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Original Research Article

The correlation of response to induction chemotherapy with neutrophil lymphocyte ratio and platelet lymphocyte ratio in oral cavity malignancy

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ABSTRACT

Aims and Objectives: Induction chemotherapy yields significant response in locally advanced squamous cell carcinoma of oral cavity. Pre-treatment biomarkers can help to predict response to chemotherapy. The neutrophil–lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) are cost-effective and simple parameters that can predict response to chemotherapy. This study aims to find the correlation between NLR, PLR and response to induction chemotherapy in oral cavity malignancies.

Materials and Methods: Details of 32 patients with locally advanced squamous cell carcinoma of oral cavity who received induction chemotherapy from Jan 2017- March 2019 were collected and the following were recorded. Pre-treatment total leukocyte count, neutrophil, lymphocyte and platelet counts. Post induction chemotherapy, reduction in size of tumour. Patients were categorised into complete, partial and non- responders.The mean NLR and PLR, and the significance in variation of NLR and PLR between the three groups was calculated and the statistical significance analysed.

Results: The mean NLR is significantly low in both partial (2.62) and complete response groups (2.4) compared to the patients with static response (5.6). The mean PLR is also low in responders (124) when compared to the static group (180), but it is not statistically significant. With a cut-off value of 3.95 for NLR and 153 for PLR, response could be predicted with high positive predictive value. When both the ratios are combined the predictive value is further increased as shown in this study.

Conclusion: Pre-treatment NLR and PLR are reliable biomarkers of the systemic immunologic phenotype of the cancer patients. They predict the response to chemotherapy in patients with oral cavity malignancy.

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) accounts for about 5% of all cancers in the West. In India, they form around 25-30% of all cancers and 60-70% of these present as locally advanced (stage III/IV) cancers.[1,2] Induction chemotherapy using cisplatin based combination has yielded major response rates of upto 90% and clinical complete response rates of around 30% in locoregionally advanced head and neck SCC.[3]

Pre-treatment biomarkers can help to predict response to chemotherapy. The systemic inflammatory response has been regarded as an independent prognostic factor in patients with various malignancy.[4] Neutrophils can facilitate tumour proliferation, invasion, and distant metastasis by secreting factors that promote tumour growth.[5–7] Platelets are cells containing the largest quantity of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β and platelet-derived endothelial cell growth factor (PD-ECGF).[8] These platelet-derived growth factors are often produced in large quantities by cancer cells and contribute to cancer growth and histology. In contrast, lymphocytes, particularly cytotoxic T cells, play a crucial role in the anti - tumour immune response by promoting apoptosis and suppressing tumour growth.[9,10] Accordingly, the neutrophil–lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR) a re cost-effective and simple parameters that can predict response

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to chemotherapy.

This study aims to find the correlation between NLR, PLR and response to induction chemotherapy in oral cavity malignancies.

2. Materials and Methods

Details of 32 patients with locally advanced squamous cell carcinoma of oral cavity who received induction chemotherapy from Jan 2017- March 2019 were collected and the following were recorded.

1. Pre - treatment total leukocyte count, neutrophil, lymphocyte, platelet counts. Using automated analyser
2. Tumour size - Clinical, radiological, and post operative specimen.

2.1. Treatment and response assessment

2.2. Three cycles of chemotherapy are given:

Premedication (Inj Hydrocortisone 100 mg, InjOndansetron 8mg, Inj Pheniramine 10mg) were given half an hour before starting chemotherapy Day 1: Paclitaxel 175 mg/m^2 as 3 hrs. infusion or Docetaxel 75 mg/m^2 as 2 hours infusion, Cisplatin 75 mg/m^2 as divided doses on Day 1 and Day 2 as 3 hrs infusion Day 2- Day 5: 5 Fluorouracil 750 mg/m^2 as 24 hrs. continuous infusion Prophylactic GM-CSF given.

2.3. 21 day cycle

The pretreatment clinical measurement of maximum tumour size and post operative histopathological maximum tumour size is compared for response assessment in operated patients. The radiological (CT or MRI) change in size post three cycles of induction chemotherapy is used in non - operated patients to assess response. Patients are grouped into three categories. Those with histopathological or radiological complete response are complete responders. Patients with more than 30% of reduction in tumour size are grouped as partial responders, and those with less than 30% of reduction in tumour size are grouped as non-responders.

2.4. Blood analysis for the determination of the NLR and PLR

The blood samples were collected before the initiation of chemotherapy. Complete blood counts were measured using peripheral blood samples with automated analyser. The total count, differential neutrophil, lymphocyte count and platelet counts were measured. AbsoluteNeutrophil and lymphocyte counts calculated. Neutrophil and lymphocyte ratio obtained. Platelet count divided by absolute lymphocyte count to obtain PLR ratio.

2.5. Statistical analysis

Software used is SPSS Statistics for windows, version 23.0, Armonk, NY :IBM Corp. Released 2015

The mean value of NLR was calculated for the three groups. Kruskal Wallis test was used to calculate the significance of variation between the three groups. The significance in variation of NLR between two groups was calculated using Mann- whitney U and Wilcoxon w test.

The mean PLR was calculated and the significance in change of PLR across the three groups analysed by ANOVA test. Inter group analysis of significance in change was done by post Hoc tests.

3. Results

4. Results for NLR

The mean NLR is shown in Table 1. The mean NLR in the complete and partial response group is significantly low compared to static group.

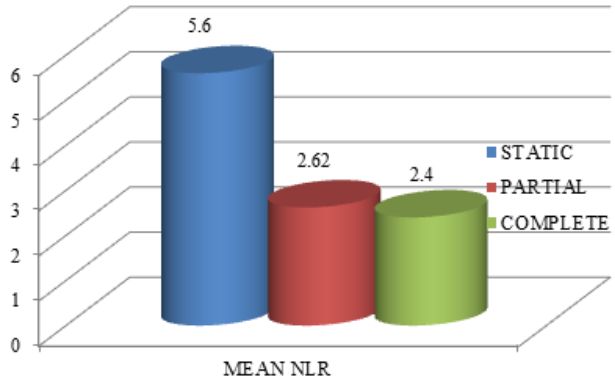

Fig. 1:

There is a statistically significant difference in NLR when the three groups are analysed together (p=.007). [Table 2]

Inter group analysis revealed that there is no statistical difference in NLR between complete and partial responders (p= 0.785). There is statistical difference in the mean NLR between the partial and static responders (p=0.003). Significant difference is observed between static and complete response group. (p=0.009). [Table 3].

From ROC curve, a cutoff value of 3.95 is chosen.

When cutoff value of 3.95 is used 95.8% of patients with NLR below the value have either complete or partial response and 75% of patients with NLR above it are static responders [Table 4].

5. Results for PLR

The mean PLR in complete response group is 124. For partial response group the mean PLR is 137 and for the static

Table 1: Mean NLR

	N	Mean	Std. Deviation
Complete response group	7	2.494	.9688
Partial response group	18	2.622	1.5791
Static response group	7	5.614	2.1130
Total	32	3.249	2.0083

Table 2: Kruskal wallis test

	Group	N	Mean Rank
NLR	Complete response group	7	14.21
	Partial response group	18	13.56
	Static response group	7	26.36
	Total	32	
		NLR	
Chi-Square		9.931	
Df		.007	
Asymp. Sig.		2	

Table 3: Intergroup comparison

(I) Group	(j) Group	P value
Complete response group	Partial response group	0.785
Partial response group	Static response group	0.003
Static response group	Complete response group	0.009

Table 4: ROC cutoff value for NLR

			Group Complete / Partial Response Group	Static Response Group	Total
NLR	> = 3.95	Count	2	6	8
		% within NLR	25.0%	75.0%	100.0%
	< 3.95	Count	23	1	24
		% within NLR	95.8%	4.2%	100.0%
Total		Count	25	7	32
		% within NLR	78.1%	21.9%	100.0%

response group is 180.[Table 5]

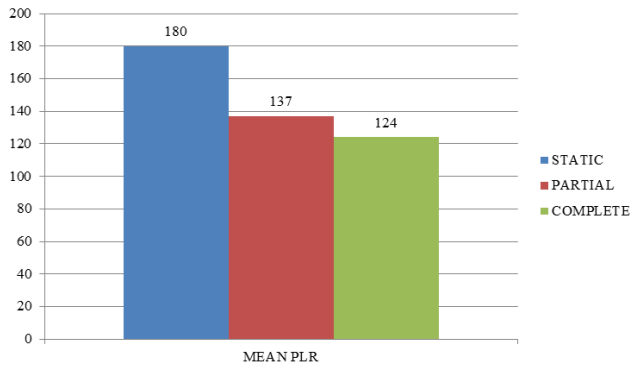

Fig. 2:

There is no statistically significant difference in the mean when all the three groups are compared (p=0.05).[Table 5].

As shown inTable 7, inter group analysis of mean PLR revealed that the re is no statistically significant difference in mean PLR between the complete and partial response groups (p=0.772). There is no significant difference in PLR between the partial and static response group (p=0.09) and static and complete response group (p=0.58).

Using ROC curves a cut-off value of 153 was determined, 94.7% of patients with PLR below 153 were responders to chemotherapy and 46.2% of patients with PLR above 153 were having static disease [Table 8]

5.1. Combined NLR and PLR

To identify the impact of combining NLR and PLR a score of 0 is assigned for patients who have low NLR and PLR.,

Table 5: Mean PLR

	N	Mean	Std. Deviation
Complete response group	7	124.00	32.609
Partial response group	18	137.50	47.243
Static response group	7	180.43	44.328
Total	32	143.94	47.165

Table 6: Significance of difference between groups (PLR)

Anova Test					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	12849.661	2	6424.830	3.320	.050
Within Groups	56112.214	29	1934.904		
Total	68961.875	31			

Table 7: Inter group analysis PLR

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
Complete response group	Partial Response Group	-13.500	19.594	.772
Partial Response Group	Static Response Group	-42.929	19.594	.090
Static Response Group	Complete Response Group	56.429	23.512	.058

Table 8: ROC cutoff value PLR

			Group		Total
			Complete / Partial Response Group	Static Response Group	
PLR	> = 153	Count	7	6	13
		% within PLR	53.8%	46.2%	100.0%
	< 153	Count	18	1	19
		% within PLR	94.7%	5.3%	100.0%
Total		Count	25	7	32
		% within PLR	78.1%	21.9%	100.0%

1 for patients who have either low NLR or PLR and 2 for patients with high PLR and NLR.

As shown in table 9, no patient with high value of either NLR or PLR was present in the complete response group. None of the patients who had a low NLR or PLR was present in the static group. In the partial response group except for 1 patient the other 16 patients had either a low NLR or PLR.

6. Discussion

There are different original studies and meta-analysis that show a prognostic and predictive role for NLR in solid tumours, including head-and-neck malignancies. In the present study, pre - treatment NLR and PLR have been demon strated to be correlating with response to platinum-based chemotherapy in epithelial oral cavity malignancy.

The mean NLR is significantly low in bothpartial and complete response groups compared to the patients with static response. The mean PLR is also low in responders when compared to the static group but it is not statistically significant. With a cut-off value of 3.95 for NLR and 153 for PLR, response could be predicted with high positive predictive value. When both the ratios are combined the predictive value is further increased as shown in this study.

Only a few studies have been done to evaluate the significance of pre-treatment NLR or PLR in head and neck malignancies. In a study to evaluate the association between pre- treatment NLR and outcome for locally advanced oral cavity cancers, Perisanidis *et al*. obtained mean NLR of 2.6 for their patients who responded to chemotherapy.[11] An *et al*. in a similar study reported mean NLR value of 3.07 for their total cohort of patients with nasopharyngeal cancer.[9] Jin *et al*. compared outcome and response to platinum-based chemotherapy in metastatic nasopharyngeal carcinoma. They determined a cut -off of 3.6 for NLR, based on the median of the values and showed that the response (CR + PR) rate is better with low NLR values.[12] Karpathiou *et al*. in a retrospective study, analysed the clinical and histologic predictive factors of response to induction chemotherapy

Table 9: Combined NLR/PLR

Score	0	1	2
Complete	6	1	0
Partial	11	6	1
Static	0	2	5

in 81 HNC patients. The patients were divided into good (62%) and poor (38%) responder groups. They selected a cut-off of 7 for NLR, and no significant difference for response rate between the two groups of low and high NLR was detected although the survival was significantly different.[13] The most common primary sites in their study were hypopharynx and oropharynx (totally 86%). The discrepancy between their results and our study may be explained with the different primary sites and also the unusual NLR cut -off selected by them.

7. Conclusion

Pretreatment NLR and PLR are reliable biomarkers of the systemic immunologic phenotype of the cancer patients. The se predict the response to chemotherapy in patients with oral cavity malignancy. Combining NLR and PLR has better predictive value than either of them taken alone.

8. Source of funding

None.

9. Conflict of interest

None.

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