Platelet-lymphocyte and neutrophil-lymphocyte ratios: Predictive factors of response and toxicity for docetaxel-combined induction chemotherapy in advanced head and neck cancers

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Abstract

Background: Although the effect of induction chemotherapy (IC) is still controversial in cancers of the oral cavity, the oropharynx, and the sinonasal tract, it is still used in some inoperable cases and for organ preservation in laryngeal or hypopharyngeal cancers. Taxane has played a greater role and produces a better overall response but a higher rate of acute toxicity. We investigated the response and risk of IC with docetaxel-combined regimens in advanced head and neck cancers.

Methods: We retrospectively reviewed the medical history of patients with advanced head and neck cancer between 2011 and 2017. We enrolled 40 patients who completed the initial tumor survey, ICs with docetaxel-combined regimens, and definite therapeutic strategies including concurrent chemoradiation or surgery. The demographic data, laboratory results, overall response, and acute toxicity were analyzed.

Results: There were 14 patients (35.0%) with partial response at least. There were 24 (60.0%) with at least one acute toxicity beyond grade III. Univariate analysis and multivariate linear regression analysis showed that a platelet-lymphocyte ratio (PLR) <8.5 correlates with a better overall response ($p < 0.05$), and a neutrophil-lymphocyte ratio (NLR) ≥3.5 correlates with a higher possibility of severe acute toxicity within one month after ICs ($p < 0.05$), especially hematologic side effects.

Conclusion: A pretreatment PLR <8.5 could predict better overall response, and a pretreatment NLR ≥3.5 could predict more severe acute toxicity after docetaxel-combined ICs. Through a simple hematological examination, we could try to identify a better response of tumor regression and anticipate potentially harmful side effects after ICs.

Keywords: Acute toxicity; Docetaxel; Induction chemotherapy; Neutrophil-lymphocyte ratio; Overall response; Platelet-lymphocyte ratio

1. INTRODUCTION

Head and neck cancer is the seventh most common type of cancer worldwide, and the vast majority of the disease is squamous cell carcinoma (SCC).[1] Two-thirds of patients with head and neck cancer present with advanced stage disease, commonly involving regional lymph nodes.[2] The frequency, incidence rates, and locations of head and neck SCCs vary widely among countries and continents.[1,3]

Head and neck SCCs are mostly treated with surgery, radiotherapy, and systemic therapy, either alone or in combination, depending on the patient's condition. Definite treatments including surgery and concurrent chemoradiation are crucial for eradicating the diseases, but induction chemotherapy (IC) has been discussed more in the past decade. IC is defined as chemotherapy before definitive intervention, which improves oncologic outcomes for cancers in other sites, such as gastric cancers, esophageal cancers, and bladder cancers. However, its role in locally advanced head and neck SCC remains controversial.[4]

In 2007, the TAX-323 and TAX-324 trials showed better survival in inoperable advanced head and neck SCCs with docetaxel-cisplatin-fluorouracil (TPF) IC than with the traditional cisplatin-fluorouracil (PF) regimen, which also had more acute toxicities within one month.[5–7] In 2013, Blanchard et al performed a meta-analysis of individual patient data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC). They found better 5-year overall survival (OS), progression-free survival (PFS), loco-regional control, and distal control with TPF regimens. Significantly more cases of grades 3 to 4 of neutropenia and febrile neutropenia were found in some studies, but a high number of missing values limits conclusions regarding the greater toxicity with TPF.[8] Another meta-analysis by Xu et al in 2015 revealed a similar conclusion.[9]

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Taxane-containing regimens of IC might result in a better oncological outcome for locally advanced head and neck SCCs than PF regimens,[7–10] and even better success for chemoselection and laryngeal preservation in SCCs of the larynx and hypopharynx.[11,12] The National Comprehensive Cancer Network guidelines first recommended the docetaxel-PF regimen of chemotherapy as initial and salvage treatments for several advanced head and neck cancers in 2016, and they continue emphasizing this approach in the newest version in 2018.[13]

However, myelosuppression is regarded as the taxane-containing IC with the most severe acute toxicity.[5,6,8,9,14] Sometimes, the therapy is interrupted. No specific predictive factor has been identified for physicians to alert patients, who may have more risk after chemotherapy. In this study, we tried to identify the possible demographic and laboratory factors that might influence the chance of more severe acute toxicities and better response after docetaxel-combined IC.

2. METHODS

2.1. Patients, evaluations, and treatments

This study is based on the Cancer Registry Database provided by the Cancer Center of Kaohsiung Veterans General Hospital. The study has been approved by the institutional review board. Between April 2011 and March 2017, data were reviewed for patients who were diagnosed with head and neck cancers except nasopharyngeal carcinoma.

In the first surveillance and follow-ups, the disease status was clinically evaluated routinely and included basic physical examinations, pan-endoscopy, laboratory studies, and radiological examinations. The radiological examinations included chest plain films, computed tomography (CT) scans or magnetic resonance imaging (MRI) of the head and neck, abdominal sonography, bone scintigraphy, and additional positron emission tomography/CT as necessary. Using this information, a decision about the treatment strategy was made or adjusted by a multidisciplinary tumor board, which consisted of oncologists, otolaryngologists, maxillofacial surgeons, radiotherapists, and pathologists.

Docetaxel-combined IC was initiated for the first treatment under suitable conditions if the patient was in stage III or IV with Eastern Cooperative Oncology Group performance status 0 to 1, inoperable, or attempting organ preservation. In our hospital, the standard docetaxel-combined regimen of IC is 60 to 75 mg/m^2 of docetaxel and 60 to 75 mg/m^2 of cisplatin with or without 600 to 800 mg/m^2 of 5-fluorouracil. After each IC, no prophylactic antibiotics are prescribed unless a severe toxicity occurs. There was a 3-week interval between each course of IC. Three to four weeks after the last IC, the patient is re-evaluated by physical examination, pan-endoscopy, and image studies to identify the overall response and determine the treatment to perform next.

Patients were enrolled in this study after completing at least one course of IC with docetaxel-combined regimens and postchemotherapy evaluation. The exclusion criteria were cancers of nasopharyngeal origin, a non-SCC pathology, patients with another known cancer, incomplete treatment, or lost follow-up. Demographic and laboratory information were recorded after diagnosis and before the first treatment modality, including pretreatment body mass index (BMI), complete blood counts and differential counts, biochemistry data, the chemotherapy regimen, and the response and side effects after IC. In cases where the patients received more than one serum study prior to treatment, we utilized the one closest to the diagnostic biopsy.

We recorded the efficacy based on OS, PFS, and overall response rate with the definitions of response evaluation criteria in solid tumors (RECIST), which are based on endoscopy, direct inspection, or image study within 1 month after IC.[15] Acute toxicities were measured clinically using the definition from the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, from the first course to 1 month after all courses of IC.[16] No prophylactic antibiotics were given after every course of IC, and supportive care was initiated if more severe toxicity was found.

2.2. Statistics

After data collection, receiver operating characteristic (ROC) curves were obtained for each factor to identify the best cut-off points. To examine acute toxicities, patients were divided into milder (grade 0 to II) and more severe (grade III to V) groups. To examine the initial response, patients were divided into groups according to the RECIST definitions of complete response (CR), partial response (PR), stable disease (SD), and progressing disease (PD).

Univariate analysis and a multivariate logistic regression model were applied to the response and acute toxicity data. p value <0.05 was considered as statistically significant. The statistical analyses were done using SPSS statistical software (SPSS, Inc., Chicago, Illinois).

3. RESULTS

3.1. Patient population

Based on the inclusion criteria, 40 patients were enrolled in this study. The median age was 55 years (range: 38 to 80 years old), and the majority of patients were male (95%). There were 20 patients who received intravenous TPF regimens and 20 who received intravenous TP regimens. There were 36 patients (90%) who were locally advanced (clinical T3-4) and 29 patients (72.5%) who were regionally advanced (clinical N2-3). The mean number of ICs courses was 2.18 ± 0.71 (Table 1).

3.2. Overall response

Among the 40 patients, 14 (35.0%) showed CR and PR in image studies, physical examination, or pan-endoscopy within 1 month after all courses of IC. Another 26 patients (65.0%) were SD or PD. The univariate analysis showed that many prechemotherapy hematological factors were significantly correlated with the overall response after IC, including a white blood cell (WBC) count ≥10.3 × 10^3/μL and a hemoglobin level ≥14.8 mg/dL. A percentage of neutrophils <73.5% and lymphocytes ≥16.5% revealed by differential WBC counts also had statistical significance, as did a neutrophil-lymphocyte ratio (NLR) ≥4.4 and a platelet-lymphocyte ratio (PLR) <8.5. No factor with significance could be found in the prechemotherapy serum biochemistry studies. Patient characteristics all had no statistical significance in the overall response, including age, gender, prechemotherapy BMI, alcohol habits, betel nut use, cigarette consumption, the primary site of cancer, and cell differentiations (Table 2).

Independent factors with statistical significance according to the univariate analysis were selected for multivariate analysis to identify the factors that might predict better OS before IC. A WBC count ≥ 10.3 × 10^3/μL, hemoglobin level ≥ 14.8 mg/dL, NLR ≥ 4.4, and PLR < 8.5 were analyzed via stepwise backward multivariate linear regression analysis. The only factor that showed statistical significance for the overall response after ICs was PLR <8.5 (Table 3).

3.3. Acute toxicity

Within the period of the first course of IC to one month after the last one, 24 out of 40 patients (60.0%) showed acute toxicities more than CTCAE v4.03 grade III, and five (12.5%) died of

Table 1

Patient characteristics (n = 40)

Parameters	Value	
Age, median (range), y	55	(38-80)
Sex (%)		
Male	38	(95.0)
Female	2	(5.0)
Localization (%)		
Oral cavity	14	(35.0)
Oropharynx	8	(20.0)
Hypopharynx	12	(30.0)
Larynx	4	(10.0)
Sinonasal tract	2	(5.0)
Stage (%)		
III	4	(10.0)
IV	36	(90.0)
Clinical T classification (%)		
cT0-2	4	(10.0)
cT3-4	36	(90.0)
Clinical N classification (%)		
cN0-1	11	(27.5)
cN2-3	29	(72.5)
Cell differentiation (%)		
Good to moderate	34	(85.0)
Poor to undifferentiated	6	(15.0)
Alcohol consumption (%)		
Yes	25	(62.5)
No	15	(37.5)
Betel nuts chewing (%)		
Yes	17	(42.5)
No	23	(57.5)
Cigarette consumption (%)		
Yes	30	(75.0)
No	10	(25.0)
Overall response to IC (%)		
CR or PR	14	(35.0)
SD or PD	26	(65.0)
Acute toxicities after IC (%)		
Grade 0-II	16	(40.0)
Grade III-V	24	(60.0)
Mean course of IC (±SD), times	2.18	(±0.71)

CR = complete response; IC = induction chemotherapy; PD = progressing disease; PR = partial response; SD = stable disease.

severe sepsis. Furthermore, 35 patients tolerated ICs well and continued with definite treatments.

Some pretreatment factors showed statistical significance with respect to the more severe grade of acute toxicity in univariate analysis. A hemoglobin level <12.2 mg/dL, percentage of neutrophils ≥67.5% and lymphocyte <19.5%, NLR ≥ 3.5, PLR ≥ 15.0, serum creatinine level ≥ 1.12 mg/dL, and potassium level <3.9 mEq/L showed a statistically significant relationship with having more than grade III acute toxicity. Alcohol consumption was the only characteristic factor of patients that showed statistical significance (Table 4).

Multivariate linear regression analysis was performed to identify the factors that truly contribute to a higher risk of more severe acute toxicity. Hemoglobin level <12.2 mg/dL, NLR ≥ 3.5, PLR ≥ 15, serum creatinine level ≥ 1.12 mg/dL, and potassium level <3.9 mEq/L were selected. The result showed that NLR ≥ 3.5 was the only predicting factor with statistical significance for a higher risk of severe acute toxicity (Table 5).

Since the discovery that NLR ≥ 3.5 might be associated with more severe acute toxicities, we also analyzed the relationship between acute side effects and the pretreatment NLR. Among all the acute toxicities, the status of NLR ≥ 3.5 was statistically significantly correlated with more severe acute hematologic toxicities (p = 0.026). However, only a significant association could be found with the risk of grade III-IV anemia (p = 0.006) in the group (Table 6).

4. DISCUSSION

Few studies have mentioned predictive factors for the overall response and acute toxicities after chemotherapy, particularly for taxane-containing regimens. For patients with advanced head and neck SCCs, we developed cut-off values of all parameters to overall response and acute toxicities by ROC curves, including PLR and NLR. We found out that a pretreatment PLR <8.5 could predict a better overall response, and NLR ≥3.5 could predict more severe acute toxicity after IC with docetaxel. In consideration of the risks and benefits of IC, these results could provide more precise information for making better therapeutic decisions.

The frequency of circulating hematopoietic precursors with lymphoid potential is significantly reduced in cancer patients, along with preferential expansion of granulocytic progenitor cells.[17] Thus, neutrophil and lymphocyte counts in peripheral blood could be attractive prognostic factors as a gauge of myeloid-lymphoid interactions.[18] The entry of cancer cell into the blood stream triggers platelet-mediated recognition, which is amplified by cell surface receptors, cellular products, extracellular factors, and immune cells.[19] Thus, platelet counts play an important role in the spread of cancer dissemination. Recently, blood NLR and PLR have emerged as important predictive factors for therapeutic outcomes in head and neck cancer of various anatomic sites, stages, and treatment modalities.[18,20] Among them, Chen et al demonstrated a result that the preoperative PLR is superior to NLR as an independent indicator in predicting DFS and OS in patients who undergo oral cancer resection for oral SCC.[21] However, the significance of these parameters has not been studied much in relation to the efficacy and risk of ICs, especially in docetaxel-combined regimens

IC has potential in treating advanced-staged head and neck cancers. It is capable of controlling microscopic metastasis and inhibiting tumor growth before definite treatments.[22] It also has potential for chemoselection before treating locally advanced cancers in the larynx or hypopharynx with organ preservation strategies.[11,12] In past years, platinum-based IC has become an initial therapeutic option in certain conditions. Moreover, better prognosis has been demonstrated with TPF than PF by many systemic reviews and randomized clinical trials, but the definite impact on survival is still controversial.[7–10,23,24] Based on the suggestions from the NCCN guidelines of 2018, an organ preservation strategy can be considered in some circumstances for laryngeal or hypopharyngeal SCCs if the overall response has reached PR or CR.[13]

The overall response after IC is important for patients who are in an advanced stage but are reluctant or unsuitable for radical surgery. A better quality of life can be established with successful organ preservation. In our study, PLR could predict the overall response for IC combined with docetaxel. Thus, physicians were able to screen patients for suitable organ preservation candidates and abandoned unnecessary ICs as the first treatment modality. Sato et al first revealed the predictive role of pretreatment NLR in the overall response after neoadjuvant chemotherapy with PF in patients with esophageal SCC.[25] Similar to our study results, Georgia et al demonstrated the predictive role of a lower pretreatment PLR level in achieving a better overall response rate of advanced head and neck SCCs.[26] Based on previous studies mentioning the relationship between platelet metabolism and cancer spread,[27,28] antiplatelet treatment is an

Table 2

Correlation of better overall response after docetaxel-combined IC with prechemotherapy characteristic and laboratory factors

Parameters	SD, PD (n = 26)		CR, PR (n = 14)		p
Age, y (%)					
≥65	4	(15.4)	1	(7.1)	0.64
<65	22	(84.6)	13	(92.9)	
Gender (%)					
Male	25	(96.2)	13	(92.9)	1
Female	1	(3.8)	1	(7.1)	
BMI, kg/cm^2 (%)					
≥23.1	13	(50.0)	3	(21.4)	0.101
<23.1	13	(50.0)	11	(88.6)	
Clinical T classification (%)					
cT0-2	2	(7.7)	2	(14.3)	0.602
cT3-4	24	(92.3)	12	(85.7)	
Clinical N classification (%)					
cN0-1	8	(30.8)	3	(21.4)	0.715
cN2-3	18	(69.2)	11	(88.6)	
Alcohol consumption (%)					
Yes	15	(57.7)	10	(71.4)	0.502
No	11	(42.3)	4	(28.6)	
Betel nuts chewing (%)					
Yes	12	(46.2)	5	(35.7)	0.739
No	14	(53.8)	9	(64.3)	
Cigarette consumption (%)					
Yes	18	(69.2)	12	(85.7)	0.446
No	8	(30.8)	2	(14.3)	
Cancer from pharyngeal origin (%)					
Yes	12	(46.2)	8	(57.1)	0.741
No	14	(53.8)	6	(42.9)	
Cell differentiation					
Good to moderate	24	(92.3)	10	(71.4)	0.159
Poor to undifferentiated	2	(7.7)	4	(28.6)	
WBC, 10^3/μL (%)					
≥10.3	14	(53.8)	2	(14.3)	0.02*
<10.3	12	(46.2)	12	(85.7)	
Neutrophils, percent (%)					
≥73.5	14	(53.8)	2	(14.3)	0.02*
<73.5	12	(46.2)	12	(85.7)	
Lymphocytes, percent (%)					
≥16.5	10	(38.5)	12	(85.7)	0.007*
<16.5	16	(61.5)	2	(14.3)	
NLR (%)					
≥4.4	16	(61.5)	2	(14.3)	0.007*
<4.4	10	(38.5)	12	(85.7)	
Hemoglobin, mg/dL (%)					
≥14.8	8	(30.8)	10	(71.4)	0.021*
<14.8	18	(69.2)	4	(28.6)	
Platelet count, 10^3/μL (%)					
≥276.5	15	(57.7)	2	(14.3)	0.017*
<276.5	11	(42.3)	12	(85.7)	
PLR (%)					
≥8.5	24	(92.3)	7	(50.0)	0.004*
<8.5	2	(7.7)	7	(50.0)	
BUN, mg/dL (%)					
≥14.5	16	(61.5)	4	(28.6)	0.096
<14.5	10	(38.5)	10	(71.4)	
Serum creatinine, mg/dL (%)					
≥1.02	11	(42.3)	9	(64.3)	0.32
<1.02	15	(57.7)	5	(35.7)	
AST, U/L (%)					
≥26.0	11	(42.3)	4	(28.6)	0.502
<26.0	15	(57.7)	10	(71.4)	
ALT, U/L (%)					
≥18.5	18	(69.2)	6	(42.9)	0.176
<18.5	8	(30.8)	8	(57.1)	
Serum sodium, mEq/L (%)					
≥138.5	12	(46.2)	4	(28.6)	0.329
<138.5	14	(53.8)	10	(71.4)	
Serum potassium, mEq/L (%)					
≥4.2	7	(26.9)	7	(50.0)	0.178
<4.2	19	(73.1)	7	(50.0)	

*$p < 0.05$.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; CR = complete response; IC = induction chemotherapy; NLR = neutrophil-lymphocyte ratio; PD = progressing disease; PLR = platelet-lymphocyte ratio; PR = partial response; SD = stable disease; WBC = white blood cells.

interesting issue for cancer management. To date, the effects and risks of antiplatelet treatment are still controversial.[29]

After IC with docetaxel, alopecia and diarrhea were common,[8,9] but more severe hematological toxicities including leukopenia, anemia, and thrombocytopenia were also observed with fatality. If leukopenia is accompanied by sepsis, it often becomes disastrous. Severe side effects might hinder further treatments for crucial tumor eradication, such as surgery or radiotherapy. Many patients have died with acute toxicity instead of tumor progression. Thus, prediction and prevention of acute hematological toxicities after IC are important, especially in regimens combined with docetaxel. However, no predictive factor has been found for predicting acute toxicities after ICs combined with docetaxel before. An NLR level ≥3.5 was identified as a

Table 3

Independent predicting factors of better overall response after docetaxel-combined IC, determined via stepwise backward multivariate linear regression analysis

Variable	Standard coefficient (β)	p
PLR < 8.5	2.599	0.016*
WBC count ≥ 10.3 × 10^3/μL	1.536	0.093

*$p < 0.05$.

IC = induction chemotherapy; PLR = platelet-lymphocyte ratio; WBC = white blood cells.

Table 4

Hematological and nonhematological adverse events after docetaxel-combined IC (n = 40)

Toxicity				
Hematologic (events)	Grade 0-II, %		Grade III-V, %	
Neutropenia	31	(77.5)	9	(22.5)
Febrile neutropenia	36	(90.0)	4	(10.0)
Anemia	32	(80.0)	8	(20.0)
Thrombocytopenia	38	(95.0)	2	(5.0)
Nonhematologic (events)				
Nausea/vomiting	38	(95.0)	2	(5.0)
Mucositis	39	(97.5)	1	(2.5)
Diarrhea	38	(95.0)	2	(5.0)
Acute kidney injury	38	(95.0)	2	(5.0)
Acute liver injury	38	(95.0)	2	(5.0)
Overall acute toxicity (patients)	16	(40.0)	24	(60.0)
Death	0	(0.0)	5	(12.5)

IC = induction chemotherapy.

Table 5

Correlation of more than grade III acute toxicity after docetaxel-combined IC with prechemotherapy characteristic and laboratory factors

Parameters	Grade 0-II (n = 16)		Grade III-V (n = 24)		p
Age, y (%)					
≥65	2	(12.5)	3	(12.5)	1
<65	14	(87.5)	21	(87.5)	
Gender (%)					
Male	15	(93.8)	23	(95.8)	0.767
Female	1	(6.2)	1	(4.2)	
BMI, kg/cm^2 (%)					
≥19.6	1	(6.2)	6	(25.0)	0.126
<19.6	15	(93.8)	18	(75.0)	
Clinical T classification (%)					
cT0-2	1	(6.2)	3	(12.5)	0.519
cT3-4	15	(93.8)	21	(87.5)	
Clinical N classification (%)					
cN0-1	5	(31.2)	6	(25.0)	0.665
cN2-3	11	(68.8)	18	(75.0)	
Alcohol consumption (%)					
Yes	13	(81.2)	12	(50.0)	0.046*
No	3	(18.8)	12	(50.0)	
Betel nuts chewing (%)					
Yes	7	(43.8)	10	(41.7)	0.896
No	9	(56.2)	14	(58.3)	
Cigarette consumption (%)					
Yes	13	(81.2)	17	(70.8)	0.456
No	3	(18.8)	7	(29.2)	
Cancer from pharyngeal origin (%)					
Yes	9	(56.2)	11	(45.8)	0.519
No	7	(43.8)	13	(54.2)	
Cell differentiation					
Good to moderate	13	(81.2)	21	(87.5)	0.588
Poor to undifferentiated	3	(18.8)	3	(12.5)	
WBC, 10^3/μL (%)					
≥8.8	10	(62.5)	10	(41.7)	0.197
<8.8	6	(37.5)	14	(58.3)	
Neutrophils, percent (%)					
≥67.5	6	(37.5)	19	(79.2)	0.018*
<67.5	10	(62.5)	5	(20.8)	
Lymphocytes, percent (%)					
≥19.5	12	(75.0)	5	(20.8)	0.001*
<19.5	4	(25.0)	19	(79.2)	
NLR (%)					
≥3.5	4	(25.0)	19	(79.2)	0.001*
<3.5	12	(75.0)	5	(20.8)	
Hemoglobin, mg/dL (%)					
≥12.2	15	(93.8)	16	(66.7)	0.044*
<12.2	1	(6.2)	8	(33.3)	
Platelet count, 10^3/μL (%)					
≥256.0	8	(50.0)	12	(50.0)	1
<256.0	8	(50.0)	12	(50.0)	
PLR (%)					
≥15.0	20	(50.0)	16	(66.7)	0.011*
<15.0	20	(50.0)	8	(33.3)	
BUN, mg/dL (%)					
≥14.5	5	(31.2)	14	(58.3)	0.093
<14.5	11	(68.8)	10	(41.7)	
Serum creatinine, mg/dL (%)					
≥1.12	1	(6.2)	9	(37.5)	0.025*
<1.12	15	(93.8)	15	(62.5)	
AST, U/L (%)					
≥24.5	5	(31.2)	14	(58.3)	0.093
<24.5	11	(68.8)	10	(41.7)	
ALT, U/L (%)					
≥17.5	10	(62.5)	15	(62.5)	1
<17.5	6	(37.5)	9	(37.5)	
Serum sodium, mEq/L (%)					
≥138.0	12	(75.0)	12	(50.0)	0.114
<138.0	4	(25.0)	12	(50.0)	
Serum potassium, mEq/L (%)					
≥3.9	15	(93.8)	16	(66.7)	0.044*
<3.9	1	(6.2)	8	(33.3)	

*$p < 0.05$.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; CR = complete response; IC = induction chemotherapy; NLR = neutrophil-lymphocyte ratio; PD = progressing disease; PLR = platelet-lymphocyte ratio; PR = partial response; SD = stable disease; WBC = white blood cells.

Table 6

Independent predicting factors of acute toxicities more than grade III after docetaxel-combined IC, determined via stepwise backward multivariate linear regression analysis

Variable	Standard coefficient (β)	p
NLR ≥ 3.5	2.605	0.002*
Serum potassium ≥ 3.9 mEq/L	2.326	0.065

*$p < 0.05$.

IC = induction chemotherapy; NLR = neutrophil-lymphocyte ratio.

predictive factor for acute toxicities after IC with docetaxel in our research. Interestingly, Patrice et al suggested NLR = 3.5 as a cut-off value in healthy adults.[30] A higher NLR level before treatment might lead to a concurrent subclinical inflammation, and the risks of postchemotherapy might increase.

In contrast, we also revealed that a pretherapeutic NLR level ≥3.5 was strongly correlated with more severe hematologic acute toxicities, especially grade III-IV anemia after IC with docetaxel-combined regimens. In nine patients with anemia, none of them had a hemoglobin level <8 mg/dL by the examination before treatment but five developed more than grade III anemia after the first IC (62.5%). In other 31 patients without anemia, three developed more than grade III anemia after the first IC (7.5%). It can be seen that it has a significant effect on IC in this type of patients. Vermorken et al and Posner et al revealed 9% to 12% of patients had grade III-IV anemia after IC with docetaxel-combined regimens in HNSCCs.[5,6] In our data, more events with more severe anemia (20.0%) was observed. Among patients with head and neck SCCs, chronic bleeding or chronic renal dysfunction causes few patients with severe anemia, but malnutrition is a common phenomenon. We speculate that in cases of myelosuppression due to IC, chronic malnutrition may strengthen the severity of anemia, such as folic acid and iron. Also, NLR and anemia can be used for evaluating subclinical inflammation and may covariate.[31–33] However, further research is still required for proving the true effect between NLR and the cause of anemia.

The pretherapeutic inflammation-based scores including NLR and PLR were used in many kinds of malignant tumors to predict the prognosis. In recent years, pretherapeutic serum CRP and Albumin levels were used in Glascow Prognostic Score (GPS),[34] modified Glascow Prognostic Score (mGPS),[35] and C-reactive protein/albumin ratio (CAR),[36] which were developed as a newer prognostic predicting model. GPS, mGPS, and

CAR are based on two kinds of serum protein but the PLR and NLR are purely calculated from the blood cell counts. The CRP level is more precise to detect acute infectious status and the lower albumin level is better to present the cachexic status than NLR/PLR. However, we tried to find out a simple hematologic model with PLR/NLR to predict short-term benefits and risks after IC in head and neck SCCs.

Chang et al demonstrated that pretreatment GPS can predict treatment tolerance, toxicity, and survival in patients with advanced head and neck cancer undergoing concurrent chemoradiation.[37] To the best of our knowledge, no previous study has examined the correlations between GPS, mGPS and CAR to overall responses and acute toxicities after IC with docetaxel in head and neck SCCs. Because it is a retrospective study, we have the limitation to obtain enough data to identify the significance of GPS, mGPS, and CAR to chemotherapy-related benefits and risks.

Even though the risk is deemed higher after chemotherapy, there is no well-established, comprehensive guideline for prophylactic medical treatment. For every patient with chemotherapy, a close follow-up duration is arranged to recheck laboratory data. Early intervention is initiated if abnormal. Antiemetics are used after high-dose platinum to prevent chemotherapy-induced nausea and vomiting. Once severe leukopenia is detected, granulocyte-colony stimulating factor is mostly used, and close observation is planned until the WBC count returns to a normal range. However, the majorities of cancer patients who receive chemotherapy do not need antibiotics and could tolerate the recovery period smoothly. For leukopenic patients, fluoroquinolone is the most useful for severe diarrhea and sepsis prophylaxis.[38–40]

The results of our study show that if a higher NLR is detected, a more aggressive medical intervention could be given to prevent more severe toxicity. Unnecessary medications including antibiotics and iron supplement could be abandoned to decrease the cost and probability of side effects if a lower NLR level is noted. Due to the limited case numbers, further data collection is still needed for the predictive value of NLR and indications for prophylactic medications.

In conclusion, a pretreatment PLR level <8.5 could predict a better overall response, and a pretreatment NLR level ≥3.5 could predict more severe acute toxicity after docetaxel-combined IC, especially anemia. Using a simple hematological examination, we could try to identify a better response of tumor regression and anticipate potentially harmful side effects after ICs. Adequate support strategies should be provided for patients who are expected to have higher risk to maximize the efficacy and minimize the risk of ICs.

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