Predictors of Chemotherapy Related Toxicities in Elderly Lymphoma Patients: Experience from a Tertiary Cancer Centre

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Abstract Identification of baseline parameters that predict chemotherapy related morbidities in elderly lymphoma patients can help in tailoring treatment. However, there is a paucity of tools to predict the risk of chemotherapy related toxicity in elderly lymphoma patients from India. We retrospectively analyzed 203 lymphoma patients more than 60 years of age for predictors of grade III or higher haematological and non-haematological toxicity due to chemotherapy. Eighty-five (42%) and seventy-one (35%) lymphoma patients developed grade III or IV haematological and non-haematological toxicities respectively. On multivariate analysis baseline absolute lymphocyte counts (ALC) less than 1300/ μ l, chemotherapy with anthracyclines and presence of two co-morbid conditions were significant in predicting serious haematological toxicities. For non-haematological toxicities baseline ALT levels more than 40 U/l was the only significant factor. This is the first report from India on the study of factors predicting serious chemotherapy related adverse effects in elderly lymphoma patients. Patients with low ALC, elevated ALT, multiple co-morbidities and receiving anthracyclines should be closely monitored for chemotherapy related toxicities.

Keywords Lymphoma · Geriatrics · Chemotherapy · Toxicity

Introduction

Unlike many advanced cancers, patients with lymphoma are treated with curative intent and the situation is no different for the elderly; who are also treated with dose intense chemotherapy. This puts them at higher risk of toxicities. In all the major trials the incidence of chemotherapy related severe adverse events in elderly is in the range of 20–60% [1]. Studies have shown that older patients with lymphoma experience greater toxicity in comparison to their younger counter parts, yet they would derive similar benefit from standard chemotherapy [2]. Decreased chemotherapy dose intensity translates into decreased cure rates and increased relapse in elderly lymphoma patients [2]. There is however a paucity of tools to predict which elderly patient with lymphoma will develop serious adverse events due to chemotherapy. It would be useful to know which factors predict chemotherapy related toxicities at baseline. Such knowledge would allow for personalizing treatment to optimize outcome and decrease toxicity. Therefore, we did an analysis to determine the factors that can predict serious chemotherapy related toxicities in elderly lymphoma patients at our centre.

Materials and Methods

We retrospectively analyzed the data of all consecutive previously untreated elderly lymphoma patients, more than 60 years of age who were treated at our centre from 1st January 2010 to 31st December 2014. This study was approved by the institutional ethics committee. Patients who were diagnosed but refused treatment were not included in the analysis. All the data were obtained from the patient's hospital case records for analysis. The

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diagnosis of lymphoma was confirmed by lymph-node biopsy and immunohistochemistry (IHC). Patients with the diagnosis of Hodgkins lymphoma (HL) and Non-Hodgkins Lymphoma (NHL) were included in the study. The data compiled from the records included those on baseline demographic, clinical, disease related, laboratory and treatment related parameters. The common comorbidities assessed were diabetes mellitus, hypertension, thyroid dysfunction and ischemic heart disease. The level of control of comorbidities was defined as good or uncontrolled based on the patient's laboratory values and physician notes mentioned in the records. For staging, contrast enhanced computed tomographic (CT) scan of chest, abdomen and pelvis or whole body positron emission tomography with CT (PET-CT) was done. Bone marrow biopsy was performed to look for bone marrow involvement.

The data retrieved from the records was organized into different groups for analysis. All the blood tests were performed in the hospital laboratory and the reference range provided by the laboratory was used for classifying the results as within the normal or above or below the normal range for analysis.

The primary outcome was the first development of grade III/IV haematological and non-haematological toxicity per CTCAE (Common Toxicity Criteria for adverse Events version 4).

The most common chemotherapy regimens used in NHL were Cyclophosphamide, Adriamycin, Vincristine and Prednisolone (CHOP) or Cyclophosphamide, Vincristine and Prednisolone (COP) with or without Rituximab and in HL was Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD). The choice of treatment was based on physician discretion and patient preference.

To derive the factors that were significantly associated with toxicity, logistic regression analysis was used. For the data analysis, statistical software SPSS version 17 was used.

Results

Between 2010 and 2014, 233 lymphoma patients older than 60 years of age were evaluated. 203 patients were treated and hence included in the final analysis (26 patients did not get any treatment and 4 patients were treated with radiotherapy only). The median age of the study population was 67 years; of which 128/203 (62%) were males and 75/203 (38%) were females. Co-morbidities like type-2 diabetes mellitus and hypertension were seen in 117/203 (58%) patients and one-fourth of the patients had history of addiction to alcohol or tobacco. Majority of the patients (69%) had an eastern co-operative oncology group (ECOG)

performance status(PS) of 1. The most common lymphoma subtype was diffuse large B cell lymphoma (DLBCL) (54%) followed by HL (16%). Anthracycline based chemotherapy was given to 49% patients. 50% of the patients got Rituximab with their chemotherapy. The base line characteristics of the patients are shown in Tables 1, 2 and 3.

Eighty-five patients (42%) developed grade III or higher haematological toxicity i.e. grade III/IV leucopenia. There were three deaths due to chemotherapy related toxicity all due to neutropenic sepsis. The factors found to be significant in predicting grade III/IV haematological toxicity on univariate analysis were number of co-morbidities, histology, grade of tumour, absolute lymphocyte counts (ALC) and the chemotherapy regimen. On multivariate analysis patients with two co-morbidities had significantly increased risk of developing toxicities compared to those with no co-morbidities. Similarly, patients with ALC less than 1300/ μ l had significantly increased risk of developing Grade III/IV haematological toxicity compared to those with ALC more than 1300/ μ l. Patients who got anthracyclines with their chemotherapy had significantly increased risk of developing toxicity compared to those who did not get anthracyclines. 54% of the patients exposed to anthracyclines developed serious toxicity in comparison to 33% of those not exposed to anthracyclines.

The factors that were found to be significant in predicting grade III/IV non-haematological toxicity on univariate analysis were presence of co-morbidities, PS, pedal edema, histology, bone marrow involvement, erythrocyte sedimentation rate (ESR) and alanine transaminase (ALT). On multivariate analysis, only ALT levels were significant; with those having ALT more than 40 U/l having significantly increased risk of grade III/IV non-haematological toxicity. The multivariate analysis for grade III/IV haematological toxicity is shown in Table 4 and the grade III/IV non-haematological toxicities seen in study patients is shown in Table 5. The most common non haematological toxicities are depicted in Table 6.

Discussion

We conducted an analysis of factors that can predict the chemotherapy related toxicities in elderly lymphoma patients more than 60 years of age treated at a tertiary cancer institute in India. ALC less than 1300/ μ l, chemotherapy with anthracyclines and presence of two co-morbid conditions were significant in predicting serious haematological toxicities. For non- haematological toxicities ALT levels more than 40 U/l was the only significant factor.

Table 1 Baseline patient characteristics

Characteristics n = 203	Groups	Number of patients (%)
Age (years)	(60–64)	72 (35)
	(65–69)	67 (33)
	(70–74)	39 (19)
	(>75)	25 (13)
Gender	Males	128 (62)
	Females	75 (38)
Addictions	Present	51 (25)
	Absent	152 (75)
Co-morbidities	Present	117 (58)
	Absent	86 (42)
Number of co-morbidities	Nil	86 (42)
	One	53 (26)
	Two	47 (24)
	≥ Three	17 (8)
Level of control of co-morbidities	Well	74 (36)
	Uncontrolled	26 (14)
	Unknown	17 (8)
	Not relevant	86 (42)
B symptoms	Present	43 (22)
	Absent	160 (78)
ECOG PS	1	123 (61)
	2	58 (28)
	3	16 (8)
	4	6 (3)
Pedal edema	Present	23 (11)
	Absent	180 (89)
Histology	DLBCL	110 (54)
	NHL others	60 (30)
	HL	33 (16)
Stage	1	17 (8)
	2	50 (25)
	3	59 (29)
	4	77 (38)
Bone marrow involvement	Present	58 (29)
	Absent	145 (71)
Grade	High	141 (70)
	Low	19 (9)
	Intermediate	9 (4)
	Unknown/NA	34 (17)

ECOG Eastern cooperative oncology group, PS performance score, HL Hodgkins lymphoma, NHL non-Hodgkins lymphoma, DLBCL diffuse large B-cell lymphoma, NA not available

The age limit of 60 years was arbitrarily chosen and was assumed to be more appropriate for the Indian population. Studies conducted in the west have set the age limit for elderly cancer patients as more than 65 years or more than 70 years [1, 3, 4]. We felt that more than 70 years as a cut off for elderly lymphoma patients in India is inappropriate as the average life span in India is 68 years. The Ministry

of Statistics and Programme Implementation in the Government of India defines an elderly person as one above 60 years of age [5]. Studies on epidemiology and demography from India have considered elderly cancer patients to be more than 60–70 years of age [6–8].

Since this was a preliminary study and for the uniformity of data collection, only lymphoma patients were included.

Table 2 Baseline laboratory parameters

Characteristic	Group	Number of patients (%)	Median value	Range
Haemoglobin (g/dl)	<10.5	89 (44)	11	6–14
	≥10.5	114 (56)		
Total WBC count (per mm ³)	<4000	8 (4)	7900	2300–61,200
	4000–11,000	161 (79)		
	>11,000	34 (17)		
Absolute neutrophil count (per mm ³)	<1500	6 (3)	5500	230–22,500
	1500–4000	117 (58)		
	>4000	32 (16)		
	NA	47 (23)		
Absolute lymphocyte count (per mm ³)	<1300	39 (19)	1850	150–55,100
	1300–3500	99 (49)		
	>3500	16 (8)		
	NA	49 (24)		
Platelet count (per mm ³)	<1.5 lac	24 (12)	2.5 lac	0.2–6.3 lac
	1.5–3 lac	162 (80)		
	>3 lac	17 (8)		
Total Billirubin (mg/dl)	≤1	173 (85)	0.6	0.2–5.4
	>1	30 (15)		
Alkaline phosphatase (units/l)	≤125	79 (39)	85	10–1416
	>125	24 (12)		
	NA	100 (49)		
AST (U/l)	≤40	142 (71)	32	10–196
	>40	61 (29)		
ALT (U/l)	≤40	165 (82)	19	13–122
	>40	38 (18)		
Serum Creatinine (mg/dl)	≤1.5	193 (95)	0.8	0.4–3
	>1.5	10 (5)		
Serum urea (mg/dl)	≤45	120 (90)	26	14–96
	>45	83 (10)		
Total protein (g/dl)	<6	8 (4)	7.3	5–8
	≥6	42 (21)		
	NA	153 (75)		
Serum albumin (g/dl)	<3.5	81 (40)	3.2	1.7–4.5
	≥3.5	28 (14)		
	NA	94 (46)		
ESR (mm/h)	≤30	38 (19)	40	4–277
	>30	56 (27)		
	NA	109 (54)		
Serum lactate dehydrogenase (U/L) (normal range: 200–400 U/L)	≤400	23 (11)	729	135–12,580
	>400	68 (33.5)		
	>800	69 (34)		
	NA	43 (21)		

WBC White blood cell, AST aspartate transaminase, ALT alanine transaminase, ESR erythrocyte sedimentation rate, NA not available

On final analysis Patients with ALC <1300/μL had a significantly increased risk of developing serious haematological toxicity compared to those with ALC >1300/μL. Studies

have shown that baseline ALC is predictive of response to chemotherapy and survival in Follicular lymphoma and DLBCL [9, 10]. However, there is very little data correlating

Table 3 Baseline treatment related parameters

Characteristic	Group	Number of patients (%)
Type of treatment	Chemotherapy only	147 (72)
	Combined treatment	56 (28)
Chemotherapy regimen	Anthracyclines based	100 (49)
	Non-anthracyclines based	103 (51)
Chemotherapy intensity	Standard	51 (25)
	Compromised	152 (75)

Table 4 Multivariate analysis for grade III/IV haematological toxicities

Characteristics	Groups	OR	95% CI	P value in individual group	Overall P value
No. of co-morbidities	0				0.11
	1	0.82	0.37–1.82	0.63	
	2	2.3	1.03–5.2	0.04	
	≥3	1.16	0.33–4.02	0.81	
Histology	HL				0.37
	DLBCL	0.34	0.06–1.8	0.20	
	NHL other	0.32	0.06–1.6	0.16	
Grade	High				0.37
	Low	0.63	0.14–2.93	0.56	
	Intermediate	3.44	0.65–18	0.14	
	Not relevant	1.18	0.24–5.85	0.84	
Absolute lymphocyte count	<1300/μl				0.03
	1300–3500/μl	0.31	0.13–0.73	0.008	
	>3500/μl	0.2	0.50–0.90	0.04	
	NA	0.335	0.13–0.86	0.02	
Chemotherapy regimen	No anthracycline				0.001
	Anthracycline	3.06	1.55–6		

Bold values are statistically significant

HL Hodgkins lymphoma, NHL non-Hodgkins lymphoma, DLBCL diffuse large B-cell lymphoma

ALC to chemotherapy related toxicity in lymphoma. In a study by Ray-Coquard et al. [11], baseline or day 5 lymphopenia ($ALC \leq 700/\text{mm}^3$) was significant in predicting the risk of febrile neutropenia in elderly cancer patients receiving chemotherapy. On regression analysis it was found that lymphopenia in lymphoma patients was much more predictive of febrile neutropenia compared to that in other cancers [11]. Blay et al. [12], analysed 112 cancer patients of all ages for factors that can predict the risk of febrile neutropenia. Day 5 lymphopenia less than $700/\mu\text{l}$ correlated with the risk of febrile neutropenia. The findings were further validated in patients with high and intermediated grade NHL who received doxorubicin, cyclophosphamide, bleomycin, vindesine and prednisolone (ACBVP) chemotherapy [12]. Lymphopenia at presentation is also associated with functional disability, frailty, malnutrition and cognitive impairment [11, 12]. So, either lymphopenia per se or the associated conditions such as frailty and malnutrition predispose the elderly to severe chemotherapy related adverse events.

We found that patients with co-morbidities have an increased risk of serious chemotherapy related

haematological toxicities in comparison to those without any. The most common co-morbidities in our study were type-2 diabetes mellitus and hypertension. Chronic co-morbidities have been shown to be associated with increased risk of serious chemotherapy related toxicities and the resultant hospitalization [13]. Renal disease and heart disease have been shown to increase the risk for febrile neutropenia in patients with NHL [14, 15]. Most chemotherapeutic drugs are excreted by the kidney. Renal failure due to type-2 diabetes mellitus impairs drug excretion, prolongs their half-lives and hence exacerbates toxicity. Elderly lymphoma patients with co-morbidities are on poly-pharmacy. This creates a complex web of drug interactions between these drugs and chemotherapeutic drugs based on the induction or inhibition of Cytochrome P-450 enzymes. Ultimately this leads to an alteration in the pharmacokinetics and pharmacodynamics of the chemotherapy which may lead to excessive toxicity.

In our study, patients who received anthracycline based chemotherapy were at significantly increased risk of developing serious haematological toxicities. In the

Table 5 Multivariate analysis for grade III/IV non-haematological toxicities

Characteristics	Groups	OR	95% CI	<i>P</i> value for individual group	Overall <i>P</i> value
Presence of co-morbidities	No				0.22
	Yes	1.52	0.77–2.98		
ECOG PS	1				0.12
	2	0.4	0.18–0.89	0.02	
	3	1.31	0.39–4.40	0.66	
	4	0	0	0	
Pedal edema	Yes				0.10
	No	2.85	0.82–9.96		
Histology	HL				0.19
	DLBCL	0.42	0.17–1.06	0.07	
	NHL other	0.63	0.22–1.81	0.40	
Bone-marrow involvement	Yes				0.23
	No	1.61	0.74–3.58		
ESR	<30				0.086
	>30	0.41	0.16–1.08	0.072	
	NA	0.40	0.16–0.9	0.028	
ALT	≤40				0.05
	>40	2.6	1.16–5.9	0.02	

Bold values are statistically significant

PS Performance status, ALT alanine transaminase, ESR erythrocyte sedimentation rate

RICOVER-60 trial comparing six versus eight cycles of RCHOP-14 in patients with DLBCL more than 60 years of age the rates of grade 4 leucopenia were in the range of 48–50% which is close to the rate of leucopenia seen in our study [16]. It is expected that patients who receive anthracyclines will develop more toxicity than patients who do not receive. It is important to find out factors which would predict toxicities in patients who receive anthracyclines. Tien et al. [17], conducted an analysis on more than 8000 elderly patients with DLBCL from the Surveillance, Epidemiology and End Results (SEER) data base. Out of the total number of patients, 58% received anthracycline based chemotherapy; 45% with Rituximab and 13% without Rituximab. In our study 50% patients received anthracycline based chemotherapy which is close to the findings from their study.

In our study, 71 patients out of the 203 analysed developed serious non-haematological toxicities. On multivariate analysis, only ALT level was significant in predicting occurrence of severe non-haematological toxicity, with levels more than 40 U/l predicting increased risk of toxicity. In the study by Extermann et al. [1], AST levels were significant on univariate analysis in predicting severe haematological toxicities but not non-haematological toxicities. Many of the commonly used chemotherapeutic drugs are metabolized in the liver. Transaminitis is a marker of liver injury. Therefore, drugs such as cyclophosphamide, vincristine and doxorubicin may

Table 6 Grade III/IV Non-haematological toxicities seen in study patients (n = 71)

Hyperglycemia	24
Hyponatremia	17
Ileus	11
Neuropathy	6
Fatigue	6
Cardiomyopathy	5
Diarrhoea	3
Pulmonary	2
Nausea and vomiting	2
Skin rash	2

undergo decreased metabolism with liver injury and hence predispose to increased toxicity.

Majority of the patients (89%) in the study had a PS-1 or 2. Elderly patients with poor PS who were not treated were not included in the analysis. Also, many elderly patients with poor performance status are treated with metronomic chemotherapy and referred to a local hospital for supportive care. Our study did not assess the toxicity in this group of patients.

In conclusion, elderly lymphoma patients with low baseline lymphocyte count, higher number of co-morbidities and treated with anthracyclines are likely to develop increased grade III/IV haematological toxicities and those with elevated ALT are at increased risk of non-haematological toxicities and therefore such patients should be carefully monitored. To the best of our knowledge this

study is the first of its kind from India in assessing the factors that can predispose to chemotherapy related toxicities in elderly lymphoma patients. Well planned prospective studies are needed to validate our findings.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval The study was approved by the institute ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was retrospective in nature and did not involve any intervention and therefore no informed consent was required.

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