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To study the efficacy of romiplostim in chemotherapy-induced thrombocytopenia in head and neck cancer patients

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ABSTRACT

Objectives: Scheduled delivery of adequate dose of chemotherapy is important to replicate the results expected from original trials. In head and neck malignancies, undue delay of chemotherapy is likely to be associated with poor control or progression. Chemotherapy-induced thrombocytopenia (CIT) is one of the reasons to delay chemotherapy. Thrombopoietin agonists (TPO-A) have been found to increase platelet counts by increasing production and mobilization of platelets. Romiplostim is a TPO agonist, studied widely and found to have good impact on prevention and treatment of CIT. The purpose of this study was to analyze the use and effect of romiplostim in CIT in locally advanced head and neck cancer patients.

Material and Methods: It is a retrospective study regarding practices of romiplostim use in controlling CIT, among patients of locally advanced head and neck carcinoma undergoing induction chemotherapy at a tertiary care cancer center. Data regarding delays in chemotherapy, response assessment, and modification of chemotherapy doses were also noted.

Results: Out of a total of 110 patients of head and neck malignancy enrolled during the study period, 18 patients received romiplostim support at least once in chemotherapy cycles and were analyzed. All patients were locally advanced and planned for induction chemotherapy. Median platelet counts before starting romiplostim was 76,000 per cumm. A median delay of ten days was noted among these cases where romiplostim was introduced after the first cycle of chemotherapy. Patient receiving romiplostim after the second cycle (n = 6) showed a median delay of 11.5 days (6–18 days) in the initiation of subsequent chemotherapy. None of them was shifted out of chemotherapy plan due to low platelet count. No dose reduction was noted in any of the cases.

Conclusion: This study provides a good insight about feasibility of using romiplostim in this subset of patients without delay, dose reduction, or discontinuation of chemotherapy.

Keywords: Thrombocytopenia, Chemotherapy, Locally advanced head and neck carcinoma

INTRODUCTION

Thrombocytopenia is a common symptom of cancer patients and can be brought on by the disease, its therapy, tumor infiltration of the bone marrow (BM), or other etiologies such as liver disease or infection. Chemotherapy-induced myelosuppression and subsequent thrombocytopenia is a common finding with chemotherapeutic agents like gemcitabine, taxane, or platinum.[1] Significant delay in chemotherapy can happen due to low platelet counts, and transfusion of platelets often yields temporary increments only. The delay or interruption of chemotherapy has been shown to affect outcome in a negative way.[2] Apart from chemotherapy delay, very low platelet counts also increase the risk of bleeding and thus deterioration of patient's general condition. The remedial measures in chemotherapy-induced thrombocytopenia (CIT) setting were not well defined in the past, except for platelet transfusion and delay or dose reduction of chemotherapy. Recent decade has seen emerging reports of

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use of thrombopoietin agonists (TPO-A) in the setting of CIT in a variety of malignancies.[3–5] TPO-A has been widely used for immune thrombocytopenia (ITP), hepatitis C-induced thrombocytopenia, and thrombocytopenia of other reasons.[6–8] TPO-A have been used across all ages and no major safety concern was noted. Cases of thromboembolism with TPO-A put a serious safety concern question in cancer setting, which is itself a prothrombotic state, thus in need of vigilance on platelet counts while using it.[9] This study was planned to retrospectively analyze the practice of using romiplostim and its effect on platelet count in locally advanced head and neck cancer squamous cell carcinoma (LAHNSCC) cases that developed CIT.

MATERIAL AND METHODS

Type and design

This single center-based retrospective analysis of data, conducted at the cancer research institute, swami rama himalayan university, was a study regarding the practices of romiplostim use in controlling CIT among patients of locally advanced head and neck squamous cell carcinoma with stage III and IV undergoing induction chemotherapy. Permission was obtained from the institutional research board (IRB) beforehand, with reference letter number SRHU/HIMS/E-1/2023/84.

Patients

Study period was defined from january 2022 to january 2024. Data of patient 18 years or older, with histologically proven squamous cell carcinoma head and neck (locally advanced) and eastern cooperative oncology group performance status of two or below, were analyzed to segregate the subset of cases with thrombocytopenia (defined as a platelet count of 100,000 mL).

Exclusion was made for cases with existence of primary or metastatic liver cancer, patient who had significant protocol violation (default or interruptions >6 weeks), and patients who had received chemotherapy within two weeks of the finding of thrombocytopenia (considering possibility of chemotherapy-induced transient myelosuppression).

Treatment details

Data were collected regarding baseline demographic parameters, disease stage and extent, chemotherapy detail and cycles, serial platelet counts, and required support in the form of transfusions and romiplostim administration schedule. Data regarding delay in chemotherapy and modification of chemotherapy doses were also noted. Interval admission and prolongation of stay were noted and causes for such stay were documented. Any adverse effects of romiplostim in the form of allergy or deranged biochemistry or thromboembolism were actively searched in records.

Evaluation

Response was defined as increment of platelets to get level 100,000 cmm or more. Dosage of romiplostim required per case to achieve adequate platelet counts was noted.

RESULTS

During the study period of six months, total of 110 cases were enrolled in the locally advanced head and neck squamous cell carcinoma induction chemotherapy program. Six cases opted out or defaulted and were excluded from analysis. One case died with aspiration pneumonitis before chemotherapy and was excluded. Out of 103, 18 cases (17.4 %) received romiplostim support at least once in chemotherapy cycles. Table 1 shows patients' baseline characteristics. All cases were locally advanced and planned for induction chemotherapy followed by surgery (n = 6) or Concurrent chemoradiotherapy (CTRT) (n = 12). Median platelet counts before starting romiplostim was 76,000 cmm (range 35,000–96,000 cmm). Platelet counts were low even before the first chemotherapy among three cases, with a median 80,000 cmm. All three were diagnosed with peripheral platelet destruction, possibly ITP, with normal BM examination report.

As protocol, all cases were planned for three cycles of paclitaxel (175 mg/m^2) and carboplatin (Area Under Curve (AUC) 7)-based induction chemotherapy with locally advanced HNSCC cases, planned at 21 days cycle gap; however, three cases received fourth cycle of chemotherapy as well while awaiting definitive local treatment. Three patients

Table 1: Baseline characteristics of patients treated with romiplostim for chemotherapy-induced thrombocytopenia (CIT).

Patients characteristics	
Gender (male:female)	6.2:1
Median age, years (range)	54 (40–68)
Cancer Site n (%)	
Oral Cavity	7 (39)
Oropharynx	6 (33)
Hypopharynx	2 (11)
Larynx	3 (17)
Cancer Stage n (%)	
III	5 (28)
IVa	9 (50)
IVb	4 (22)

received all chemotherapy cycles after romiplostim as their baseline platelets were low. Among six cases, romiplostim was required before the second cycle, while 15 cases required romiplostim before the third cycle of chemotherapy. A median delay of ten days was noted among these cases where romiplostim was introduced after the first cycle of chemotherapy. Patients receiving romiplostim only after the second cycle (n = 6) showed a median delay of 11.5 days (6–18 days) in the initiation of subsequent chemotherapy. Three patients received two cycles only and proceeded for definitive surgery thereafter, while one case got interruption after two cycles and shifted to palliative radiation. None of them was shifted out of chemotherapy plan due to low platelet count. No dose reduction was noted among any of the cases.

Romiplostim was given as 3–8 μg/kg dosing, weekly schedule. Round off to the available strength (250 μg and 500 μg) was done. Patients who once required romiplostim were placed on prophylactic romiplostim dosing for the subsequent duration of chemotherapy. For platelet counts more than 200,000 cmm, the dose was skipped and platelet count was followed weekly. Any fall below 150,000 cmm was taken as a trigger to restart romiplostim injection. Median doses of romiplostim were five shots at weekly intervals. Platelet counts were checked weekly in a majority of cases and chemotherapy was given on platelet counts more than 100,000 cmm on the day of chemotherapy. For one case, chemotherapy was given at platelet count >90,000 cmm. Romiplostim was given after chemotherapy on the same day. Among cases with <50,000 cmm of platelet counts, median two doses (range 1–4) of romiplostim were required to raise platelet counts >100,000 cmm. Among cases with platelet counts >50,000 cmm, five cases showed platelet count >100,000 cmm after one dose of romiplostim, while the remaining nine cases required two doses for this desired increment [Table 2]. No thrombotic event was noted among any of the cases. Post chemotherapy, two cases noted platelets of <20,000 cmm despite romiplostim. Both were supported with platelet transfusions, a total of three episodes. No chemotherapy dose reduction was done. Four cases received red blood cell transfusions as well for anemia.

DISCUSSION

As per global cancer observatory statistics, head and neck malignancies constitute 10.3% of all adult malignancies.[10] Head and neck cancer accounts for about 4% of all cancers in the united states. This year, an estimated 66,470 people (48,520 men and 17,950 women) will be diagnosed with head and neck cancer. Worldwide, an estimated 562,328 people were diagnosed with head and neck cancer in 2020.

Induction chemotherapy has been planned in stage III or IV, where upfront surgery seems difficult with the desired negative surgical margin. Paclitaxel and carboplatin have been used as chemotherapy in such cases.[11] Incidence of thrombocytopenia with platinum chemotherapy as well as taxane has been well documented.[12] Use of TPO agonists in such settings has shown encouraging results.

TPO agonists used in CIT have been elaborated in a few studies and encouraging results have been noted.

Table 2: Platelet count variation among cases in various cycles and delay in chemotherapy.

Case Number	Platelet counts (in 1000 cmm) at scheduled first cycle	Delay in first cycle (days)	Platelet count (in 1000 cmm) at scheduled second cycle	Delay in second cycle (days)	Platelet count (in 1000 cmm) at scheduled third cycle	Delay in third cycle (days)
1	300	-	120	-	78	8
2	150	-	66	10	-	-
3	85	6	150	-	280	-
4	180	-	150	-	90	6
5	200	-	89	18	-	-
6	250	-	76	14	45	18
7	70	9	225	-	300	-
8	250	-	120	-	55	9
9	200	-	80	7	-	-
10	180	-	35	10	80	10
11	325	-	45	26	35	22
12	125	-	150	-	60	14
13	250	-	200	-	48	18
14	250	-	45	12	-	-
15	80	12	140	-	125	-
16	300	-	300	-	96	-
17	190	-	220	-	76	18
18	250	-	90	6	80	7

Parameshwaran *et al*. described the use of romiplostim among 20 solid tumor cases where prolonged CIT was noted. They found encouraging results with desired platelet increment in most of the cases.[13] In a multicentric study of romiplostim use in CIT, including lymphomas and solid tumors, a noticeable response in the form of raised platelet count, decreased duration of thrombocytopenia, and reduced delay in chemotherapy was noted among solid tumors.[14] Hanny Al-Samkari *et al*. also noted similar results with romiplostim.[5] This study elaborated about the variable time lag of platelet count increment. While 59% cases achieved the desired platelet count of >100,000 cmm in one week of romiplostim, 18% cases required 7–12 weeks of therapy for such effect. This study noted a relatively quick and uniform romiplostim response and a platelet response in 1–2 weeks among most of the romiplostim group cases. It also noted prompt response among ITP cases.

CIT involves chemotherapy dose reductions and treatment delays; reduced relative dose intensity of chemotherapy may have a negative impact on optimal management of the malignancy and may lower overall and progression-free survival.[2] Our study noted no need for dose reduction among romiplostim patients, although a delay in next cycle was observed. Effect of delay and dose reduction in such subset of head and neck malignancy is not known precisely.

Romiplostim-induced thrombotic events are not noted in our study. Incidences of vascular thrombosis with romiplostim in CIT setting are variable with none to few cases.[9,14]

Our study also noted no thrombocytosis secondary to romiplostim.

There are certain limitations to our study. Retrospective, observational nature of study makes the finding less robust. This study has smaller sample size and has no control group, further making it small to draw any significant conclusion.

CONCLUSION

Romiplostim can be used effectively to raise platelet counts in CIT in head and neck cancers. A larger randomized controlled study is required to recommend this practice as standard.

Ethical approval

The research/study approved by the institutional review board (IRB) at Swami Rama Himalayan University with IRB number SRHU/HIMS/E-1/2023/84, dated 13/07/2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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