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Original Research Paper

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ROLE OF CD163+ TUMOUR ASSOCIATED MACROPHAGES IN PROGNOSTICATION OF PATIENTS DIAGNOSED OF HODGKIN'S LYMPHOMA: A PROSPECTIVE COHORT STUDY

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ABSTRACT Hodgkin's lymphoma (HL) constitutes around 30% of all lymphomas . IPS is used for the risk stratification of advanced stage HL but it lack applicability to the early stage cases ..In this prospective cohort study, we aim to confirm the relationship between CD68+TumourAssociated macrophages with treatment response (interim as well as end of treatment) of HL treated with the standard chemotherapy and radiotherapy regimens. A total of 50 patients were recruited over a period of 18 months and the patients were followed up in the hematology clinic and interim treatment responses as well as end of treatment response were assessed. Correlation of the CD163+Tumour Associated Macrophages and the treatment response showed that the Higher Percentages of CD163+Tumour Associated Macrophages were associated with more advanced stages.. Univariate analysis showed that there was no significant correlation of interim treatment response as well as end of treatment response with CD163+Tumour Associated macrophages levels .

KEYWORDS :

INTRODUCTION

Classical HL represent nearly 95% of all the cases of HL(2).A cure can be achieved in approximately 80% of the patients with current treatment regimen consisting of multi agent chemotherapy and radiotherapy (in selected cases).The remaining 20% attaining remission(4).Early identification of the patients who would fail treatment or relapse in future is currently a challenge. At present the most commonly used tool for prognostication of HL cases is international prognostic score(IPS) (on a scale of 0 -7), with higher scores indicating poorer prognosis).This score is a combination of clinical and basic haematological parameters recorded at the time of diagnosis of a case like age , gender ,stage, haemoglobin level ,albumin level and lymphocyte counts. Children and adolescents with classical Hodgkin's Lymphoma (HL) have an excellent prognosis Macrophages that infiltrate tumor tissues are referred to as tumor-associated macrophages (TAMs) and are closely involved in tumorigenesis by inducing angiogenesis, immunosuppression, and invasion.(1,2) Many studies of TAMs in human malignant tumors have been published since 2000, and they showed an association of TAMs with histological grade and clinical prognosis in many kinds of tumors including hematological malignancies.(1,2) The heterogeneity of macrophage phenotypes has also been a focus of study in recent years.(3,4) The functions and gene expression profiles of classically activated macrophages induced by c-interferon and alternatively activated macrophages induced by anti-inflammatory cytokines such as interleukin (IL)-10, macrophage colony-stimulating factor (M-CSF), IL-4, and IL-13 were found to be different, and these two types of activated macrophages were named M1 and M2, respectively.(3,4) The M2 phenotype preferentially produces angiogenic factors and immunosuppressive molecules and is associated with tissue remodeling, neovascularization, and tumor progression.(3,4) In tumor microenvironments, some kinds of tumor cells secrete many anti-inflammatory cytokines, which seem to induce differentiation of TAMs to the M2 phenotype.(5–7) Adult T-cell leukemia lymphoma (ATLL) is known to develop in people infected with human T-cell leukemia virus type. The disease is classified into four categories: acute (60%); lymphomatous (20%); chronic (15%); and smoldering (5%).

MATERIAL AND METHODS

Study Design

This was a prospective cohort study carried out in the patients diagnosed with Hodgkin's lymphoma who completed treatment at PGIMER, Chandigarh. Patients were enrolled in the study from the Adult Haematology Clinic PGIMER, Chandigarh prospectively from July 2017 to March 2018 and then they were followed up till November 2018.

Duration Of The Study

July2017 – December. 2018

Place Of The Study:

1.Department of Internal Medicine Adult Clinical Haematology Unit PGIMER,Chandigarh
2. Department of Histopathology, PGIMER, Chandigarh.

Inclusion Criteria

1.Primary diagnosis of Hodgkin's lymphoma confirmed by a tissue biopsy
2. Adequate lymph node tissue in the paraffin block
3. Treatment naive patients

Exclusion Criteria

1. Patient previously treated with chemo radiotherapy before coming to PGIMER,. Chandigarh.
2. Patients who did not complete chemotherapy or end of treatment chemotherapy response assessment were excluded from further analysis.

METHODOLOGY

PROCEDURE

1. Demographic and disease data were recorded in a predesigned performa (annexure 3) and investigations were recorded as per the performa.
2. Collection of the clinical and the laboratory data of the newly enrolled cases was done in the study performa.
3. Biopsy numbers of the lymph node were taken from the Adult Haematology Clinic case record files and the paraffin block were retrieved from the archive of the Department of Histopathology.
4. Cases with adequate tissue in the paraffin block in the archives of the Department of Histopathology were selected and immunohistochemistry staining was performed.
5. ESR levels were done before starting the treatment of the patients fulfilling the inclusion criteria.
6. Correlation of ESR levels , and treatment response (interim as well as end of treatment response was assessed.
7. The interim treatment response was assessed with the PET CT SCAN after two cycles of the chemotherapy and the response was assessed by the Deauville criteria.
8. The end of treatment response was assessed with the PETSCAN after completion of chemotherapy and the response

was assessed by Deauville criteria.

Statistical Analysis

The descriptive statistics were used to study the response rates, Correlation was assessed between ESR levels and the response rate by using Chi square test. .Differences were considered as significant if the computed p value was less than theoretical p value i.e. 0.05. Univariate analysis was performed to assess the association between the ESR levels with the treatment response with SPSS, version 22.0.

RESULTS

During the study period, we recruited 60 consecutive, treatment naive patients of Hodgkin's lymphoma. Out of this cohort, there were few exclusions as following:

A. Three patients died before starting treatment.

B. Seven patients lost to follow up before completion of therapy.

Hence, their response ~to chemotherapy was not available (due to leaving the treatment before completion). Therefore, in the end, total 50 patients were selected. The patients were followed up in the hematology clinic and interim treatment responses as well as end of treatment response were assessed.

CD163+ Tumour Associated Macrophages:

In our sample study, it was found that majority of the patient were having high percentages of CD163+ TAMs. On further subdividing into various subtypes, majority of the patients of nodular sclerosis(N=22(58%)) and mixed cellularity (N=8(90%)) were having higher percentages of CD163+IAMs. Higher percentages of CD163+TAMs were present in advanced stages of disease.

Table 1 Percentages Of CD163+ TAMs

Percentages of CD163+TAMs	Frequency(N%)
0-25%	21(40.4%)
25%-50%	16(30.8%)
50%-75%	13(25%)
75%-100%	2(3.8%)
TOTAL	52

Table 2. Percentages Of CD163+TAMs With The Different Subtypes

CD163+TAMs WITH SUBTYPES						
		HLNS N(%)	HLMC N(%)	HLNOS N(%)	NLPHL N(%)	TOTAL
CD163+ TAMs	0-25%	16 (42.1 %)	1 (11.1 %)	3(100%)	2(100%)	21
	25%-50%	14 (36.8 %)	2 (22.2 %)	0	0	16
	50%-75%	8(21 %)	4(44.4 %)	0	0	13
	75%-100%	0	2(22.2 %)	0	0	2
Total		38	9	3	2	52

ANALYSIS:

Interim Treatment Response:

Univariate analysis showed that there was also no significant correlation with the percentages of CD163+TAMs with response of interim assessed.

End Of Treatment Response:

Univariate analysis showed that there was also no significant correlation with the percentages of CD163+TAMs with response of end of treatment assessed.

DISCUSSION

In this study, which is the prospective investigation carried out over a period of 18 months based on data available , we observed no association between CD163+Tumour Associated Macrophages concentration and overall risk of Hodgkin's lymphoma . Certain clinicopathological studies recently indicated the significance of CD163-expressing M2 TAMs in the growth of tumor cells, and a high number of M2 TAMs is reportedly associated with a worse prognosis in many malignant tumors including lymphomas. The number of CD68+ TAMs, the percentage of CD163+ TAMs, and clinical stages were prognostic factors in univariate analysis. Although the number of CD163+ TAMs increased in patients with a higher clinical stage of disease, the statistical finding from multivariate analysis that only the percentage of CD163+ TAMs was associated with clinical prognosis indicated that the percentage of CD163+ TAMs was an independent prognostic factor. This may indicate that the combination of the number of CD68+ and CD163+ TAMs is more important for lymphoma progression. The fact that the number of ATLL cases. Although present study put forward some evidence which bridge the gap of existing knowledge about role of M1 and M2 tumor related macrophages phenotype in treatment response in patients with HL, there still exist some limitation in present study.

CONCLUSION

In conclusion, higher levels of CD163+Tumour Associated Macrophages were associated with advanced stages. There was no significant correlation between CD163+ Tumour Associated Macrophages percentages with the treatment response interim as well as end of treatment response.

Characteristics Of Patients With Interim Treatment Response

Table No 3. Univariate Analysis Of Interim Treatment Response With Various Prognostic Variables Shows No Significant Correlation (P Value <0.05)

Features	Number of patients in complete remission N (%)	Number of patients not in complete remission N (%)	P value
CD163+TAMs Percentages			
0 -25%	16(41%)	4(44.4%)	0.063
25-100%	23(58.9%)	5(55.5%)	

Characteristics Of Patients With End Of Treatment Response

Table No 4. Univariate Analysis Of End Of Treatment Response With Various Prognostic Variables

Features	Number of patients in complete remission N(%)	Number of patients not in complete remission N(%)	P value
CD163TAMsPercentages			
0-25%	19(39.5%)	2(50%)	0.600
25-100%	29(60.4%)	2(50%)	

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