Current Problems in Cancer 45 (2021) 100643

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Impact of active tuberculosis on treatment decisions in cancer

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A B S T R A C T

Background Tuberculosis (TB) and cancer can coexist in some patients especially from low- and middle-income countries. Impact of active TB on treatment decisions in cancer is less well studied. *Methods* A retrospective case record review of all cases of cancer diagnosed and or treated between January 2012 and December 2019 who were also diagnosed to have active TB (pulmonary or extrapulmonary) was done. *Results* Any delay or change in standard treatment of cancer because of active TB or its treatment was noted. Among a total of 32,509 cancer cases, 56 (0.17%) patients were diagnosed to have active TB. Twenty six patients (46%) had delay in starting treatment or delay during cancer treatment. Six (11%) patients were changed from curative treatment option to palliative intent (either best supportive care or palliative Radiation) or no further treatment. Three (5%) patients required change from one type of curative treatment modality to another curative option. *Conclusion* Eleven percent of patients had to be changed from curative intent to palliative treatment or no further treatment, TB being either the direct or indirect cause in

☆ Conflicts of interest: The authors declare no conflicts of interest

☆☆ Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.currproblcancer.2020.100643

all of them. A nationwide data registry of cancer patients with TB, involving multiple centers, should be considered so that specific problems in this context can be identified and addressed in larger details.

ARTICLE INFO

Keywords: Tuberculosis; Cancer; Treatment

Introduction

Tuberculosis (TB) is a major public health problem affecting one-fourth of the global population.[1] As per the 2019 World Health Organization (WHO) report, globally an estimated 10 million(range 9-11 million) population got affected with TB in 2018 and it is one of the top 10 causes of death worldwide with an estimated 1.2 million deaths. India is considered one among the high TB burden countries accounting for 27% of all global cases.[2] Cancer is yet another bigger global health problem being the second leading cause of death with an estimated 9.6 million deaths related to cancer in 2018. Nearly 70% of the deaths from cancer occur in low- and middle-income countries.[3]

Given that individually each of these diseases poses significant threats to health and life, data on the effect of one disease over the other in patients who have both diseases together are scarce. In a report by Shu et al, there was a definite increase in annual incidence rate of TB in patients with malignancy and the 12-month mortality in cancer patients during active TB was 20%.[4] Japanese group has published on the feasibility of concurrent administration of chemotherapy and anti-TB treatment (ATT) in patients with malignancy having active TB.[5,6] A single-center study from Eastern India has reported on the economic aspects of co-existence of TB and cancer.[7] Another Indian study, published only in abstract form, detailed about the clinical characteristics of newly diagnosed TB in cancer patients.[8] However, there is significant paucity of data on the impact of active TB on decisions in cancer treatment and outcomes. Hence, this study was conducted to find out, to what extent, the diagnosis of active TB affects the treatment decisions in cancer.

Methods

A retrospective case record review of all cases of cancer diagnosed and or treated between January 2012 and December 2019 who were also diagnosed to have active TB (pulmonary or extrapulmonary) was done. An official approval from the Institutional Review Board was obtained before the start of the study.

Pulmonary TB diagnosis was made by demonstration of acid fast bacilli (AFB) by Ziehl Neelsen staining from respiratory secretions, cartridge-based nucleic acid amplification test (CBNAAT), clinical features like presence of cough, fever, or by presence of classic imaging findings. Extrapulmonary TB diagnosis was confirmed by presence of classical TB granuloma on histopathologic examination, CBNAAT, or by response to ATT. All newly diagnosed cancer cases were discussed in the multispeciality board before commencing on treatment. As per institutional policy, if any patient is diagnosed to have active TB before initiation of or during anticancer treatment, ATT is started immediately and cancer-directed treatment is kept on hold for a period of 2 weeks. This is based on the general consensus that patients with active TB will rapidly become noninfectious up on initiation of ATT,[9] and because of the concern that the immune suppression from cancer treatment can worsen TB.

Table 1
Baseline characteristics (N = 56).

		Number	Percentage
Age			
	Median	55	
	Range	11-78	
Sex			
	M	32	57
	F	24	43
Type of cancer			
	Solid tumor	34	61
	Hematologic	22	39
Stage (n = 39)			
	Limited	11	28
	Advanced	28	72
ECOG PS			
	1	49	87
	2	5	9
	3	2	4

ECOG PS, Eastern Cooperative Oncology Group Performance Status; M, male; F, female.

In addition to demographics, type of TB (pulmonary/extrapulmonary) and any delay or change in standard treatment of cancer were noted. Delay in treatment was defined as delay in initiating planned treatment due to active TB or delay occurring during the planned treatment due to newly detected active TB. Change in modality of planned curative cancer treatment, for example, change from Chemotherapy (CT) to Surgery, Chemotherapy to Radiotherapy (RT), or Surgery to Radiotherapy etc. was documented. Any decision to change the treatment from curative intent to palliative treatment or no further treatment because of active TB was also noted. Data on staging details of cancers like solid tumors and lymphomas, where proper staging systems can be applied, were collected as “limited” and “advanced” stages. For other types of hematologic malignancies like acute leukemia, staging details were mentioned as “not applicable.”

Descriptive statistics were used for frequency and percentages. For comparing continuous variables between groups, either Student *t* test (if parametric distribution) or Mann-Whitney U test (nonparametric distribution) was used. For categorical variables comparison, Fisher’s exact test was used. Data were analyzed using SPSS Statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL).

Results

A total of 32,509 cases of cancer were diagnosed during the period of January 2012 to December 2019. Solid tumors constituted 29,011 (89%) cases and the remaining 3498 (11%) were hematologic cancers. Among this, 56 patients (0.17%) were diagnosed to have active TB. Only these patients were considered for further analysis. Fifteen (27%) patients were diagnosed to have TB at the time of cancer diagnostic evaluation and 41 (73%) developed TB during treatment of cancer. AFB positivity was present in 42 cases, classical TB granuloma by histopathology was detected in 14 cases and CBNAAT was positive in 8 cases. Only 1 (1.8%) patient had a past history of TB.

Median age was 55 years (range 11-78). More than half (57%) of the patients were males. Other baseline characteristics were as shown in Table 1. Thirty four patients (61%) were having solid tumors and the remaining were of hematologic malignancies. Among 39 patients with staging details available/applicable, 28 (72%) had advanced disease. Twenty three (41%) patients had comorbidities. Most common comorbidity was hypertension in 13(23%) patients followed by diabetes in 10 (18%) patients.

Table 2
Distribution of malignancy types.

Solid tumors (n = 34) Site	Number	Percentage
Breast	8	24
Lung	6	17
Thyroid	2	5.8
Prostate	2	5.8
Larynx	2	5.8
Tongue	2	5.8
Hypopharynx	2	5.8
Buccal mucosa	1	3
GBM	1	3
Skin SCC	1	3
Esophagus	1	3
Endometrium	1	3
Unknown primary	1	3
Alveolus	1	3
Osteosarcoma	1	3
Rectum	1	3
Cervix	1	3
Hematologic malignancies (n = 22)		
HL	5	23
AML	5	23
NHL	4	18
ALL	3	13.5
MM	2	9
PCL	1	4.5
PV	1	4.5
CML	1	4.5

GBM, glioblastoma multiforme; SCC, squamous cell carcinoma; HL, Hodgkins lymphoma; AML, acute myeloid leukemia; NHL, non-Hodgkins lymphoma; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; PCL, plasma cell leukemia; PV, polycythemia vera; CML, chronic myeloid leukemia.

Most common solid tumor type was carcinoma breast in 8 (24%) patients. Most common hematologic malignancy type was Hodgkin's lymphoma (HL) and acute myeloid leukemia (AML) in 5 patients each (23%). Distribution of the cases was as shown in Table 2. Other than median age (60 vs 45, $P = 0.01$) and percent of curative intent treatment (80% vs 100%, $P = 0.03$), there was no significant difference in characteristics between solid tumors and hematologic malignancies (Table 3).

Intent of treatment was curative in 49 (88%) of total 56 patients. Six (11%) patients were changed from curative treatment option to palliative intent or no further treatment. Clinical details of those patients are given in Table 4. Patient number 4, case of carcinoma buccal mucosa, was planned for radical surgery. As he was detected to have pulmonary TB on CT scan done for staging work up, ATT was started. However, the patient had progressed to an inoperable state after 3 weeks of ATT, so was given palliative RT alone. Patient number 5, case of tongue cancer, developed miliary TB while receiving therapeutic RT. Hence RT was withheld and ATT was started. However, the patient followed up only after 4 weeks, so RT was not continued because of the long break. Patient number 6, case of AML, developed recurrent pneumonia probably from sequela of TB. Hence further chemotherapy could not be continued. All of these 6 patients died, 4 from disease progression and 2 from progressive interstitial pneumonia.

Twenty six patients (46%) had delay in starting treatment or delay during cancer treatment (Table 5). Data on median delay in starting treatment were not complete and hence not included. Eighteen (32%) patients had interruptions in cancer treatment due to TB or ATT. Four (7%) patients had to be changed to best supportive care from a planned palliative intent CT or RT. Three (5%) patients required change from one type of curative treatment modality to another curative option (Surgery changed to RT for 1 patient, RT to targeted hormones in 1, and

Table 3
Comparison of characteristics between solid and hematologic malignancies.

		Solid (n = 34)	Percent	Hemat (n = 22)	Percent	*P* value
Age						
	Median	60		45		**0.012**
Sex						
	M	17	50	15	68	0.269
	F	17	50	7	32	
ECOG PS						
	1	31	91	18	82	0.569
	2	2	6	3	14	
	3	1	3	1	4	
Comorbidity		14	41	9	41	1.0
Rx intent						
	Curative	27	79	22	100	**0.035**
	Palliative	7	21	0	0	
Rx delay		17	50	9	41	0.589
Rx interruption		12	35	6	27	0.573
ATT interruption		4	12	4	18	NA
TB type						
	Pulmonary	26	76	18	82	0.746
	Extrapulmonary	8	24	4	18	

M, male; F, female; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Rx, treatment; TB, tuberculosis; ATT, anti-TB treatment.
Bold values indicate statistical significance.

neoadjuvant CT to Surgery in third patient). ATT had to be interrupted in 8 (14%) patients either because of toxicity or for avoiding drug interactions with chemotherapy.

Discussion

Significant complexity in treatment decisions can arise when both cancer and TB co-exist in the same patient. In our cohort, 46% patients either had delay in starting treatment or delay during cancer treatment. Reported literature in this regard looking for the effect of active TB or its treatment on decisions in cancer treatment is scarce. Hirashima et al had reported on the outcomes of concurrent cancer chemotherapy and ATT and concluded that it can be safe and efficacious.[5] However, the paper studied aspects related only to chemotherapy and not any other modalities of cancer treatment such as RT or surgery. There was an unavoidable delay in starting cancer chemotherapy as the authors mentioned that chemotherapy was initiated either as per the standard guidelines (1.5 months after starting ATT)[10] or only after obtaining the culture and sensitivity reports to rule out drug-resistant TB. In another similar study involving patients with colorectal cancer alone, response rates to first-line chemotherapy was less (28.6% Vs 43.5%) in patients with mycobacterial infection as some of the planned drugs (Bevacizumab) could not be delivered due to active hemoptysis from TB cavity in lungs.[6] Median time from ATT start to first line chemotherapy was 53 days (range 16-408) in the same study pointing toward significant delay in initiating anticancer treatment.

It is clear that delay or interruption of treatment will affect the final outcome in cancers. A study based on the US National Cancer Database reported that longer time to initial treatment (day from diagnosis to first treatment) was associated with worse survival in early stage breast, lung, colorectal, pancreas, and renal cancers.[11] Similarly longer time to surgery after diagnosis was associated with inferior survival in breast and endometrial cancers.[12,13] Delay in initiation of postoperative radiation led to increase in local recurrence rate in breast and head and neck cancers.[14] Similar studies in various solid tumors have shown that delay in treatment initiation is associated with inferior survival.[15-18] Delay in initiation of treatment leading to inferior survival has also been reported in younger AML patients.[19]

Table 4
Clinical details of patients who were changed from curative intent treatment to palliative intent or no further treatment.

	Diagnosis	Rx received /planned	Clinical event	TB diagnosis	Rx plan changes	Outcome/comments	Died	Cause of death
Pt 1	HL	CT 5 cycles	IP	AFB in BAL	CT D/C	Progressive IP despite ATT / Rx for IP	Yes	Progressive IP
Pt 2	Breast Ca	CT 3 cycles	IP	AFB in BAL	CT D/C	Partial improvement in lung function	Yes	Disease progression
Pt 3	Breast Ca	CT 4 cycles	IP	AFB in BAL	CT D/C	Progressive IP despite ATT/ Rx for IP	Yes	Progressive IP
Pt 4	Buccal mucosa Ca	Surgery	PTB in staging CT	AFB in BAL	Surgery changed to pall RT	Disease progression while on ATT for 3 weeks -inoperable	Yes	Disease progression
Pt 5	Tongue Ca	RT	Miliary TB while on RT	AFB in sputum	RT D/C	Patient reported back only after 4 weeks of ATT	Yes	Disease progression
Pt 6	AML	HMA induction	PTB after 2nd cycle	AFB in sputum	CT D/C	Recurrent pneumonia	Yes	Disease progression

Pt, patient; Rx, treatment; HL, Hodgkins lymphoma; Ca, carcinoma; AML, acute myeloid leukemia; CT, chemotherapy; D/C, discontinued; RT, radiotherapy; HMA, hypomethylating agent; IP, interstitial pneumonitis; PTB, pulmonary TB; CT, computed tomography scan; AFB, acid fast bacilli; BAL, broncho alveloar lavage; ATT, anti-TB treatment.

Table 5
Details of anticancer treatment alterations due to TB.

		Number	Percentage
Rx intent at baseline			
	Curative	49	88
	Palliative	7	12
Delay in Rx		26	46
Rx interruption		18	32
Change in modality of Rx		3	5
Curative to pall Rx		6	11
ATT interruption		8	14

TB, tuberculosis; Rx, treatment; ATT, anti-TB treatment.

Around one-tenth of patients in our study group had to be deviated from curative cancer treatment intent to palliative options or no further treatment, TB being either the direct or indirect cause in all of them. In general, cancer patients with poor performance status from significant comorbidities are not candidates for curative intent treatment.[20-22] It is well known that patients treated with curative intent will have better survival than patients treated with palliative intent. This has been proven even in some advanced malignancies.[23,24] Had those 11% patients not developed TB, their treatment outcome would have been better if at all not cure for all. Thus even though the overall number of TB cases was on the lower side, the final impact of it on those cancer outcomes is on the higher side.

This study, even with limitations in the form of single-center data, lack of information on median delay in initiating cancer treatment and retrospective one, throws light on the impact of TB on decisions in cancer treatment. Since 11% patients could not receive or complete curative intent treatment because of TB-related issues, further measures to identify presumptive TB cases and to implement rapid diagnostic modalities of TB among cancer cases should be promoted. In the light of our findings, we would like to propose a nationwide data registry of cancer patients with TB, involving multiple centers, so that specific problems in this context can be identified and addressed in larger details.

Acknowledgment

The authors thank Dr Aswathi Nambiar and Dr Anjali VG in helping for data collection.

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