in clinical studies conducted with cancer patients receiving treatment, the detection of senescent cells in vivo remains difficult. Identification and quantification of senescent cells is a difficult task because there are still no specific and universal markers for senescent cells. Therefore, senescence must be determined by combining measurements of different markers. In studies conducted with cancer patients, in vivo and ex vivo evidence of senescence in patient samples must be carefully evaluated, which poses a significant obstacle to the clinical identification of cellular senescence and monitoring of response to treatment.

Determination of cellular senescence is done by various methods and is associated with many biomarkers. However, certain markers are more prominent in the detection of senescence in the clinical setting (Fig. 2) [16].

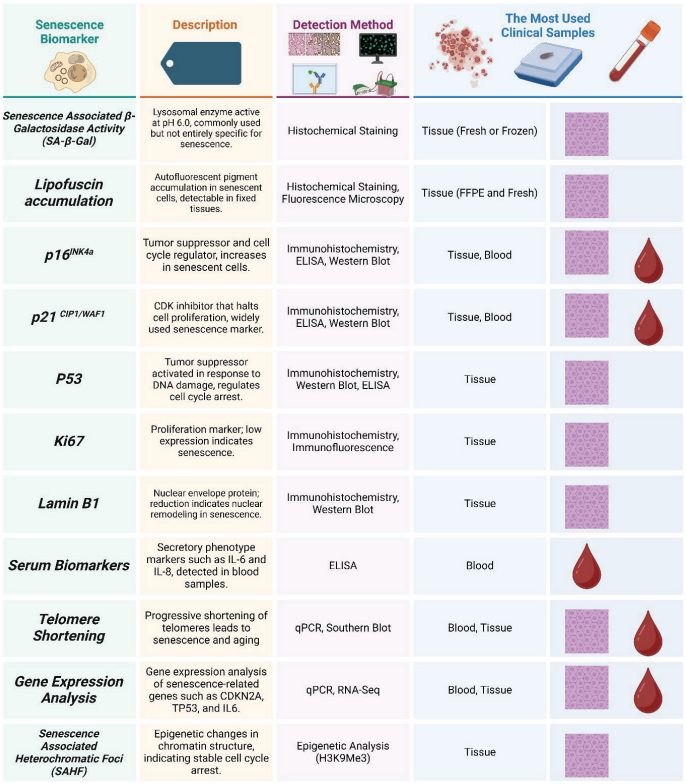

Figure 2. Senescence Biomarkers Commonly Used in Clinical Settings This figure summarizes the key biomarkers used to detect cellular senescence in clinical research and diagnostics. The figure includes the most commonly used biomarkers for clinically detecting senescence, such as SA-β-Gal, p16INK4a, p21CIP1/WAF1, P53, Ki67, Lamin B1, telomere shortening, and gene expression markers. It outlines their functional significance, detection methods, and commonly used clinical samples. This figure was generated using BioRender.

Senescence Markers and Frequently Used in Clinical Settings:

Senescence-Associated β-Galactosidase Activity (SA-β-Gal): Increased SA-β-gal activity is one of the most commonly used methods for determining senescence. Unlike normal beta-galactosidase enzymes, this enzyme, which is active at pH 6.0, is found in lysosomes and shows increased activity in senescent cells. However, SA-β-gal activity is not a specific marker for cellular senescence [17]. The method can only be applied reliably on fresh biopsy samples or frozen tissues, while its accuracy decreases in fixed tissues. This factor makes senescence difficult to detect in the clinical setting [18]. The requirement that tissue be frozen immediately after surgical resection to measure therapy-induced senescence (TIS) induction based on SA-β-gal activity in tumor samples also precludes the use of more readily available formalin-fixed paraffin (FFPE) embedded archival tissue samples. In addition, it has been reported that some cell culture conditions may increase SA-β-gal levels, resulting in false-positive results [19]. In addition, a study has shown that SA-β-Gal+ breast cancer cells maintain their proliferative abilities [20]. This suggests that SA-β-Gal alone as a marker for senescence is not a reliable strategy; measurements of multiple markers associated with senescence should be combined.

Lipofuscin accumulation: In senescent cells, accumulation of lipofuscin, a pigment with autofluorescent properties that accumulates in cells as a result of oxidative stress and cellular damage, is observed, and therefore, detection of lipofuscin accumulation can be used to determine cellular senescence [21]. Lipofuscin is a deposit of oxidized lipids and proteins that accumulates in senescent cells and can be detected in fixed tissues and, unlike SA-β-Gal activity, is amenable to measurement in fixed materials [22]. Therefore, the detection of cellular senescence in FFPE tissue samples is possible with lipofuscin. Its detection is usually carried out in tissue samples, and histochemical staining and fluorescence microscopy can be used [23, 24].

p16INK4a: p16 INK4A regulates the cell cycle, slowing down the transition from the G1 to the S phase and playing an important role in stopping cellular proliferation [25]. This protein, encoded by the CDKN2A (cyclin-dependent kinase inhibitor 2A) gene, is a senescence-associated tumor suppressor and cell cycle regulator [26]. In senescent cells, p16 INK4A levels are usually elevated, resulting in cell cycle arrest in the G1 phase. Therefore, p16 INK4A levels are considered a critical biomarker for the detection of chemotherapy-induced senescence. Extensive studies have shown that p16 INK4A expression significantly increases in senescent cells and the aging process and age-related diseases [27]. Based on this, p16 INK4A is considered a specific biomarker for the determination of senescence. In clinical applications, tissue or blood samples can be analyzed using methods such as immunohistochemistry, ELISA, and Western Blot to detect this marker [28-32].

p21 CIP1/WAF1 : p21CIP1/WAF1, an inhibitor of cyclin-dependent kinases (CDKs) regulating the cell cycle and encoded by the CDKN1A (cyclin-dependent kinase inhibitor 1A) gene, plays a critical role in cell division. This protein is involved in the regulation of cell cycle checkpoints. Increased p21 levels directly suppress the activity of CDK and proliferating cell nuclear antigen (PCNA) and indirectly inhibit it at the

transcriptional level [33, 34]. p21CIP1/WAF1 is controlled by the p53 tumor suppressor protein and is a necessary factor for p53-mediated cell cycle arrest at checkpoints [35]. Therefore, overexpression of p21CIP1/WAF1, which plays a critical role in stopping the cellular cycle, causes cell proliferation to stop and senescence to be triggered [36, 37]. In conclusion, it is a protein frequently used in determining cellular senescence, and p21Cip1/Waf1 levels are an important determinant in the determination of chemotherapeutic-induced senescence. The marker can be detected in both tissue and blood samples. Using methods such as immunohistochemistry, ELISA, and Western blot, p21Cip1/Waf1 levels can be measured, and these levels can be evaluated as indicators of senescence [29, 31].

P53: p53 is a tumor suppressor protein that is activated in response to DNA damage and cellular stress and arrests the cellular cycle. p53 is an essential tumor suppressor protein that regulates the G1/S and G2/M checkpoints of the cell cycle [35, 38]. It is activated in the event of cellular stress or DNA damage, stopping cell growth and activating DNA repair mechanisms to prevent the proliferation of damaged DNA. If the damage to DNA is beyond repair, it leads the cell to apoptosis or senescence [35]. As a result, activation and expression of p53 increases in response to cellular stress and DNA damage, and this process is used to assess senescence induced by treatments such as chemotherapy. p53 levels are usually measured by methods such as immunohistochemistry, Western blotting, and ELISA and are more commonly examined in tissue samples [39, 40].

Ki67: : First described as a monoclonal antibody found only in proliferating cells, Ki-67 is a nuclear antigen indicative of cell proliferation [41-43]. It is usually expressed in cells with an active cell division process, and in senescent cells, Ki67 expression is generally absent or very low because proliferation has stopped. Therefore, low Ki67 expression can be used to indicate chemotherapeutic-induced senescence. In the clinical detection of cellular senescence, the Ki67 marker is usually detected in tissue samples. Ki67 expression can be measured using methods such as immunohistochemistry and immunofluorescence, and low Ki67 levels are considered as indicators of senescence [44, 45].

Lamin B1: Lamin B1 is encoded by the LMNB1 gene in humans and plays a role in important cellular processes such as maintaining the structural integrity of the cell nucleus, gene expression, and cell division. The decrease in the level of Lamin B1 in senescent cells is considered an indicator of nuclear remodeling in these cells. Therefore, downregulation of Lamin B1 can be an important biomarker in determining cellular senescence. It is usually analyzed clinically on tissue samples and detected using methods such as immunohistochemistry and Western Blot [45-47].

Serum Biomarkers: Serum markers for the clinical detection of chemotherapeutic-induced cellular senescence can be detected through biomolecules obtained from blood samples. Serum levels of SASP components (inflammatory cytokines such as IL-6, IL-8, MMP-3, PAI-1, and proteases) can be measured by the ELISA (immunosorbent assay) method [48].

Telomere Shortening: Telomeres are special DNA sequences located at the ends of chromosomes and play an important role in protecting genetic material. Each time a cell divides, telomeres shorten somewhat, and when they fall below a certain threshold, the cell loses its ability to divide and enters the senescence process. This mechanism is directly linked to cellular senescence and is important to the organism's overall aging process. Therefore, telomeres' shortening indicates cellular senescence, and telomere length analysis helps identify senescence. This method uses qPCR [49] or Southern blot [48, 50] techniques to perform senescence analysis on blood and tissue samples.

Gene Expression Analysis: In the determination of chemotherapy-induced senescence, the detection of various senescence markers using gene expression analyses allows the evaluation of senescence status. Using methods such as qPCR and RNA-Seq, expression levels of senescence-related genes can be measured in tissue and blood samples. LMNB1 (Lamin B1), CDKN2A (p16INK4a), MKI67 (Ki-67), CDKN1A (p21CIP1/WAF1), TP53 (P53), IL6, IL8, MMP3 expressions are genes that are frequently analyzed to determine senescence [45, 51, 52].

Senescence Associated Heterochromatic Foci (SAHF): Senescent cells form epigenetic structures called SAHF that regulate the expression of proliferation-related genes and contribute to the senescence process. These structures may contain specific epigenetic marks such as H3K9Me3. The alteration of gene expression by SAHFs leads to permanent loss of the ability of cells to divide. Therefore, an increase in H3K9Me3 levels is considered an important marker indicating the onset of senescence, while the formation of SAHF is considered one of the key indicators of cellular senescence [45, 53, 54].

In the clinical setting, the determination of senescence is much more difficult than in vitro studies, and quite complex results can be obtained. None of the biomarkers can be considered specific for senescence independently, and the combination of multiple markers gives more reliable results. For this reason, many markers are used together to determine cellular senescence.

Table 1 summarizes the methods and biomarkers used to determine chemotherapeutic-induced senescence in clinical studies in the literature:

Table 1. Methods and markers used in the determination of chemotherapeutic-induced senescence

Reference	Type of Cancer	Chemotherapy Administered	Senescence Indicator Used
[48]	Blood samples from 33 women with stage I-III breast cancer were collected before, immediately after, 3 months after, and 12 months after chemotherapy.	Anthracycline	Increased expression of p16 INK4a, ARF, VEGFA and MCP1 was observed, Telomere length has been shown not to change
[52]	Esophageal squamous cell carcinoma (ESCC) patients who received cisplatin treatment before surgical resection (25) and those who did not (control) were studied.	Platinum-based chemotherapy such as cisplatin (CDDP)	SA-β-gal positivity+, DNA damage marker γH2AX was examined, and DNA damage increased, Increased mRNA and protein expression of p53, p21, IL-1α, IL-1β, IL-6 and IL-8 were observed. Up-regulation of MMP3 was observed.
[55]	Peripheral blood samples from surviving testicular cancer patients exposed to chemotherapy were studied.	Bleomycin, etoposide, cisplatin	Increased expression of CDKN2A/p16 INK4a was observed.
[56]	Tumor samples from a patient with metastatic head and neck cancer and a patient with endometrial cancer were studied.	Bleomycin	SA-β-gal positivity+, increased expression of p21 and morphological features of senescence were observed
[45]	Biopsies and archived formalin-fixed, paraffin-embedded (FFPE) tissue samples of surgically resected tumors from patients with invasive breast cancer who received various neoadjuvant therapies before surgical resection were studied.	Neoadjuvant chemotherapy (NAC): doxorubicin, cyclophosphamide, docetaxel, trastuzumab, pertuzumab, epirubicin, 5-fluorouracil, and anti-HER2-neu targeted therap	Down-regulation of Lamin B1 and Ki-67 and Up-regulation of p16INK4a was observed.
[57]	Tumor samples from 55 breast cancer patients with stages I-III were studied.	Neoadjuvant chemotherapy (NAC)	Lamin-B1 and Ki-67 down-regulation, up-regulation of p16 INK4a was observed
[39]	Frozen breast tumor biopsies from untreated patients with breast cancer or patients who had received therapy were studied.	Cyclophosphamide, Adriamycin, 5-fluorouracil	SA- β-gal positivity + High p16 INK4a staining and Low p53 staining was observed.
[58]	Formalin-fixed paraffin-embedded (FFPE) specimens from surgically resected non-small cell lung cancer patients with stage I-IV were used.	Adjuvant (neo)adjuvant: Cisplatin-based chemotherapy	High lipofuscin expression High p16 INK4a expression High p21 WAF1/Cip1 expression and Low Ki67 expression was observed.
[54]	Formalin-fixed paraffin-embedded (FFPE) tumor samples from non-metastatic, invasive breast cancer patients were studied.	Docetaxel, doxorubicin, cyclophosphamide, paclitaxel, 5-fluorouracil,	p21 CIP1 , H3K9Me3 (histone H3 lysine 9 trimethylation), Lamin B1 insignificant reduction in p21 CIP1, H3K9Me3), A significant decrease in lamin B1 expression level was observed.
[59]	Samples were collected from rectal cancer patients with or without neoadjuvant chemotherapy.	5-fluorouracil (5-FU)	SA- β-gal positivity + Increased expression of p21Waf1/Cip1 and IL-8 was observed.
[60]	Tissue samples from patients treated for MPM (malignant pleural mesothelioma) were studied.	Neoadjuvant chemotherapy (NAC): cisplatin and or cisplatin and	SA- β-gal positivity + increased expression of p21 and PAI-1, ALDH1A3 and IGFBP7 were shown to be unchanged.
[61]	Normal lung and tumor samples were obtained from non-small cell lung cancer patients.	Carboplatin and taxol	SA-β-gal positivity+ was observed.
[40]	Samples from 4 patients with clear cell carcinoma (RCC) (Renal cell carcinoma) were studied	Sunitinib	increase in p53, Dec1 and SA-β-gal staining A decrease in Ki67 staining was observed.
[62]	Studies have been conducted in normal breast epithelium, malignant breast tissue, and malignant tissue exposed to neoadjuvant chemotherapy (NAC) in three groups of breast cancer patients.	Docetaxel, cyclophosphamide, paclitaxel, doxorubicin, 5-fluorouracil,	A decrease in Lamin B1 expression level was observed.
[63]	Blood samples from stage I-III breast cancer patients were studied.	Doxorubicin, cyclophosphamide, paclitaxel, docetaxel,	Increased p16 INK4a expression was observed.
[10]	Tissue samples were obtained from prostate cancer patients before and after chemotherapy.	Mitoxantrone	Increased p16INK4a and p21 mRNA expression was observed. Low expression of proliferation-associated mRNAs encoding cyclin A, MCM-3, and PCNA, Increased IL-6, IL-8, GM-CSF, GRO-a, IGFBP-2, and IL- mRNA expression was observed.

Clinical Implications and Significance of Cellular Senescence

Therapy-induced senescence (TIS) is the cessation of proliferation and senescence of cancer cells under the influence of various therapeutic agents (chemotherapy, radiotherapy, etc.) used in cancer treatment. Although TIS has been accepted as a potent tumor suppressor mechanism in cancer treatment, cellular senescence can lead to various side effects and diseases, leading to quite complex and negative results (Fig. 3) [2, 64-66].

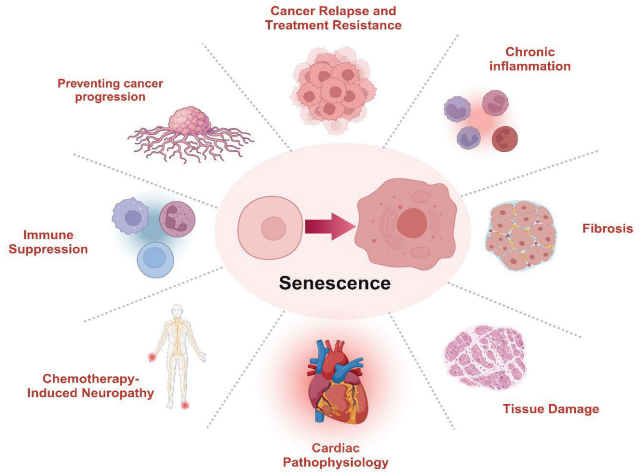

Figure 3. Clinical Consequences of Chemotherapeutic Induced Senescence This figure illustrates the various potential clinical consequences of chemotherapy-induced senescence. senescent cells can contribute to both beneficial and detrimental effects, including inhibition of cancer progression, cancer recurrence and treatment resistance, fibrosis, tissue damage, cardiac pathophysiology, chemotherapy-induced neuropathy, immune suppression, and chronic inflammation. This figure was created using BioRender.

Recent studies have shown that chemotherapy causes senescence in cancer and normal cells, which has important consequences on treatment efficacy and side effects. Namely, cells that undergo senescence can remain metabolically active and secrete a series of inflammatory and growth factors called SASP. These secretions can cause chronic inflammation in surrounding tissues and conditions such as immune system suppression. In addition, these cells can affect other cells in the microenvironment, leading to tumor progression and an increased risk of metastasis. In some cases, senescent cells can regain the capacity to divide and cause tumor recurrence. Therefore, the use of senescence in cancer treatment should be carefully evaluated. In order to be successful in cancer treatment, it is necessary to address the relationship between cellular senescence and tumor cells comprehensively and to consider potential adverse effects [3, 4].

Listed below are some of the clinical outcomes that may occur due to chemotherapeutic-induced senescence:

3.1.Preventing cancer progression: Cellular senescence is an important mechanism to prevent cancer cells from multiplying and acts as a barrier against tumor formation by stopping the cells from multiplying. Entering a state of senescence prevents these potentially cancerous cells from dividing and accumulating further mutations, thus reducing the risk of cancer progression. In addition, SASP can attract immune cells to the area where senescent cells are located and facilitate their clearance by the immune system, helping to prevent cancer development by helping to remove damaged or potentially malignant cells from tissues [67-69].

3.2. Cancer Relapse and Treatment Resistance: Cellular senescence is a frequently used treatment approach in cancer treatment. However, studies have shown that senescence causes very complex results, can promote tumors in addition to tumor suppression, and can cause tissue repair in addition to aging and tissue damage. Although senescent cells do not proliferate, they remain metabolically active and produce proteins with both tumor suppressor and tumor promoter activities [70]. The results of SASP or the senescence secretome message (SMS) [71] can be beneficial or harmful [65]. Therefore, it is important to understand the role of senescence in cancer treatment and to use its benefits while suppressing its disadvantages [72]. SASP, secreted by senescent cells, can lead to chronic inflammation, which in turn can cause changes in the tumor microenvironment and trigger cancer recurrence. SASP includes inflammatory cytokines, growth factors, and proteases, which can increase tumor growth, angiogenesis (formation of new blood vessels), migration, and invasion [4, 73, 74]. In a study, it was shown that increased SASP as a result of chemotherapy-induced cellular senescence causes epithelial-mesenchymal transition (EMT) and increases invasiveness in rectal cancer [59]. There is also evidence that senescent cells can be reprogrammed to re-enter the cell cycle after chemotherapy [61] and that they can reprogram stem cell-like properties and increase the capacity of cancer cells to re-proliferate and form tumors [75].

3.3. Chronic inflammation: Chronic inflammation plays a role in the pathogenesis of many age-related diseases, such as Alzheimer's, diabetes, osteoarthritis, atherosclerosis, muscle wasting, and cancer [76]. In general, chronic inflammation is thought to increase tumor risk and promote tumor progression and metastasis by creating a tumor-supportive microenvironment [77]. However, it is known that cellular senescence causes an increase in the secretion of proinflammatory cytokines and that senescent cells can

cause chronic inflammation in the surrounding tissues [78]. This inflammation can lead to additional complications by impairing patients' general health, and substances secreted by senescent cells (SASP) play an important role in this process, damaging the surrounding tissues [73, 79]. It is known that the level of IL6, which is one of the factors secreted by SASP and is known to be a pro-inflammatory cytokine, increases with senescence [80]. Studies have shown that senescent cells formed after chemotherapy in acute myeloid leukemia (AML) patients cause up-regulation of proinflammatory genes (including IL1, IL6, and IL8) and increase the abundance of SASP cells expressing inflammatory signatures [81]. Chemotherapy-induced senescent T cells have been shown to secrete SASP components such as IL-6 and IL-8, leading to increased chronic inflammation [82, 83]. Another study has demonstrated that senescent fibroblasts stimulate premalignant and malignant epithelial cells and function as tumor promoters [84]. In addition, inflammatory responses have an important role in eliminating cancer cells, but at the same time, an inflammatory microenvironment is known to promote cancer development, and proinflammatory cytokines, which are the main mediators of inflammation, can promote cancer progression [85].

3.4. Immunosuppression: While many studies have shown that senescent cells mount an immune response and promote immune clearance, other studies have suggested that senescence may have immunosuppressive and tumor-promoting effects [86].

Chemotherapeutic-induced senescence is used to stop tumor growth in cancer treatment, but it can also suppress the immune system, reducing treatment efficacy and increasing the risk of cancer recurrence. Studies have shown that cellular senescence promotes the development of an immunosuppressive microenvironment and contributes to the suppression of antitumor immunity, thus facilitating immune escape [79]. Another study suggests that the protein called PD-L2 (Programmed Death-Ligand 2) is expressed by senescent cells and may develop resistance to chemotherapy by suppressing immune responses [56]. This study, which was conducted with tumor samples obtained from cancer patients, determined that the expression of the immune checkpoint inhibitor PD-L2 increased simultaneously with the induction of cellular senescence with chemotherapeutics in different cancer cells. This suggests that senescence will contribute to the escape of tumor cells from the immune system and their survival intratumorally.

3.5. Fibrosis, Tissue Damage, and Cardiac Pathophysiology: Fibrosis can occur in various organs, including the lungs, liver, kidneys, and heart, often as a result of chronic inflammation and tissue damage. Failure to remove senescent cells and their accumulation can lead to increased SASP strengthening, which can lead to decreased tissue regeneration and increased fibrosis [87]. The development of fibrosis is a common complication of many chronic lung diseases, especially idiopathic pulmonary fibrosis (IPF). Senescence is thought to contribute to the pathologic process of IPF and play an important role in disease progression. Although studies on this subject are scarce, the available evidence supports this. One study has shown that leukotrienes secreted by senescent lung fibroblasts promote pulmonary fibrosis [88]. However, in studies investigating the relationship between IPF and Chronic obstructive pulmonary disease (COPD) pathogenesis [89], it is observed that chronic inflammatory processes occurring in the lungs of COPD patients and detectable in the circulation contain many inflammatory cytokines similar to SASP [90, 91]. Considering that PAI-1, another SASP factor, plays an important role in the development of lung fibrosis [92], all these data suggest that cellular senescence and its result, SASP, may contribute to lung structural changes and cause lung diseases.

Cellular senescence also plays an important role in the pathophysiology of heart disease and is a risk factor for many heart diseases, including cardiac hypertrophy, coronary artery disease, heart failure, and atrial fibrillation [93]. In addition, although the exact role of cellular senescence in the progression of calcific aortic valve disease is unknown, there is evidence that senescence of SASP interstitial cells and decreased regenerative capacity of valve endothelial cells due to fibrosis lead to valve destruction and degenerative aortic stenosis [94].

3.6. Chemotherapy-Induced Neuropathy: Chemotherapy-induced peripheral neuropathy is a condition that occurs as one of the side effects of chemotherapy treatment with damage to peripheral nerves. This pathology is a negative effect of chemotherapy that complicates lives and limits the treatment of many individuals who have survived cancer or are undergoing cancer treatment [95]. This suggests the role of treatment-induced senescent cells in promoting neurodegenerative effects and neuropathy. It has therefore been suggested that TIS may serve as a mechanism leading to chemotherapy-induced peripheral neuropathy and it has been suggested to investigate senotherapeutics to alleviate chemotherapy-induced peripheral neuropathy [96].

Conclusion

Cellular senescence is a condition in which cell proliferation is permanently stopped and inevitably occurs during treatment with chemotherapeutic agents. Induction of cellular senescence by chemotherapy and, thus, loss of the ability of cells to divide serves as an important tumor suppressor mechanism by preventing tumor growth and

disease progression. SASP stimulates the immune system and increases this effect by attracting immune system cells to the region in question, facilitating the destruction of these cells by the immune system. However, the adverse effects of senescent cells due to the various factors they secrete should not be ignored. The role of SASP in cancer treatment is quite complex and can paradoxically contribute to tumor recurrence, chronic inflammation, and fibrosis. The presence of SASP factors can facilitate cancer progression and metastasis by affecting the tumor microenvironment. An adequate understanding of the tumor microenvironment will enable the development of new strategies in cancer treatment in order to prevent the adverse effects caused by SASP. In this context, the amount and functional properties of SASP formed by chemotherapy-induced senescence in the tumor microenvironment are of critical importance for the success of the treatment. In order to develop more effective and safe treatment methods for cancer, the determination of senescent cells and the number of these cells are of critical importance. Since there are no universally available specific markers and the use of markers alone does not provide reliable results, it is quite difficult to determine senescent cells in the clinical setting. For these reasons, more accurate results can be obtained with the combined use of more than one biomarker, and the combined use and evaluation of these markers allows for a more accurate determination of chemotherapy-induced senescence in patients.

In cancer treatment, reducing the negative effects of chemotherapy-induced senescence is an important research topic, and senotherapeutic strategies have been developed thanks to the studies conducted on this subject. These treatment approaches targeting senescent cells aim to maximize the positive effects of senescence while minimizing its negative effects. Senolytic agents, which selectively kill senescent cells or promote their death, and senomorphic agents, which target the potentially harmful secretions (SASPs) secreted by senescent cells without clearing them, are used for this purpose [97-99]. The combined use of these treatment approaches with chemotherapeutic agents aims to eliminate senescent cells caused by therapy or to reverse the negative changes caused by senescence, thereby increasing the effectiveness of chemotherapy applied to cancer patients and improving the prognosis of the disease [97, 100].

This article comprehensively demonstrates that cellular senescence, in addition to being a tumor suppressor mechanism, can also have critical consequences in terms of treatment resistance, recurrence, and tumor microenvironmental reorganization. In particular, the development of treatment resistance and the risk of recurrence, one of the most significant challenges faced in current cancer treatments, appear to be closely linked to SASP, an inevitable consequence of senescence. Therefore, understanding both the positive and negative effects of senescence will directly contribute to the development of more effective and safe treatment strategies in clinical practice. Furthermore, identifying cellular senescence with reliable and specific biomarkers is crucial for accurately assessing treatment responses in clinical trials. Further clinical studies are undoubtedly needed to better understand the potential role of cellular senescence and SASP components in cancer treatment. In this context, increasing the number of clinical trials investigating the use of senolytic and senomorphic agents in conjunction with chemotherapy is crucial for the positive outcomes of cancer patients and the success of treatment.

Declaration of conflict of interest

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Contribution of The Authors

F.Ö.Y conducted the literature review, wrote the main manuscript, edited the content, designed the figures, and performed the final review and validation. Y.D.Ş.D contributed to the literature review, manuscript editing, and writing, and assisted in the final review and validation. M.A contributed to manuscript writing, editing, and participated in the final review and validation. All authors contributed to the writing, revision, and refinement of the manuscript. Additionally, all authors have read and approved the final published version of the manuscript.

Abbreviations

CIS: chemotherapy-induced senescence; SASP: senescence-associated secretory phenotype; TIS: therapy-induced senescence; SA-β-Gal: senescence-associated β-galactosidase; SAHF: senescence-associated heterochromatin foci; PD-L2: programmed death-ligand 2; NAC: neoadjuvant chemotherapy; FFPE: formalin-fixed, paraffin-embedded; IL-6: interleukin 6; IL-8: interleukin 8; MMP3: matrix metalloproteinase 3; CDK: cyclin-dependent kinase; qPCR: quantitative polymerase chain reaction; RNA-Seq: RNA sequencing.

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