Original Research Article

Chemotherapy Induced Eosinophilia and its Significance among the Cancer Patients Treated at a Tertiary Care Teaching Hospital, West Bengal

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Abstract

Background: Cancer is a major burden and threat to global society. It is one of the leading causes of death in both developed and developing countries. The main modalities used for its treatment include surgery, radiation, chemotherapy, immunotherapy, and hormones.

Materials & Methods: The current study was performed to find incidence of chemotherapy induced eosinopillia in patients with different cancers who were receiving standard chemotherapy regimens (minimum two cycles and maximum six to eight cycles). Total leucocyte count, absolute eosinophil count and differential leucocyte count was done just before starting of chemotherapy. Differential leucocyte count (DLC) was reported after 1st cycle of chemotherapy agents, before last dose of chemotherapy, after 6 weeks of completion of chemotherapy, and after six month of completion of chemotherapy to see the changes on eosinophil counts.

Results: Most commonly used anticancer agents were 5 FU 61 (61%), doxorubicin 43 (43%), cyclophosphomide 53 (53%), cisplatin 10 (10%), paclitaxel 20 (20%), carboplatin 25 (25%), gemcitabine 11 (11%), oxaliplatin 14 (14%) and capecitabine 11 (11%). The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 1st dose had a mean of 5.06 (range, 3 to 8) ($p < 0.0001$). The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 6 months of chemotherapy had a mean of 6.85 (range, 5 to 8) ($p < 0.0001$). Increased eosinophil count after 1st dose and 6 months completion of chemotherapy was highly significant from baseline values ($P < 0.0001$).

Conclusion: Study has generated a hypothesis that administration of many anticancer agents may increase eosinophil count or peripheral eosinophilia. Additional large scale prospective studies must be performed to confirm our results.

Keywords: Cancer chemotherapy, chemotherapy induced eosinophilia, drug reaction with eosinophilia and systemic symptoms (DRESS), West Bengal

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Introduction

Eosinophils are predominantly tissue dwelling cells and express a specific chemo-attractant receptor and respond to a specific chemokine, eotaxin. They are moderately effective as a phagocyte for bacteria, yeast and protozoa but less effective than neutrophils.[1] The major function of eosinophil as a cytotoxic cell is against helminthic infections. Eosinophils can kill a wide variety of helminthic worms especially in their larval stages, by depositing cationic proteins on the surface of the parasite.[2] Conventionally eosinophils have been considered as an end-stage cells involved in host protection against parasites. Numerous lines of evidence however have now changed this perspective by showing that eosinophils are pleiotropic multifunctional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity.[1]

As a key player of the immune system eosinophils play an important role in combating parasitic infections in vertebrates and potentially cancer cells. Eosinophils secreted chemokines and other cellular mediators participate in immunomodulation and tissue remodeling. Study published in the Journal of Clinical Oncology examined the relationship between eosinophils in peripheral blood and the incidence of colorectal cancer.[3] The researchers found that a higher number of peripheral blood eosinophils were associated with a reduced risk of dying from colorectal cancer, especially in patients who never smoked and in males.[4]

Chemotherapy has dramatically changed the outcome of cancer patients. Despite this success, word of caution regarding toxicities of antineoplastic drugs deserves highlighting. It is vital to recognize these toxicities. Drug hypersensitivity should always be considered as a cause for unexplained eosinophilia. The list of agents is extensive and includes dietary supplements and herbal remedies.[5] The clinical manifestations associated with drug-induced eosinophilia range from asymptomatic to life-threatening.[5] Rarely a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) occurs 3-6 weeks after the introduction of a new drug. This syndrome is characterised by a triad of a skin eruption, fever and internal organ involvement (lung, liver, kidneys, lymph nodes or heart).[6, 7] Drug-induced vasculitis and eosinophilia is also reported, manifesting with purpura, arthralgia and myalgia with possible kidney and lung involvement.[8]

The approach to the identifying the cause of marked, persistent eosinophilia after cancer chemotherapy is a challenging problem. Excluding many causes of marked peripheral blood eosinophiliais required for making the diagnosis of cancer chemotherapy induced eosinophilia.

We hypothesized that drug-induced blood eosinophilia, probably underreported, could be a biological sign of hypersensitivity reaction, and could also predict severe delayed visceral hypersensitivity reactions. Keeping this in view, the present study will be undertaken to find out the incidence of chemotherapy induced eosinophilia, impact on absolute eosinophil count before and after cancer chemotherapy and the causality assessment for estimating the strength of relationship between drug(s) exposure and occurrence of eosinophilia inpatients admitted in Bankura Sammilani Medical College and Hospital.

Materials & Methods

A hospital OPD based prospective observational study was done Dec 2018– Nov 2019 in the Department of Chemotherapy and Department of Pathology. Approx 100 or more cases of cancer patients under cancer chemotherapy on day care basis were collected by simple random sampling procedure. There was variation in the inflow of cancer patients in Chemotherapy OPD at Bankura Sammilani Medical College and hospital. Moreover only day care basis cancer chemotherapy had been provided to cancer patients. So we had fixed 100 patients for logistic reasons.

Inclusion Criteria: The study was aimed to conduct among the patients who are seeking treatment in the chemotherapy department and on day care basis cancer chemotherapy with those who understood the purpose of the study and are ready to provide information regarding their health status and those who signed an informed consent document. Patient who have no prior eosinphilia during treatment seeking or have no prior hematological

malignanicies or have no blood dyscrasis or parasitic infestations will be included.

Exclusion criteria:

1. Under 18 years of age
2. Contraindication to cancer chemotherapy etc.
3. Patient who have prior eosinphilia during treatment seeking or have prior hematological malignanicies or have blood dyscrasis or parasitic infestations
4. Any condition resulting in severe learning disability (e.g. brain injury) or
5. Those unable to comprehend for other reasons will be excluded from the study.

The current study was performed to find incidence of chemotherapy induced eosinopillia in patients with different cancers who were receiving standard chemotherapy regimens (minimum two cycles and maximum six to eight cycles). Blood samples were collected aseptically from each of the 100 patients' pre cancer chemotherapy and after each chemotherapy cycle. Total leucocyte count, absolute eosinophil count and differential leucocyte count was done just before starting of chemotherapy. Differential leucocyte count (DLC) was reported after 1st cycle of chemotherapy agents, before last dose of chemotherapy, after 6 weeks of completion of chemotherapy, and after six month of completion of chemotherapy to see the changes on eosinophil counts. Absolute eosinophil count was also done after completion of cancer chemotherapy. Initially, all patients should have a full blood count performed and a blood film examined. This is to verify the eosinophil count because hypogranular eosinophils may not be counted accurately by automated counters. In patients who are otherwise well with mild to moderate eosinophilia between 0.5 and 1.5x 10^9/l, further testing may not be indicated. Patients with systemic symptoms or those with persistent eosinophilia (at least 1.5x 10^9/l), with or without suspected organ damage, should be considered for additional testing for primary and secondary causes of eosinophilia and for evaluation of organ damage.

Data was compiled in MS Excel, and then was presented as descriptive statistics mean and standard deviation. The statistical analysis was performed using SPSS version 19.0. Analysis of demographic data was done by Chi-square test and a "p-value" of less than 0.05-which was considered statistically significant.

Results

The study was conducted under the purview of Bankura Sammilani Medical College and hospital, a tertiary care hospital in Bankura District, West Bengal in the Department of Chemotherapy and Department of Pathology. About 100 or more cases of cancer patients under cancer chemotherapy on day care basis were collected by simple random sampling procedure.

Table 1: Distribution of different cancer patients under chemotherapy [n=100]

Type of malignancy or cancer	Number of cases	Percentage
CA Breast	40	40%
CA Lung	09	9%
CA Colon	05	5%
CA Gallbladder	07	7%
CA Testis	05	5%
CA Cervix	02	2%
CA Ovary	05	5%
CA Stomach	04	4%
CA Rectum	02	2%
CA Rt. Supraglottic mass	03	3%
CA prostate	02	2%
CA Penis	1	1%
Multiple Myeloma	2	2%
Miscellaneous malignancy	13	13%
Total	100	100%

There were 100 cancer patient's records reviewed at the tertiary care hospital pre and post cancer chemotherapy (CT). Among them 37 (37%) were males and 63 (63%) were females. Mean age of the participants was 49.86 (13.90). Minimum age was 16 and maximum was noted 76 years. Majority of patients fell in the age group of 35-64 years. Male to female ratio was 0.59:1. Cancer breast (40%) was leading site of cancer among participants for chemotherapy followed by cancer lungs (9%), cancer gallbaldder (7%), and cancer colon, cancer testis, cancer ovary (5%)[Table 1].

Table 2: Pattern of anticancer therapies used [n=100]

Anticancer agents	Number of pts prescribed (%)
Injection 5 FU	61 (61%)
Injection Doxorubicin	43 (43%)
Injection Cyclophosphomide	53 (53%)
Injection Cisplatin	10 (10%)
Injection Etoposide	6 (6%)
Injection Bleomycin	6 (6%)
Injection Paclitaxel	20 (20%)
Injection Carboplatin	25 (25%)
Injection Docetaxel	2 (2%)
Injection Gemcitabine	11 (11%)
Injection Oxaliplatin	14 (14%)
Tab. Capecitabine	11 (11%)
Injection Rituximab	2 (2%)
Injection Bendamustine	1 (1%)
Injection Actinomycin D	1 (1%)
Injection Methotrexate	1 (1%)
Injection Epirubicin	3 (3%)
Injection Iminodecan	1 (1%)
Tab. Thalidomide	2 (2%)
Injection Bevacizumab	2 (2%)
Injection Zoledronate	1 (1%)
Injection Leuprolide	1 (1%)
Tab Bicalutamide	1 (1%)
Injectable formulations	20
Tablets or syrup or suspension	03

Most commonly used anticancer agents were 5 FU 61 (61%), doxorubicin 43 (43%), cyclophosphomide 53 (53%), cisplatin 10 (10%), paclitaxel 20 (20%), carboplatin 25 (25%), gemcitabine 11 (11%), oxaliplatin 14 (14%) and capecitabine 11 (11%). Majority cases injectable preparations were administered. Only in 3 patients oral formulations of anticancer agents were administered Majority of the cancer patients had received 3-drugs regimen 75% followed by 2-drugs regimen 13% and 4-drugs regimen 11% [Table 2].

Table 3: TLC values before and after cancer chemotherapy

	TLC before chemotherapy [/cmm]	TLC after chemotherapy [/cmm]
Number of values	100	100
Minimum	6000	3000
25% Percentile	7225	3800
Median	8200	4200
75% Percentile	9175	4700
Maximum	10000	7200
Mean	8172	4311*
Std. Deviation	1096	721.4
Std. Error	109.6	72.14
Lower 95% CI	7954	4168
Upper 95% CI	8390	4454

The blood cell data was evaluated before and after the chemotherapy (CT). The pre-CT leukocyte count had a mean of 8172/uL (range, 6000/uL to 10000/uL) and post-CT leukocyte count had a mean of 4311/uL (range, 3000/uL to 7200/uL) ($p < 0.0001$) (Table 3). There was reduction in the total leukocyte count after completion of cancer chemotherapy ($p < 0.0001$). *P value and statistical significance: the two-tailed P value is less than 0.0001 when compared before and after chemotherapy. By conventional criteria, this difference is considered to be extremely statistically significant. Confidence interval: the mean of Group One minus Group Two equals 3861.000 95% confidence interval of this difference: from 3602.249 to 4119.751 Intermediate values used in calculations: t = 29.4259, df = 198, standard error of difference = 131.211

Table 4: AEC values before and after cancer chemotherapy

	AEC after chemotherapy	AEC before chemotherapy
Number of values	100	100
Minimum	120	126
25% Percentile	190.5	240
Median	218	283
75% Percentile	240	336
Maximum	336	396
Mean	220.02	279.8*
Std. Deviation	43.05	72.19
Std. Error	4.305	7.219
Lower 95% CI	211.5	265.4
Upper 95% CI	228.6	294.1

The blood cell data was evaluated before and after the CT. The pre-CT absolute eosinophil count (AEC) had a mean of 220.02 (range, 120 to 336) and post-CT AEC had a mean of 279.8 (range, 126 to 396)

(p <0.0001) [Table 4]. There was significant increase in the AEC after chemotherapy from baseline level (p <0.0001). P value and statistical significance: The two-tailed P value is less than 0.0001.

Table 5: Eosinophil count before, after 1st chemo dose and after cancer chemotherapy

	Eosinophil before chemo	Eosinophil after 1st dose chemo	Eosinophil after 6 months chemo
Number of values	100	100	100
Minimum	2	3	5
25% Percentile	3	5	6
Median	4	5	7
75% Percentile	4	5	7
Maximum	4	8	8
Mean	3.41	5.06*	6.85**
Std. Deviation	0.8177	0.9516	0.7437
Std. Error	0.08177	0.09516	0.07437
Lower 95% CI	3.248	4.871	6.702
Upper 95% CI	3.572	5.249	6.998

The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 1st dose had a mean of 5.06 (range, 3 to 8) (p <0.0001)*. The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 6 months of chemotherapy had a mean of 6.85 (range, 5 to 8) (p <0.0001)**. Increased eosinophil count after 1st dose and 6 months completion of chemotherapy was highly significant from baseline values (P < 0.0001) [Table 5].

Difference	1.650
Standard error	0.125
95% CI	1.4026 to 1.8974
t-statistic	13.151
DF	198
Significance level	P < 0.0001*
Difference	3.440
Standard error	0.111
95% CI	3.2220 to 3.6580
t-statistic	31.122
DF	198
Significance level	P < 0.0001**

Discussion

In the present study there were 100 cancer patient's records reviewed at the tertiary care hospital pre and post cancer chemotherapy (CT). Among them 37 (37%) were males and 63 (63%) were females. Mean age of the participants was 49.86 (13.90). Minimum age was 16 and maximum was noted 76 years. Majority of patients fell in the age group of 35-64 years. Male to female ratio was 0.59:1. Cancer breast (40%) was leading site of cancer among participants for chemotherapy followed by cancer lungs (9%), cancer gallbaldder (7%), and cancer colon, cancer testis, cancer ovary (5%). There were 4% cases gastric cancers, 3% cases right supraglotic malignant masses, and 2% cases multiple myeloma. About 13% cases there were miscellaneous malignancy like cancer cheek, follicular lymphoma, molar pregnancy, tongue cancer, carcinoma of head pancreas etc.

In Mathew M et al study[9], most of the patients were in the age group of 45–60 years (47%); this was in correspondence with the study carried out by Catic et al.[10], where 48% of patients were in the age group of 45–60 years. However, contradictory findings were also observed in a study conducted by Onwusah and Korubo[11] where 19.6% patients were in the age group of 61–70 years. Out of 230 patients, 51.7% were females and 48.3% were males. The study carried out by Manichavasagam et al. reported that females (54.57%) were predominant than the males (45.42%).[12] The present study is in concurrence with the reference study.

The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 1st dose had a mean of 5.06 (range, 3 to 8) (p <0.0001). The pre-CT eosinophil count had a mean of 3.41 (range, 2 to 4) and post-CT after 6 months of chemotherapy had a mean of 6.85 (range, 5 to 8) (p <0.0001). Increased eosinophil count after 1st dose and 6 months completion of chemotherapy was highly significant from baseline values (P < 0.0001).

To the best of our knowledge, circulating eosinophil counts have been reported by two studies in the literature of breast tumors. Gunduz and colleagues observed a survival benefit for patients with lower baseline eosinophil counts in a cohort of 62 HER2+ breast cancers treated with adjuvant trastuzumab.[13]

Conversely, Ownby and colleagues described a positive association between high baseline eosinophil counts and lower recurrence rates (2-year DFS rate, 21 ± 2% vs 34 ± 8%, $p < 0.02$) in 419 patients of all subtypes.[14] Better known is the impact of peripheral eosinophil count in melanoma patients treated with immunotherapy. Associations linking both high baseline eosinophil counts and increased counts during treatment, with both improved treatment response and increased survival rates, were observed.[15-17] Additionally, one report of an immunotherapy-induced increase in eosinophil count was published for lung cancer patients, but no efficacy data were presented.[18] In Onesti CE et al study, we observed a decrease in circulating lymphocyte numbers after primary treatment without significant variation at relapse. No significant impact on survival for post-surgery RLC was detected. Conversely, we observed an increase in circulating eosinophil number after surgery and a significant reduction at relapse.[19]

C.S. Spina et al study[19] hypothesized that granulocytes, including neutrophils and eosinophils, influence the immunologic response to chemoradiation therapy (CRT) and patient outcomes. Kaplan-Meier analysis demonstrated that patients with a persistently increased eosinophil count (> 150 cells/uL) 3 months after CRT lived 45% longer than patients with lower (or < 59 days confirmed that increased steroid use correlated a 35% decrease in overall survival (639 (CI 513-759) vs. 988 (856-1121) days, p<0.01), independent of initial performance status. Study demonstrates that treatment-induced increase in eosinophil count is the strongest hematologic predictor of overall survival in newly diagnosed GBM. Eosinophil count may serve as a proxy for immunologic response to therapy and thus yield more prognostic insight than ALC.[20]

Conclusion

Most of the patients were prescribed with a 3-drugs regimen anticancer drug. Most commonly used anticancer agents were 5 FU 61 (61%), doxorubicin 43 (43%), cyclophosphomide 53 (53%), cisplatin 10 (10%), paclitaxel 20 (20%), carboplatin 25 (25%), gemcitabine 11 (11%), oxaliplatin 14 (14%) and capecitabine 11 (11%). There was significant increase in the AEC after chemotherapy from baseline level (p <0.0001).

We have extensively searched published scientific documents to find out similar kind of study and to correlate. But we didn't find any of the published articles similar or identical to our study. Our study has generated a hypothesis that administration of many anticancer agents may increase eosinophil count or peripheral eosinophilia. Additional large scale prospective studies must be performed to confirm our results and to understand the mechanism by which anticancer agents increase eosinophil count which may have affect on the patient prognosis, with the goal of exploiting this natural anticancer mechanism to personalize patient treatment.

Conflict of interest: None

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Ethical Clearance: The study proposal along with other relevant documents was approved by the institutional ethical committee.

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