Risk Scoring for Predicting Mucositis in Indian Patients With Esophageal Carcinoma Receiving Concurrent Chemoradiotherapy

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ABSTRACT

Purpose: Mucositis is a common and troublesome adverse effect of concurrent chemoradiotherapy, often causing treatment interruption and compromising treatment outcome. We sought to identify predictors of mucositis in southern Indian patients treated for gastroesophageal carcinoma.

Methods: Patients (N = 90) receiving cisplatin 40 mg/m^2 and concurrent local radiotherapy at 40 to 50 Gy for esophageal carcinoma were retrospectively assessed for predictors of mucositis. Hypothesized risk factors were age, presence of comorbid conditions, low white blood cell (WBC) count, nutritional status (assessed by serum albumin level), continuing tobacco use, elevated erythrocyte sedimentation rate (ESR) as a measure of acute inflammation, World Health Organization (WHO) performance status, and disease stage. Receiver operating characteristic (ROC) curves were drawn to identify cut-off values for risk factors, and a risk scoring model was developed.

Results: On the basis of cutoff values on ROC analysis, a risk score of 1 was assigned for each risk factor as follows: age > 50 years, ESR > 3 times upper limit of normal, albumin < 3.3 g/dL, WBC < 2.5 $\times 10^9$/L, WHO performance status > 2, and > stage III disease, with use of tobacco and presence of any comorbid condition also each being assigned a score of 1. For individual patients, a score of < 3 was associated with a 25% risk of grade 3 or 4 mucositis, whereas a score of ≥ 6 was associated with 80% risk.

Conclusion: The scoring system is accurate in predicting the development of mucositis in southern Indian patients receiving concurrent chemoradiotherapy for esophageal carcinoma.

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Mucositis is one of the most troublesome adverse events associated with cancer treatment. The lesions restrict oral intake, thereby adversely affecting nutritional status and immune status, and they act as entry sites for oral flora and sites of secondary infection.[1] Mucositis often results in treatment interruption and dose reduction, and may compromise survival in the adjuvant/neoadjuvant settings and quality of life in the palliative setting.

The incidence of mucositis during cancer chemotherapy ranges from 15% to greater than 70%.[2] Various studies have identified potential risk factors, including primary diagnosis, age, oral hygiene status, nutritional status, history of oral tobacco use, and nature of treatment (dose, frequency, number of drugs).[2] However, risk of mucositis appears to be variable even among patients with similar characteristics receiving identical treatments, and currently there is no comprehensive tool to assess the actual risk for the development of mucositis in ethnic southern Indian patients. We thus conducted a study to evaluate the predictors for mucositis in Indian patients with upper digestive tract malignancies receiving chemoradiotherapy.

PATIENTS AND METHODS

This was a retrospective analysis drawn from data in case records at two tertiary cancer centers serving two major states in southern India — Kidwai Memorial Institute of Oncology, Bangalore and MNJ Cancer Hospital, Hyderabad. Patients with esophageal carcinoma undergoing standard chemoradiotherapy with cisplatin 40 mg/m^2/week and concurrent local radiotherapy at 50 to 60 Gy were enrolled. Patient characteristics and laboratory details were noted from case records.

MedCalc for Windows version 7 (MedCalc Software, Mariakerke, Belgium) was used to perform the statistical analysis. The hypothesized risk factors were age,

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Table 1. Patient characteristics

Characteristic	Value/No. patients
Age (mean ± SD)	45 ± 14 years
Ratio men:women	4:1
Stage of disease, n (%)	
I	9 (10)
II	13 (15)
III	45 (50)
IV	23 (25)
WBC count (mean ± SD)	4.12 ± 1.44 × 10^9/L
ESR (mean ± SD)	25 ± 16 in 1st hour
WHO performance status, n (%)	
1	9 (10)
2	54 (60)
3	18 (20)
4	9 (10)
Serum albumin (mean ± SD)	2.8 ± 2.2 g/dL
Tobacco use, n (%)	40 (45)
Comorbid conditions, n (%)	54 (60)
Mucositis, n (%)	
Grade 1	13 (15)
Grade 2	18 (20)
Grade 3	23 (25)
Grade 4	36 (40)

Abbreviations: SD = standard deviation; WBC = white blood cell; ESR = erythrocyte sedimentation rate; WHO = World Health Organization

Table 2. Sensitivity and specificity of mucositis risk scoring model

Risk group	Score	Incidence of mucositis	Sensitivity to predict mucositis > grade 3	Specificity to predict mucositis > grade 3
High	6–8	Grade 3, 50% Grade 4, 30%	80%	75%
Intermediate	3–5	Grade 3, 35% Grade 4, 15%	55%	40%
Low	<3	Grade 3, 20% Grade 4, 05%	35%	15%

comorbid conditions such as diabetes and immunosuppressive treatment, low white blood cell (WBC) count, nutritional status (measured as serum albumin level), history of continuing tobacco use as a marker of poor oral hygiene as well as ongoing oxidative injury, elevated erythrocyte sedimentation rate (ESR) as a marker for acute inflammatory reaction; World Health Organization (WHO) performance status, and disease stage. Receiver operating characteristic (ROC) curves were drawn to determine cutoff values of these parameters, and the final scoring system was presented with sensitivity and specificity data.

Risk was assessed by 10-year interval for age, 0.5 × 10^9/L interval for WBC count, units of 1 for disease stage (I–IV), units of 1 for WHO PS, 0.5 gm/dL intervals for albumin levels, and number of times above upper limit of normal for ESR. For comorbid conditions and tobacco use, ROC curves were not drawn — indications of "yes" or "no" were assigned a score of 1 and 0, respectively. For the remaining parameters, based on the results of ROC curves, values above cutoff were scored as 1 and values below cutoff were scored as 0. Sensitivity and specificity for the final score were assessed for each score level, and based on the percentage of patients experiencing severe mucositis, they were grouped into low-, intermediate-, and high-risk groups.

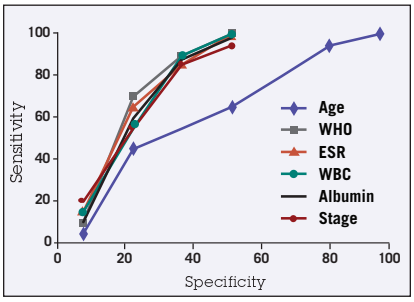

Figure 1. Receiver operating characteristic (ROC) curves for risk factors.
Abbreviations: WHO = World Health Organization; ESR = erythrocyte sedimentation rate; WBC = white blood cell (count)

RESULTS

A total of 98 patients with esophageal carcinoma receiving standard cisplatin plus local radiotherapy were enrolled in the study. The analysis was restricted to 90 patients for whom complete data on study variables were available. Baseline characteristics of the study participants are shown in Table 1. Patients had a mean age of 45 years (most in the fourth and fifth decades), the majority were male, half had stage III disease, more than half had comorbid conditions, and nearly half used tobacco (chewing as well as smoking).

The ROC curves plotted for 10-year intervals of age, 0.5 × 10^9/L intervals for WBC count, each unit of WHO performance status, each stage of disease, ESR level, and albumin level are shown in Figure 1. The cutoff values for high- vs. low-risk indicated by ROC curve analysis were 50 years of age or greater, WHO performance status of greater than 2, WBC count less than 2.5 × 10^9/L, ESR greater than 3 times the upper limit of normal, albumin level less than 3 g/dL, and disease stage of III or greater. For developing a risk score, a score of 1 was assigned to each of the following: age greater than 50 years, ESR greater than 3 times upper limit of normal, albumin less than 3.3 g/dL, WBC count less than 2.5 × 10^9/L, WHO performance status greater than 2, disease stage greater than III, use of tobacco, and presence of any comorbid condition. All other values, absence of tobacco use, and absence of any comorbid condition were assigned a score of 0.

Using this scoring system, the categories were chosen again by using ROC curves. Patient scores of 3 or less and 6 or more accurately predicted differences in the incidence of grades 3 and 4 mucositis in the study population. The sensitivity and specificity of the scoring system for predicting risk are shown in Table 2.

DISCUSSION

It is conventionally thought that mucositis is due to the direct inhibitory effects of chemoradiotherapy on DNA replication and mucosal cell proliferation, with reduction in the renewal capabilities of the basal epithelium eventually resulting in collagen breakdown, mucosal atrophy, and ulceration.[3] High cellular proliferation makes the mucosa more susceptible to this cytotoxicity.[4] In addition, associated inflammation and secondary infections further delay the healing process. It is clear that various treatment-related factors (eg; specific drugs, dose, schedule, use of radiotherapy and site of radiation therapy)[5] and patient factors (eg; age, type and stage of malignancy, oral hygiene, nutritional and immune status, and performance status)[4–7] play an important role in risk, duration, and severity of mucositis.

In the current study, differences in treatment-related factors were minimized by inclusion of only patients with esophageal carcinoma receiving cisplatin 40 mg/m^2 per week with concurrent radiotherapy at 50 to 60 Gy. The findings indicate that development of mucositis is likely multifactorial, with risk increasing as the number of patient-related risk factors increase. We found that older age was associated with increased risk. Although younger patients generally are considered to be at greater risk of mucositis (in association with a high mitotic rate due to high levels of growth factor receptors in the mucosa of young patients), poor repair capacity and greater frequency of comorbidities have been implicated in studies in which risk appears to be increased in older patients;[4] we believe that the latter hypothesis is more appropriate to our patient population. The association of such prognostic factors as poorer performance status and nutritional status (reflected by low serum albumin level) and lower WBC counts with increased risk for mucositis is not surprising, since these factors are interdependent and would predispose patients to compromised repair capacity of the mucosa after damage induced by chemoradiotherapy. Similarly, since inflammation is a proposed mechanism in the pathophysiology of mucositis, it is not surprising that elevated ESR contributed to risk in the current study.

More advanced disease stage, which requires larger radiation portals, is also recognized as a risk factor for mucositis. We observed that patients with more advanced disease stage had poor nutritional status and poorer performance status, again indicating that risk of mucositis is likely multifactorial. The effect of poor oral hygiene and use of tobacco (particularly chewing tobacco) in increasing risk of mucositis in our study was similar to that observed in prior studies.

In conclusion, we identified a scoring system that accurately predicts the probability of development of mucositis in Indian patients receiving concurrent chemoradiotherapy for esophageal carcinoma. This system has proved helpful in categorizing patients according to risk and allowing appropriate application of preventive strategies, such as use of growth factors and topical agents. To further develop and validate this model, we are planning a larger study across multiple cancer types.

REFERENCES

1. Sonis S: Oral complications. In: Holland JF, Frei E III, Bast RC Jr, (eds) Cancer Medicine, (4th ed) Philadelphia, PA, Lea & Febger, pp 3255–3264, 1997
2. Wilkes JD: Prevention and treatment of oral mucositis following cancer chemotherapy. *Semin Oncol* 25:538–551, 1998
3. Guggenheimer J, Verbin RS, Apple BN, et al: Clinico-pathologic effects of cancer chemotherapeutic agents on human buccal mucosa. *Oral Surg Oral Med Oral Pathol* 44:58–63, 1997
4. Pico J-L, Avila-Aaravito A, Naccache P: Mucositis: its occurrence, consequences, and treatment in the oncology setting. *Oncologist* 3:446–451, 1998
5. Kim JG, Sohn SK, Kim DH, et al: Phase II study of concurrent chemoradiotherapy with capecitabine and cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck. *Br J Cancer* 93:1117–1121, 2005
6. Mahood DJ, Dose AM, Loprinzi CL, et al: Inhibition of 5-fluorouracil-induced mucositis by oral cryotherapy. *J Clin Oncol* 9:449–452, 1991
7. Borowski B, Benhamou E, Pico JL, et al: Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation: a randomized controlled trial comparing two protocols of dental care. *Eur J Cancer B Oral Oncol* 30B:93–97, 1994

Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.