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Original research article

Predictors of chemoradiation related febrile neutropenia prophylaxis in older adults – Experience from a limited resource setting



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ARTICLE INFO

Article history:

Received 9 December 2017

Received in revised form

8 January 2018

Accepted 13 February 2018

Keywords:

Oncology in older adults
 Limited resource practice
 Febrile neutropenia
 Antibiotic prophylaxis
 Chemotherapy
 Fluoroquinolones

ABSTRACT

Aim: To identify risk factors that lower efficacy of antibiotic prophylaxis of febrile neutropenia among older patients on chemoradiation.

Background: Audit of institutional data showed that older adults are at higher risk of febrile neutropenia during chemoradiation. In limited resource settings widespread use of Granulocyte-Colony Stimulating Factor (G-CSF) is not economically feasible and antibiotics are used commonly. Despite compliance with antibiotics, prophylaxis is inadequate in many patients owing to patient and tumor related factors.

Materials and methods: Data from records of 219 older patients receiving antibiotic prophylaxis during chemoradiation were studied. Baseline assessment data and predisposing factors for febrile neutropenia were recorded. All patients received prophylactic fluoroquinolones. Incidence of febrile neutropenia and association with predisposing factors at baseline was analyzed by multiple logistic regression.

Results: 38.4% developed febrile neutropenia despite compliance. Multiple logistic regression revealed geriatric assessment (G8) score and tumor stage to be significant predictors of febrile neutropenia while on antibiotics ($p < 0.0001$). Odds ratios for two significant predictors G8 score and tumor stage, respectively, were 2.9 (95% CI 1.8036–4.6815) and 2.7 (95% CI 1.7501–4.1318). Correlation between these two significant predictors was found to be low in our cohort (Spearman's coefficient of rank correlation (ρ) = 0.431, $p < 0.0001$).

Conclusion: G8 score and tumor burden are significant predictors of efficacy of antibiotic prophylaxis among older adults receiving chemoradiation. In older patients having poor G8 scores and advanced tumors, antibiotic prophylaxis is unsuitable. Interestingly, comorbidities and poor performance status did not impact efficacy of antibiotic prophylaxis among our elderly patients.

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E-mail address: mails7778@gmail.com<https://doi.org/10.1016/j.rpor.2018.02.004>

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1. Background

Febrile neutropenia is a major determinant of dose reduction among patients on chemotherapy and is related to the extent and duration of neutropenia.¹ Guidelines suggest that patients at high risk of febrile neutropenia, particularly those receiving chemotherapy regimens that carry greater than 20% risk, should receive prophylaxis.² Older adults are identified as being at higher risk than the general population in clinical studies. Findings of the MONITOR-G-CSF study reinforce the evidence that patients older than 65 years of age are independently at higher risk of febrile neutropenia; which is further increased by chemotherapy regimens known to have a higher than 20% risk. In a limited resource practice scenario, elderly patients are particularly vulnerable to ill health largely owing to socioeconomic disadvantages that restrict access to adequate healthcare facilities and proper nutrition. Cost intensive treatments are not afforded by most patients and nursing care is mostly inadequate. Prophylaxis with Granulocyte-Colony Stimulating Factor (G-CSF) is not feasible universally among all older adults in our practice owing to financial constraints, and prophylaxis with antibiotics is the mainstay in practice.

A Cochrane review including 109 trials and over 13,000 patients revealed that antibiotic prophylaxis significantly reduced the risk of all causes of mortality, the risk of infection-related death, the occurrence of fever, and clinically documented infection.³ Prophylactic fluoroquinolones are the preferred choice.⁴

The issue of antibiotic resistance in patients receiving fluoroquinolones prophylaxis is of particular concern with reports of lower benefit in communities where resistance to fluoroquinolones is prevalent.⁵ However, studies have shown that patients receiving fluoroquinolone prophylaxis did not fare significantly worse in terms of morbidity and mortality from infection with resistant organisms.⁶ A study also revealed that developing fluoroquinolone resistance did not increase incidence and mortality of febrile neutropenia.⁷

The incidence of febrile neutropenia among older adults on chemo radiation at this institute is considerable, warranting antibiotic prophylaxis. An analysis at this tertiary cancer institute has revealed that a considerable number of those who received antibiotic prophylaxis presented with febrile neutropenia despite compliance and many of them required hospitalization and administration of parenteral antibiotics with or without G-CSF. Hospital admission places a considerable burden on the healthcare system; added costs of treatment with parenteral antibiotics and additional G-CSF, as appropriate, often exceed costs of primary prophylaxis with G-CSF. Any additional costs and hospital admissions have a considerable impact on an already burdened healthcare system where economic constraints demand prudent utilization of all available resources.

2. Aim

This study was intended to identify predisposing patient and tumor related factors that may lower the efficacy of prophylactic antibiotics among older adults during chemo radiotherapy.

3. Materials and methods

Data from records for 219 patients over the age of 65 years, who completed chemoradiation at our institute from September 2011 to January 2016, were studied. All these patients were prescribed fluoroquinolone prophylaxis (Table 1).

For every individual, predisposing patient and tumor related factors for febrile neutropenia at baseline were noted; poor performance status, poor nutritional status, previous chemotherapy, advanced disease, low baseline blood cell counts, low body surface area and presence of co-morbidities were taken into account. Nutritional status was assessed using Subjective Global Assessment score (SGA), performance status was assessed according to ECOG (Eastern Cooperative Oncology Group) score and geriatric screening was done by the G8 questionnaire. Among co-morbidities, organ dysfunction, congestive heart failure, chronic obstructive pulmonary disease and thyroid disease were considered most relevant in our practice.

The incidence of febrile neutropenia and consequent hospitalization were recorded in each patient. Concurrent chemotherapy for head and neck and cervical cancer was weekly Cisplatin. 5-Fluorouracil and Mitomycin C was administered concurrently with radiation for all anal cancer patients and 5-fluorouracil and leucovorin was concomitantly administered in rectal carcinoma patients. Accordingly, these patients were considered for fluoroquinolone prophylaxis, particularly

Table 1 – Demographic data of patients in study.

Patient characteristics (n = 219)	
Gender	
Male	92
Female	127
Age	65–89 years (median 78 years)
Primary site and stage	
Uterine cervix	121
FIGO stage II	53
FIGO stage III	37
FIGO stage IVA	31
Head and neck	36
Stage III (T3N0, T1–3N1)	19
Stage IVA (T4aN0 or N1, T1–4a N2)	10
Stage IVB (T4b any N, any T N3)	7
Esophagus	5
Stage I, II (T1–3, N0)	2
Stage III A (T1–2 N2, T3N1, T4aN0)	2
Stage IIIC (T4aN1–2, T4b, N3)	1
Anal canal	9
Stage II	5
Stage III	4
Rectum	48
Stage II	19
Stage III	29
Antibiotic prophylaxis	
Ciprofloxacin	72
Levofloxacin	147

for the first cycle of chemotherapy as the risk of febrile neutropenia is usually the highest for this cycle.

The institutional Director had kindly approved the study.

3.1. Statistical analysis

Single factor regression to identify significant predictors was followed by multiple logistic regression to analyze the association of recorded predisposing factors with the incidence of febrile neutropenia. Statistical analysis was done using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium).

4. Results

Among 219 individuals who completed chemoradiation, females represented the larger group (127/219). Treatment interruption was necessary in 21 patients owing to low hemoglobin levels and in 17 patients owing to grade 4 mucositis, none of these treatment gaps exceeded one week. Cervix cancer was the most common primary site constituting 55.3% of the study population. Levofloxacin was the more popular choice of antibiotic with 67.1% patients receiving it.

135/219 (61.6%) of all patients studied did not develop febrile neutropenia while on antibiotic prophylaxis. 84 (38.4%) patients presented with febrile neutropenia despite being compliant with antibiotic prophylaxis. Among 84 patients, 26 required hospitalization and treatment with parenteral antibiotics. Mucositis with poor nutrition was the cause of admission in 16 patients, 8 patients had diarrhea requiring intravenous fluids and 2 patients had vomiting that warranted intravenous fluids. 11 patients additionally required G-CSF to manage febrile neutropenia. 3 patients died due to neutropenic sepsis.

Low body surface area (BSA), nutrition grade (SGA), G8 score and tumor stage were found to have statistical significance ($p < 0.001$) by single factor regression analysis. These factors were included in the multiple logistic regression model using the stepwise method. On performance of multiple logistic regression, only G8 score and tumor stage were found to be statistically significant predictors of the development of febrile neutropenia while on antibiotic prophylaxis ($p < 0.0001$).

Multiple logistic regression performed by the stepwise method showed a good overall model fit ($p < 0.0001$). Results of the Hosmer–Lemeshow test confirmed the suitability of the

model for assessing the chosen variables (Chi square = 4.51, $p = 0.8084$).

Odds ratios for the two significant predictors were similar; 2.9 (95% CI 1.8036–4.6815) and 2.7 (95% CI 1.7501–4.1318) for G8 score and tumor stage, respectively (Table 2).

Kruskal–Wallis test showed significant differences in the occurrence of febrile neutropenia in this cohort between groups based on G8 score ($p = 0.0086$) and tumor stage ($p = 0.0101$).

Correlation between the two significant predictor variables was low (Spearman's coefficient of rank correlation (ρ) = 0.431, $p < 0.0001$).

5. Discussion

Older patients are at a higher risk of febrile neutropenia, and in our practice the incidence of febrile neutropenia among older patients on chemo radiation is considerably high. The practice of fluoroquinolone prophylaxis is widely prevalent among patients with hematological malignancies and also solid tumors receiving chemotherapy with a moderate to high risk of febrile neutropenia. In limited resource oncology settings it is the mainstay of prophylaxis. G-CSF can only be instituted when patients are able to afford it or if funding is available. At this institute, prophylactic fluoroquinolones were used for these elderly patients on chemoradiation.

The efficacy of antibiotic prophylaxis in the prevention of febrile neutropenia is reported in literature to be fairly reliable.⁸ Guidelines recommend antibacterial prophylaxis with a fluoroquinolone for high-risk patients expected to be neutropenic over 7 days.⁹ However, a considerable number of older adults in our practice presented with febrile neutropenia despite being compliant with antibiotic prophylaxis and a sizeable proportion of that population needed hospitalization. This study intended to investigate the association of patient related factors with the occurrence of febrile neutropenia in our patients who were on antibiotic prophylaxis during chemoradiation. A search of literature revealed that the major patient related predisposing factors were poor performance status, poor nutritional status, advanced disease, low baseline blood cell counts, low body surface area and presence of co-morbidities.¹⁰

In this study cohort, G8 score ($p = 0.0086$) and tumor burden ($p = 0.0101$) appeared to be significantly associated with febrile neutropenia occurrence while on antibiotic prophylaxis. Patients' risk of developing febrile neutropenia was

Table 2 – Coefficients and Odds ratios for the significant predictors.

Coefficients and standard errors			
Variable	Coefficient	Std. error	<i>p</i>
G8 score	1.06669	0.24333	<0.0001
Tumor stage	0.98918	0.21915	<0.0001
Odds ratios and 95% confidence intervals			
Variable	Odds ratio	95% CI	
G8 score	2.9057	1.8036–4.6815	
Tumor stage	2.6890	1.7501–4.1318	

found to be nearly three times as likely to be significantly affected by changes in G8 score (Odds ratio 2.9) and tumor stage (Odds ratio 2.7). The impact of the other predisposing factors was rendered insignificant by the use of antibiotic prophylaxis.

The coexistence of poor G8 scores with a large tumor burden could have explained the higher risk of febrile neutropenia despite prophylaxis. However, statistical correlation was found to be low between these two factors in our cohort.

Of particular interest was the finding that a poor performance status did not worsen the benefit of antibiotic prophylaxis although it is widely acknowledged that the performance status plays a significant role in cancer therapy related febrile neutropenia. Patients with co-morbidities also did not have a significantly high incidence of febrile neutropenia; apparently fluoroquinolone prophylaxis was adequate for these patients.

The findings reinforce the importance of geriatric assessment in older patients starting chemoradiation. Clearly, geriatric assessment score and tumor burden helps identify those patients requiring special attention with regard to G-CSF prophylaxis for lowering neutropenia related morbidity and hospitalization. The presence of co-morbidities and a poor performance status in older patients should not by themselves deter physicians from prescribing antibiotic prophylaxis in the limited resource scenario when financial constraints limit the use of G-CSF. Without any prophylaxis, neutropenia related morbidity and mortality is high among older patients on chemo radiation in our practice. Dose reductions and delays are also a commonplace; a third of these patients in our practice are unable to complete their prescribed course of treatment.

The findings of this study cannot be generalized among older adults in clinical practice where financial constraints do not limit the use of G-CSF. Differences owing to ethnicity have also not been accounted for. Future studies comparing these predictors with the use of G-CSF prophylaxis are necessary to identify those groups who have a clear benefit from primary prophylaxis with G-CSF to reduce healthcare costs.

Conflict of interest

None declared.

Financial disclosure

None declared.

Acknowledgements

The author would like to thank Dr Jaydip Biswas, Director of this institute for his kind approval and Dr Partha Nath for his support.

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