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Evaluation of cancer patients receiving concurrent chemotherapy and antituberculosis treatment: Review and case series of a single-center experience

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Ethics Committee Approval
Approval of the institutional review board Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethical committee (approval date Oct 08, 2021; approval number 902)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Cancer and tuberculosis are common in the world, and the intersection of these two diseases affects oncology practice inevitably. Fortunately, the co-occurrence of cancer and tuberculosis is rare and there are no guidelines for the management of therapy in these patients. The information on these patients is obtained from small-scaled studies. This study aimed to question the efficacy and safety of tuberculosis treatment in cancer patients receiving chemotherapy.

Methods: Twenty-two patients who were treated with chemotherapy due to cancer and followed up and treated for concurrent tuberculosis in Diyarbakır Gazi Yaşargil Training and Research Hospital Medical Oncology Clinic between February 2009 and March 2021 were included in this retrospective case-control study. The clinical laboratory and treatment data of these patients were reviewed retrospectively. Then, the clinical, laboratory and treatment data of twenty-two cancer patients of the same age, who had the same stage cancer and received the same chemotherapy treatment but did not have tuberculosis disease were compared with the patients with tuberculosis. Thus, the efficacy, safety, and effect of tuberculosis treatment on cancer treatment were investigated.

Results: Twenty-two patients were diagnosed with tuberculosis and cancer. Six (27.3%) patients were receiving single agent chemotherapy, 16 (72%) were receiving combination chemotherapy, and 5 (22.5%) were receiving a combination of chemotherapy and targeted therapy. While 10 (45.5%) patients were diagnosed with non-pulmonary tuberculosis, 12 (54.5%) patients were diagnosed with pulmonary tuberculosis. Among all patients, the rate of completion of antituberculosis treatment was 77.2%, and the success rate with initial antituberculosis agents was 72.7%. Except for elevated liver enzymes, nausea-vomiting and grade-3 neutropenia ($P<0.001$, $P<0.001$, $P=0.012$ respectively), there was no significant difference in toxicity between the patients with and without tuberculosis. The mortality rate in the first 6 months of anti-tuberculosis treatment was 18.2% in patients who received tuberculosis and cancer treatment, compared to 9.1% in cancer patients who did not receive tuberculosis treatment. There was no significant difference in the mortality rate in both groups at the end of 12-year follow-up period ($P=0.658$).

Conclusion: Our results show that the combined use of chemotherapy and antituberculosis treatment in patients with cancer and tuberculosis is effective and safe.

Keywords: Cancer, Antituberculosis treatment, Chemotherapy, Tuberculosis

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Introduction

In 2020, approximately 19.3 million new cancer cases were diagnosed around the world, and 10 million cancer patients died because of it [1]. Cancer is the second most common cause of mortality after cardiovascular diseases, which is responsible for one out of every six deaths [2]. Tuberculosis disease (TBC), which has an origin as old as human history, is the most common infectious disease with high mortality rates worldwide. According to the 2018 data of the World Health Organization (WHO), approximately one quarter of the entire world population is infected by Mycobacterium Tuberculosis. While approximately 10 million people suffer from active TBC, approximately 1.3 million people die each year due to TBC [3-4].

The cancer itself, cancer-related malnutrition, local and systemic treatments such as surgery, chemotherapy and radiotherapy lead to an immunosuppressive state in cancer patients, causing them to become sensitive to various infectious agents [5-6-7].

The intersection of these two diseases, which are common in the world, affects the practice of oncology inevitably. New and more intensive cancer treatment modalities developed since 1970, when cancer was accepted as a risk factor for the development of TBC, and increased overall survival in cancer patients, albeit rendering cancer patients more vulnerable to this disease [8-9].

Although both diseases are frequent separately, the rate of coexistence of TBC and cancer disease in the entire cancer patient population is unknown [10]. Today, although cancer is considered a risk factor for TBC disease, there is no specific guideline regarding the coexistence of the two. Information on this condition is derived mostly from case series and reviews with a small number of patients.

This study aimed to examine the patients with concomitant cancer and TBC disease in our clinic over a 12-year period and to evaluate the effect of concomitant cancer and TBC treatment on patients by comparing them with the patients diagnosed with cancer, without TBC receiving the same treatment for the same stage cancers within the same age groups.

Materials and methods

The data of 26 patients diagnosed with cancer and concurrent TBC, who were followed up and treated in Diyarbakır Gazi Yaşargil Training and Research Hospital Medical Oncology Clinic between February 2009 and March 2021, were evaluated retrospectively. Four patients were excluded from the study due to reasons such as cancer or TBC treatment incompatibility, lack of data, dropping out of follow-up, emergence of TBC disease while receiving treatment other than chemotherapy, and having hematological malignancy. The data of the remaining 22 patients were evaluated with the help of our hospital database, TBC dispensary records and the national E-Pulse health information system. In addition to demographic characteristics of patients such as age, gender, location, age at cancer diagnosis, cancer type, residental area , patient performance score (PS), chemotherapy agents used, presence of B symptoms, how the diagnosis of TBC was made, location of TBC disease, clinical data (pulmonary, non-pulmonary), antituberculosis treatment agents used, toxicities developed during treatments, how antituberculosis and chemotherapy treatments were managed in patients who developed toxicity, treatment durations, follow-up periods, cancer-related overall survival were evaluated. Then, the clinical, laboratory and treatment data of 22 cancer patients with the same cancer diagnosis and stage within the same age group, who were receiving the same cancer treatment but did not have TBC disease, were compared with the group with TBC. Thus, the safety of TBC treatment and its effect on cancer treatment were investigated. This study was conducted in concordance with the current law, Good Clinical Practice guidelines, and the ethical principles of Declaration of Helsinki. Approval of the institutional review board Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethical committee was obtained (approval date Oct 08, 2021; approval number 902).

Tuberculosis treatment

The patients who were diagnosed with TBC were started on a quadruple antituberculosis treatment consisting of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) as standard treatment. Patients who used this treatment for at least two months then received maintenance isoniazid (H) and rifampicin (R) for four months. Ethambutol (E), streptomycin (S), moxifloxacin (M), cycloserine (C) and pyridoxine (P) treatment were given to some patients who used chemotherapy agents such as paclitaxel and irinotecan or who developed recurrent liver toxicity and one patient was treated with isoniazid (H), ethambutol(E), streptomycin(S), and moxifloxacin(M) due to hepatotoxicity.

Statistical analysis

Statistical package for the social sciences (SPSS) 18.0 software was used to estimate survival rate, and descriptive data were analyzed using the same program. Kaplan-Meier curves and a log-rank test were used to analyze the survival data, and *P*-values of <0.05 were considered statistically significant.

Results

Of the 22 patients diagnosed with TBC and cancer, 13 (59.1%) were male and 9 (40.9%) were female. The male/female ratio was 1.4/1. The median age of the patients was 59 (range: 30-68) years and the median age of diagnosis of cancer was 57 years (range: 30-67). While 14 (63.6%) patients resided in the city center, 5 (22.7%) patients resided in the village and 3 (13.6%) patients resided in the district. Thirteen (59.1%) of the patients had PS: 0-1, 6(27.3%) patients had PS:2, 3 (13.6%) patients had PS:3. Of the patients, 4 (18.2%) had diabetes, 8 (36.4%) hypertension, 1 (4.5%) had COPD, 1 (4.5%) had heart failure and 1 (4.4%) had kidney failure. While 16 (72.7%) patients had type B symptoms, 6 (27.3%) patients did not. Twelve (54.5%) patients smoked, and one (4.5%) patient had a history of steroid use.

The most common cancer diagnosis was lung cancer with 7 (31.8%) patients, followed by breast cancer with 6 (27.3%) patients. Of the remaining patients, 3 (13.6%) had colon cancer, 3 (13.6%) had gastric cancer, 2 (9.1%) had prostate cancer and 1 (4.5%) had pancreatic cancer. While 6 (27.3%) patients diagnosed with TBC were receiving

neoadjuvant/adjuvant chemotherapy, 16 (72.7%) patients were receiving chemotherapy with the diagnosis of metastatic disease. Nine (40.9%) of the patients were diagnosed before starting chemotherapy, and 13 (59.1%) patients were diagnosed after chemotherapy was started. Six (27.3%) patients were receiving single agent chemotherapy, 16 (72%) were receiving combination chemotherapy and 5 (22.5%) were receiving a combination of chemotherapy and targeted therapy. While 10 (45.5%) of the patients were diagnosed with non-pulmonary TBC, 12 (54.5%) patients were diagnosed with pulmonary TBC. All patients diagnosed with nonpulmonary (Table 1) TBC were diagnosed with lymph node excisional biopsy or lymph node dissection performed during the operation. Six (50%) patients diagnosed with pulmonary TBC had cavitary lesions, 3 (25%) patients had infiltrative areas in the upper lobe of the lung, 2 (16.7%) patients had multiple nodules, and 1 (8.3%) had multiple nodules and pleural effusion. Nine (75%) patients diagnosed with pulmonary TBC were diagnosed with acid-resistant bacteria (ARB) screening in sputum, and 3 (25%) patients were diagnosed with a mycobacterial culture.

Table 1: General characteristics of patients with cancer and tuberculosis disease

	n	%		n	%
Gender			Tuberculosis diagnosis		
Male	13	59.1%	Pulmonary	12	54.5%
Kadın	9	40.9%	Non-pulmonary	10	45.5%
Performance score			Metastasis		
0-1	13	59.1%	Available	16	72.7%
2	6	27.3%	None	6	27.3%
3	3	13.6%	Chemotherapy type		
Comorbidity			Adriamycin/Cyclophosphamide	3	13.6%
Diabetes	4	18.2%	Paclitaxel/Trastuzumab	2	9.1%
Hypertension	8	36.4%	Paclitaksel	2	9.1%
ASHD/Heart failure	1	4.5%	Gemcitabine	1	4.5%
COPD	1	4.5%	Capecitabine	1	4.5%
Chronic renal failure	1	4.5%	Cisplatin/Pemetrexed	2	9.1%
B symptom			Cisplatin/Gemcitabine	3	13.6%
Available	16	72.7%	Cisplatin/Vinorelbine	1	4.5%
None	6	27.3%	FOLFIRINOX	1	4.5%
Smoke			FOLFOX/Bevacizumab	1	4.5%
Available	12	54.5%	5FU/Cetuximab	1	4.5%
None	10	45.5%	FOLFOX	1	4.5%
Cancer type			FOLFOX/Herceptin	1	4.5%
Lung	7	31.8%	Docetaksel	2	9.1%
Breast	6	27.3%	Anti-tuberculosis treatment		
Colon	3	13.6%	HRZE	16	72.7%
Stomach	3	13.6%	Quinolone based therapy	6	27.3%
Prostate	2	9.1%			
Pancreas	1	4.5%			

Chemotherapy was initiated in a median of 9 days (range: 3-21 days) in cancer patients without TBC, and a median of 24 days (range: 19-45 days) in patients with cancer and TBC. In patients diagnosed with TBC during chemotherapy, chemotherapy administration was delayed for a median of 18 days (range: 7-26 days). Eighteen (81.8%) patients were started on a quadruple antituberculosis treatment consisting of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). Quinolone-based antituberculosis treatment was started instead of an R-containing antituberculosis combination due to the use of paclitaxel in 3 (13.6%) of the remaining patients and irinotecan in 1 (4.5%). Quinolone-based combination therapy was initiated due to hepatotoxicity in 2 (9.1%) patients who received HRZE combination therapy. ARB and culture scans became negative in 8 (66.7%) patients diagnosed with pulmonary TBC at the second month and 2 (16.7%) patients at the 3rd month. One (8.3%) patient was referred to an advanced center with the diagnosis of multidrug-resistant TBC, and 1 (8.3%) patient dropped out of follow-up. While 16 (72.7%) patients finished TBC treatment, death occurred in 4 (18.2%) patients during cancer and antituberculosis treatment. One (4.5%) patient was discontinued from follow-up and treatment and 1 (4.5%) patient was treated in an advanced center with the diagnosis of multidrug resistance (MDR) tuberculosis. The cause of death of all patients who died was due to cancer. During the same period, 2 (9.1%) cancer patients without TBC died.

The median duration of antituberculosis treatment was 192 (range: 32-553) days. The median duration of chemotherapy and antituberculosis treatment was 168 (range: 32-553) days. During the combination of antituberculosis and chemotherapy treatment, the most common side effect was liver enzyme elevation, which was significantly higher than in patients with cancer without a diagnosis of TBC (P<0.001). The rate of neutropenia and use of GCSF during treatment were similar in both groups, but grade 3 neutropenia was more common in the group receiving antituberculosis treatment (P=0.012). There was no significant difference between the two groups in terms of anemia or thrombocytopenia. Gastrointestinal side effects such as nausea and vomiting were more common in the group receiving antituberculous therapy (P<0.001) (Table 2). The chemotherapy response of cancer patients receiving TBC treatment was similar to the chemotherapy response of cancer patients without TBC during the same period (P>0.05 for all) (Table 3). At the end of the 12 year-follow-up, 15 (68.2%) patients diagnosed with TBC and cancer, and 14 (63.6%) patients with cancer without TBC died. There was no significant difference in terms of mortality rates (P=0.658) (Figure 1).

Table 2: Side effect evaluation

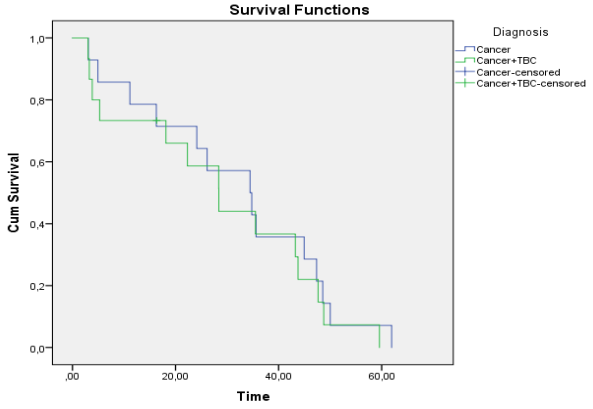
	Chemotherapy+Antituberculosis treatment group		Chemotherapy group		
	n	%	n	%	*P*-value
Neutropenia					
Grd-1	6	27.3	5	22.7	0.282
Grd-2	3	13.6	2	9.1	0.234
Grd-3	3	13.6	1	4.5	0.012
Thrombocytopenia					
Grd-1	4	18.2	3	13.6	0.286
Grd-2	1	4.5	1	4.5	0.632
Grd-3	-		-		-
Anemia					
Grd-1	4	18.2	3	13.6	0.198
Grd-2	1	4.5	1	4.5	0.610
Grd-3	1	4.5	1	4.5	0.623
AST/ALT increase	10	45.5	3	13.6	<0.001
Grd-1	5	22.7	2	9.1	<0.001
Grd-2	3	13.6	1	4.5	0.008
Grd-3	2	9.1%	0		<0.001
Nausea/Vomiting	9	40.9%	6	27.3%	<0.001
Diarrhea	6	27.3%	5	22.7%	0.308

Table 3: Response rates in the first 6 months of tuberculosis treatment

	Chemotherapy+Antituberculosis treatment group		Chemotherapy group		
	n	%	n	%	*P*-value
CR	4	18.2	5	22.8	0,276
PR	8	36.4	7	31.8	0,142
SD	6	27.3	7	31.8	0,253
PRG	4	18.2	3	13.6	0,268

CR: Complete Remission, PR: Partial Remission, SD: Stable Disease, PRG: Progression

Figure 1: Survival graph



Discussion

Our study was designed to evaluate the efficacy and safety of the combined use of TBC and cancer treatments. Our results are in line with previous studies with a small number of patients showing that antituberculous therapy can be used effectively and safely in cancer patients.

There are two theories linking TBC and cancer. The first of these is the breaking of the immune resistance to TBC infection due to the immunosuppressive environment occurring during the cancer disease and/or its treatment, and the emergence of new or reactivation TBC infection due to the broken immune defense. The second theory is the existence of factors such as smoking, chronic obstructive pulmonary disease, alcoholism, human immunodeficiency virus infection (HIV) that facilitate both cancer and TBC infection [11-13]. Apart from the fact that cancer is a facilitating cause for TBC infection, current information has shown that TBC, a chronic inflammatory disease, can stimulate carcinogenesis in the lung tissue [14]. It should also be kept in mind that tuberculosis disease can mimic lung and bone tumors in patients with suspected cancer [15].

While the incidence of TBC disease in our country is 17/100000 in the general population, this rate is 231/100000 in African countries and 3.1/100000 in the USA. Despite the TBC elimination and TBC disease treatment follow-up programs, it is still an important public health problem in our country. The highest risk for TBC in the cancer population is patients with respiratory tract and hematological malignancies, presumed to be the most susceptible group to TBC. The incidences in these patients are 892/100000 and 489/100000, respectively [9].

In the literature, there are conflicting results regarding the success rate of antituberculosis treatment in patients with cancer and TBC diagnosis. In the study conducted by Chai et al. [16] in 31 patients with lung cancer and concurrent pulmonary TBC, the completion rate of antituberculosis treatment was 87%, while the success rate of TBC treatment was 80.7%. In the case series of 30 patients by Hirashima et al. [17] the success rate of antituberculosis treatment was 70% in patients diagnosed with cancer and TBC. The reason for the difference in the success rate of antituberculosis treatment in studies seems to be that countries have different health systems and patient follow-up programs. In our study, when all patients were included, the rate of completion of antituberculosis treatment was 77.2%, and the success rate with initial antituberculosis agents was 72.7%. This rate is below the 87% TBC treatment success rate in the general population in our country. The reasons for this were thought to be the administration of antituberculosis treatment in the immunosuppressive patient population, the small patient population in our study, the high number of patients with metastatic disease, and cancer-related deaths while antituberculous treatment was continued [18].

The use of antituberculosis treatment agents in patients with lung cancer was shown to be associated with shorter survival by Shieh et al. [19]. In another study conducted by Chung Su et al. [20], the mortality rate from any cause in the first 6 months was 15.6% in cancer patients diagnosed with TBC, and the mortality rate from any cause between 6-12 months was 5%. In the same study, 12-month all-cause mortality was 20.56% in patients with cancer and TBC, and 11.84% in patients without a diagnosis of TBC. Parallel to these findings, in our study, the mortality rate in patients with cancer and TBC diagnosis during antituberculosis treatment was 18.2%, and 9.1% in cancer patients who were not diagnosed with TBC during the same period. Although the mortality rate in the first 6 months was high in our study, there was no significant difference in the number of patients who survived in both groups after 12 years of follow-up.

Most studies with a small number of patients on the coexistence of cancer and TBC also questioned the safety of using chemotherapy and antituberculosis treatment together. In a case series of 30 patients with lung cancer and TBC by Kim et al. [21], the safety of the combined use of chemotherapy and antituberculosis treatment was demonstrated. In another study conducted by Chai et al. [22] on 31 patients with lung cancer and TBC disease, combined treatment was effective and safe. In our study, there was no significant difference in hematological side effects. Although nausea and vomiting and AST/ALT elevation were more frequent in patients receiving combination therapy, it was a manageable side effect and none of the patients required interruption of chemotherapy or antituberculosis therapy.

The use of R in combination therapy stimulates cytochrome P450 enzymes such as CYP3A4 and CYP2C8. This accelerates the metabolism of chemotherapy agents such as erlotinib, irinotecan, and paclitaxel, reducing the effectiveness of chemotherapy agents. Therefore, 6 of the patients in our study received quinolone-based antituberculosis therapy at the beginning of the treatment (use of paclitaxel or irinotecan) or during the treatment period (hepatotoxicity) [23].

Limitations

Our study has some limitations, including the small number of patients and its retrospective nature. Power analysis could not be performed in our study due to the small number of patients. However, the population with cancer and TBC coexistence is fortunately small, and when we look at the literature, studies on patients with these two diseases together feature a small number of patients as well. In this respect, we think that our results will contribute to the literature. The second is the inclusion of a single center and the lack of country-wide data such as MDR tuberculosis and treatment response.

Conclusion

Our results show that the combined use of chemotherapy and antituberculosis treatment in patients with cancer and TBC is effective and safe.

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