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C O N T E N T S

Impact of diabetes on cancer chemotherapy outcome: A retrospective analysis

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BACKGROUND: Diabetes mellitus (DM) and cancer are common causes of morbidity and mortality. This study was designed to retrospectively study from hospital data the treatment outcome in three common cancers among our diabetic population. **METHODOLOGY:** Patients with histologically-proven breast, lung, or colorectal cancers were analyzed. Patients were stratified into those with or without diabetes. Duration of diabetes, end-organ damage and glycemic control were recorded from the case records. "Response Evaluation Criteria In Solid Tumors" (RECIST) criteria were used to assess response. Common Toxicity Criteria, version 3.0, was used to assess toxicity. Disease-free and overall survival, as well as toxicity, were calculated for both groups and compared using the Student's *t* test. **RESULTS:** A total of 119 diabetic patients who presented to the department of medical oncology over a 6-year period between 2000 and 2005, and who met the inclusion criteria, were analyzed. One control was chosen for each case randomly from the same population. Both groups were matched for baseline characteristics. The mean duration of diabetes was 2.6 years in the present study. Diabetics have significantly lower response rates and poor overall and disease-free survival. The toxicity profile is not different in both the groups. **CONCLUSION:** Our data supports the concept that DM is associated with an increase in mortality and poor response rates. This mechanism is probably independent of the glycemic control, comorbid conditions, or the treatment modality used for control of diabetics. We did not find any significant increase in the complication rates in our diabetic patients. The possible reason for this clinical paradox could be the relatively good glycemic control: all the diabetics in the present study have near-normal blood sugar levels throughout.

KEY WORDS: Cancer chemotherapy, diabetes

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Introduction

Diabetes mellitus (DM) and cancer are among the common causes of morbidity and mortality globally, irrespective of the ethnicity. The interaction between these two common diseases is quite complex and variable. A recent review mentioned that only few studies have directly addressed the relationship between the two or the impact of diabetes on cancer outcomes.[1] In such studies, the major finding is an increased risk for development of cancer among diabetics (particularly malignancies of the pancreas, colon, liver, endometrium, and breast in type 2 DM and cervical and stomach cancers in type 1 DM).[1] The hypothetical pathophysiological mechanisms of carcinogenesis include insulin resistance and hyperinsulinemia or aberrant growth hormone stimulating growth factor receptors or hyperglycemia leading to abnormal growth regulation.[2-4] In type 1 DM, immunological mechanisms, like immune tolerance may produce cervical and stomach cancers.

Besides its role in the carcinogenesis, DM will affect management strategies also, as the patients are prone to have comorbid conditions (e.g., renal insufficiency, cardiomyopathy, and neuropathy) that might compromise the dose and schedule of the therapy, thereby reducing cure rates. Various prospective cohort studies have shown that adults with DM have a greater risk of cancer development and mortality compared to those without diabetes.[5-14] In one of the recent reviews, the authors could not find any study that addressed how diabetes uniquely affects clinical decision making in the cancer patient. Some of the recent data indicate that hyperglycemic patients have a poor cancer-related survival compared to their euglycemic counterparts. However the major criticisms in those trials relate to improper balance of the confounding prognostic markers;[12] lack of details regarding the cancer-specific

mortality;[11] a subset of patients not completing the therapy as planned, owing to the comorbid conditions; lack of uniformity in the treatment protocols; lack of data on the glycemic control during, before and after therapy; duration of DM; and the amount of end-organ damage present.

Therefore, we decided to do this retrospective analysis of hospital data to address these issues.

Methodology

This is a retrospective analysis of case records at Kidwai Memorial Institute of Oncology (KMIO), Bangalore, a tertiary care cancer center, with an annual attendance of 15,000 new cases. Patients with histologically-proven breast, lung, or colorectal cancers were analyzed. Patients were stratified into those with and without diabetes. Duration of diabetes, end-organ damage, and the glycemic control were recorded from the case records. RECIST criteria were used to assess response. Common Toxicity Criteria, version 3.0 was used to assess toxicity.

Inclusion criteria

1. Age >21 years
2. Patient willing to give informed consent for using their data
3. ECOG performance status of <2
4. Histologically-proven malignancy
5. Presence of at least one measurable lesion by RESICT criteria
6. Adequate renal and hepatic function and bone marrow reserves to allow chemotherapy
7. Must have completed chemotherapy as planned
8. In diabetics, the end-organ damage should not be such that the management plan is compromised
9. Patients with regular and adequate follow-up

According to the type of cancer, further inclusion criteria were as follows:

Breast

Subset 1

- All female patients with breast cancer
- ER/PR negative
- Had received anthracycline in neoadjuvant/adjuvant setting
- Progressed within 3 years of initial diagnosis.
- Visceral metastasis alone (patients with local recurrences were excluded as survival in that subset is better and because we could not match cases and controls)

Subset 2

- Female patients diagnosed as metastatic breast cancer at presentation
- ER/PR negative
- Did not receive any chemotherapy
- Visceral metastasis

Lung

- All patients had non-small-cell lung cancer
- Stage III B/IV
- chemo-naïve
- Nonsmokers

Colorectal

- Patients with visceral metastasis
- Previously untreated with 5-FU

Exclusion criteria

- Those not meeting the above criteria
- Patients having received more than one chemotherapy for the same malignancy (as the survival is different in that subset of patients)
- Patients where the cause of death is not cancer related
- Patients with poor glycemic control in the recent past or during the therapy.
- Pregnant and lactating women
- Serious coexisting comorbid conditions

Treatment received

Breast cancer: All patients in subset 1 received Paclitaxel (175 mg/m^2 × 3 weekly) for a minimum of 6 courses or till disease progression, whichever was earlier. In subset 2, all the patients received adriamycin/60 mg/m^2, 5FU 600 mg/m^2, and cyclophosphamide 600 mg/m^2, given 3 weekly for a minimum of 6 courses or till disease progression, whichever was earlier.

Lung cancer: All patients received gemcitabine (1250 mg/m^2 on day 1 and 8) and carboplatin (AUC - 6) given at 3 weekly intervals for a minimum of 4 courses or till disease progression, whichever was earlier.

Colon cancer: Patients received leucovarin (20 mg/m^2) - given as a bolus injection prior to the 5FU - and 5FU (425 mg/m^2 day 1-5) every 4 weeks according to the Mayo protocol. All patients received a minimum of 6 courses or till disease progression, whichever was earlier.

Study endpoints

Eligible patients were assessed for the

- Overall survival (OS): Defined as time from the study entry to the death of the patient (expressed in weeks)
- Time to tumor progression (TTP): defined as time from the entry into the study to the tumor progression (expressed in weeks)
- Response rates (complete and partial) (expressed in percentage)

Statistical analysis

Medcalc, version 7.5 for Windows, was used for the analysis. Means and standard deviations for all the study variables were generated. They were compared using Student's *t* test. The percentages were also compared in a similar way.

Results

A total of 119 diabetic patients who met the inclusion criteria, presenting to the Department of Medical Oncology over a 6-year period between 2000 and 2005, were analyzed. One control was chosen for each case randomly from the same population (i.e., those without diabetes but having similar characteristics, who underwent treatment in the same period of time). Both groups were matched for baseline characteristics. The mean duration of diabetes was 2.6 years in the present study. All the patients have a proper glycemic control and those without adequate glycemic control were excluded from the analysis. Intent-to-treat analysis was used for evaluating the OS and TTP. The details of each subset were represented in Tables 1-5.

Discussion

The reviews regarding the relation of diabetes with cancer suggested a significant increase in the overall mortality among diabetics after adjusting for the age, sex and tumor size.[1] However as discussed above, there are major drawbacks in the majority of those studies. Therefore we did a retrospective data analysis of hospital data after balancing all known confounding factors in three common cancers (viz, breast, colon and lung) to check whether diabetics have different response rates or survival. We found a significant decrease in the TTP and lower response rates as compared to the nondiabetics. Single institutional data in a retrospective analysis has the advantage of uniform treatment modality (according to the institutional standards), detailed information on all the prognostic variables, and uniformity in the selection criteria.

Breast

Up to 16% of patients with breast cancer have diabetes. Preclinical and clinical data suggest complex associations between diabetes, especially type 2 diabetes and breast

Table 1: Details of the breast cancer patients - subset 1

Patient characters	No diabetes	Diabetes	*P** (95% CI for *t* test)
Number of patients	57	57	ND
Age (mean ± SD)	42.8 ± 12.8	44.8 ± 13.6	NS
Stage	100% stage IV	100% stage IV	NS
Interval from initial diagnosis	1.8 ± 0.5	2.1 ± 0.6	NS
Grade of tumor			
I	0	0	NS
II	33%	25%	NS
III	67%	75%	NS
ECOG			
0	10%	15%	NS
1	25%	20%	NS
2	65%	65%	NS
CR	17 (30%)	13 (23%)	ND
PR	33 (59%)	25 (44%)	ND
RR	50 (89%)	38 (67%)	0.4
TTP (weeks) (mean ± SD)	23 ± 10	16 ± 7	0.02 (3.8 to 10.2)
Toxicity grade III/IV	59%	67%	NS
OS (weeks) (mean ± SD)	32 ± 10	28 ± 9	0.03 (0.5 to 7.5)

*Values are shown wherever they are significant

Table 2: Details of the breast cancer patients - subset 2

Patient characters	No diabetes	Diabetes	*P** (95% CI for *t* test)
Number of patients	20	20	ND
Age (mean ± SD)	66.8 ± 15.8	68.9 ± 17.8	NS
Stage	100% stage IV	100% stage IV	NS
Interval from initial diagnosis	2.2 ± 0.7	2.6 ± 0.9	NS
Grade of tumor			
I	25%	30%	NS
II	20%	25%	NS
III	55%	45%	NS
ECOG			
0	30%	25%	NS
1	45%	40%	NS
2	25%	35%	NS
CR	2 (10%)	4 (20%)	ND
PR	15 (75%)	14 (70%)	ND
RR	17 (85%)	18 (90%)	NS (0.8)
TTP (weeks) (mean ± SD)	25 ± 8	20 ± 6	0.03 (0.5 to 9.5)
Toxicity grade III/IV	70%	75%	NS
OS (weeks) (mean ± SD)	39 ± 14	22 ± 13	0.003 (8.4 to 25.6)

*Values are shown wherever they are significant

Table 3: Details of the patients with lung cancer

Patient characteristics	No diabetes	Diabetes	*P** (95% CI for *t* test)
Number of patients	22	22	ND
Age (mean ± SD)	54.6 ± 14.8	56.8 ± 18.2	NS
Stage			
IIIB	36%	32%	NS
IV	64%	68%	NS
Duration of symptoms (months)	4.8 ± 2.5	4.1 ± 2.6	NS
Smokers	68%	73%	NS
Nonsmokers	32%	27%	NS
ECOG			
0	18%	32%	NS
1	23%	27%	NS
2	59%	41%	NS
CR	2 (9%)	1(5%)	ND
PR	16 (73%)	14 (64%)	ND
RR	18 (82%)	15 (69%)	NS (0.4)
TTP (weeks) (mean ± SD)	24 ± 8	19 ± 6	0.02 (0.7 to 9.3)
Toxicity grade III/IV	56%	63%	NS
OS (weeks) (mean ± SD)	29 ± 7	18 ± 5	0.001 (7.3 to 14.7)

*Values are shown wherever they are significant

cancer. Three mechanisms have been postulated for the association between diabetes and breast cancer[15]: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and regulation of endogenous sex hormones.

As the main focus of this observational study is to find out the effect of diabetes on the treatment outcome, we did not try to prove or disprove the pathophysiological mechanisms discussed above. The outcome in diabetics with breast cancer are difficult to compare with that in nondiabetics, mainly because of the presence of confounding factors such as obesity, old age, and comorbidity which, in turn, will determine the treatment allocation that might contribute to the low survival.[15-17] However, most studies on the effects of diabetes on breast cancer outcome did not control for these factors.

Table 4: Details of the patients with colorectal cancer

Patient characteristics	Diabetes	No diabetes	*P** (95% CI for *t* test)
Number of patients	20	20	ND
Age (mean ± SD)	38.6 ± 12.8	42.8 ± 13.6	NS
Stage	All stage IV	All stage IV	NS
Interval from initial diagnosis	2.4 ± 0.8	2.1 ± 0.6	NS
Grade of tumor			
II	40%	45%	NS
III	60%	55%	NS
ECOG			NS
0	5%	10%	NS
1	15%	25%	NS
2	80%	65%	NS
CR	1 (5%)	4 (20%)	ND
PR	12 (60%)	11 (55%)	ND
RR	13 (65%)	15 (75%)	0.9
TTP (weeks) (mean ± SD)	34 ± 12	26 ± 11	0.03 (0.6 to 15.4)
Toxicity grade III/IV	55%	60%	NS
OS (weeks) (mean ± SD)	43 ± 13	34 ± 12	0.03 (1 to 17)

*Values are shown wherever they are significant

Table 5: Major studies focusing on breast cancer and diabetes

Author	No. of patients	End points	Conclusion	Comments
Satariano 1994[18]	936	OS	Comorbidity was associated with higher mortality, even after control for variables such as age, stage, and grade	Treatment received is not uniform
Yancik[19]	1800	OS	An enhanced all-cause mortality in patients with diabetes	About 50% causes of death were not cancer-related but could be affected by diabetes (e.g., heart disease)
Fleming[20]	848	OS	No increase in mortality	No comments on RR/uniformity of treatment protocol
Unterberg[21]	176	DFS	Positive correlation between diabetes and development of metastatic disease	Adjustment for other prognostic factors or treatment methods was done
Lancet[15]	237		Diabetes present with breast cancer at a more advanced stage	

The summary of few important trials addressing this problem is tabulated below.

In the present study, we found a significant decrease in the TTP and OS in both the subsets of patients after matching for all the prognostic variables. We deliberately avoided ER/PR-positive patients as the biological interaction of the insulin and hormone receptors is quite complex and choosing a control group is difficult. Subset 1 behaved worse than subset 2, as the former patients are chemo-naïve and are known to have better prognosis and the later group had aggressive disease (represented by relapse within 3 years). However, the complication rates in the present study were similar in both the groups (diabetics *vs.* nondiabetics).

Chemotherapy-related toxicity and diabetes

Several prospective studies have addressed this issue.[11,22,23] In a prospective trial of ALL patients treated with hyper-CVAD, the authors found that patients with hyperglycemia were more likely to have infections leading to sepsis and severe complications.[22] Similarly, in head and neck cancers, where patients were treated with cisplatin, 5-fluorouracil, leucovorin and alpha-interferon, the authors observed an increased fatal toxicity in diabetics. In another retrospective analysis, diabetic patients enrolled in an adjuvant chemotherapy clinical trial for colon cancer experienced a higher incidence of diarrhea compared with patients without diabetes.[11] Finally, in a retrospective study of data from adjuvant breast cancer clinical trials using prednisone, approximately 2.4% of the women

developed severe or life-threatening hyperglycemia, which led to the death of two study participants.[24] The different chemotherapeutic drugs used in the present study were very similar to those used in the above mentioned studies; however, we did not find any significant increase in the complication rates in our patients. The possible reason for this clinical paradox could be because of the better glycemic control in the present study (all the diabetics have near-normal blood glucose levels in the present study throughout). The second reason could be the small sample size compared to the previous trials. Therefore, we conclude that in the absence of associated comorbid conditions, diabetics under good glycemic control are at equal risk of complications compared to nondiabetics.

Colon

Review of the literature showed a single study in colon cancer addressing the effect of diabetes. Meyerhardt and co-workers[11] analyzed data from a large randomized controlled trial of adjuvant chemotherapy in colon cancer and showed that diabetes had direct adverse effects on recurrence and mortality for patients. These findings remained significant even after control for disease manifestations and treatment allocation. However the main criticism for that study was that there was no mention of cancer-specific mortality and the disproportion between cases (diabetics) and controls (nondiabetics). The present study (though it contains only a very small number of patients) suggests a significant increase in mortality and short TTP for the patients who are diabetics.

Lung

The high percentage of patients expressing elevated levels of various growth factors like EGFR and VEGFR which can, in turn, be stimulated by insulin and IGF supports our hypothesis that diabetics will probably have a poorer response to chemotherapy and have early relapses. We were unable to find any study addressing the problem of diabetes in lung cancer. However, the present study results indicate that the behavior of lung cancer is not very much different from that of the other two cancers.

Confounders - hyperglycemia and end-organ damage

The possibility of the increased mortality being due to concurrent adverse health conditions or severe hyperglycemia was ruled out with reasonable confidence on the basis of the following observations:

- No differences in the performance status between diabetics and nondiabetics.
- None of our diabetics had significant comorbid conditions that might explain the poorer survival.
- All the diabetics had an adequate control of their blood glucose during the treatment course as well as overall glycemic control, as indicated by their glycosylated hemoglobin levels.
- All our diabetics had low response rates and shorter TTP (earlier and more tumor recurrences), thereby indirectly indicating that the mortality was due to disease progression.

To summarize, our data support the concept that DM is associated with an increase in mortality and poor response rates. This mechanism is probably independent of the glycemic control or comorbid conditions. The probable increased risk of recurrence might be a result of some underlying mechanisms that occurred before or during the carcinogenesis. However, in contrast to the previous reports, our population tolerated chemotherapy reasonably well, without any significant increase in the toxicity rates. Therefore, if there are no comorbid conditions, individuals with diabetes should be treated with the same standard protocols that are followed for nondiabetics. However, despite the standard care the response rates are inferior in diabetics.

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