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Original Research Article

A retrospective analysis: comparison of nephrotoxicity caused by concurrent weekly cisplatin in patients of head & neck cancer and cervical cancer

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ABSTRACT

Background: Cisplatin is the most common chemotherapeutic drug which is used concurrently with radiation therapy due to its radio sensitizing effect. Cisplatin is known to cause substantial amount of nephrotoxicity and adequate hydration is absolutely essential while administering cisplatin. Once weekly regimen is widely used both in the treatment of head & neck cancers as well as cervical cancer. The main aim of this study is to compare the incidence and severity of nephrotoxicity in patients of head and neck and cervical cancer treated with concurrent chemoradiation
Methods: From January 2023 to December 2023, data of 50 patients each of head and neck cancer and cervical cancer patients treated at our institute was evaluated. Cisplatin was used weekly at the dose of 40 mg/m2 with adequate hydration and necessary pre medications in all the patients. CBC, RFT and Serum Electrolytes were done prior to each cycle. RIFLE criteria were used to classify renal impairment
Results: 50 patients each of head and neck and cervical cancer were selected. Total 5 cycles of concurrent cisplatin were planned in both the arms according to the institutional protocol. During the course of treatment, Renal impairment was seen in 32 out of 50 patients (64%) in head and neck cancer arm whereas in ca cervix arm it was seen in only 14/50 patients (28%)
Conclusions: Renal impairment is more pronounced in head and neck cancer patients as compared to cervical cancer patients thus more aggressive hydration measures are required in patients of head and neck cancer

Keywords: Carcinoma cervix, Concurrent chemoradiation, Head and neck cancer, Nephrotoxicity

INTRODUCTION

Cisplatin is the most common chemotherapeutic drug used concurrently with radiotherapy.[1] Cisplatin is known to cause substantial amount of nephrotoxicity which is the major dose limiting toxicity.[2] Adequate hydration and frequent monitoring of Renal function tests and Serum electrolytes is mandatory while administering cisplatin.[2] It is a very common practice to administer once weekly regimen of cisplatin in both head and neck and cervical cancer patients. The main aim of this study is to compare the incidence and severity of nephrotoxicity in patients of head and neck and cervical cancer treated with concurrent chemoradiation.

METHODS

From January 2023 to January 2024, 50 patients each of head and neck cancer (HNC) and cervical cancer patients treated at Sri Ramachandra Institute of higher education

and research, Chennai were evaluated. The sample size calculated for this study was based on the methodology delineated in Bagri et al, to ensure methodological consistency and to enhance the comparability of the findings with prior research. Inclusion criteria for HNC patients were Eastern cooperative oncology group (ECOG) performance status of 0-2, Age 18-70 and histopathologically proven squamous cell carcinomas (SCC). Inclusion criteria for Cervical cancer patients were ECOG performance status 0-2, age 18-70, histopathologically proven SCCs and FIGO stage II-IVA without any obstructive uropathy. Exclusion criteria were patients treated with chemotherapy for any other prior malignancy, renal and liver function impairment, cardiac abnormalities, significant hearing loss, prior peripheral neuropathy and pregnancy.

Both the arms were treated with concurrent chemoradiation. HNC patients were planned for EBRT on Elekta for a total dose of 66-70 Gy in 33-35 fractions by IMRT. Cervical cancer patients were also planned for EBRT on Elekta for a total dose of 50.4 Gy in 28 fractions followed by 3 fractions intracavitary brachytherapy of 7 Gy each using Iridium-192. Brachytherapy was initiated a week after the completion of EBRT and each fraction was given one week apart.

Cisplatin was administered weekly at a dose of 40 mg/m^2 with 1 litres of Normal Saline (NS) before and after the administration of cisplatin. Premedication included Inj Pheniramine 2 cc, Inj Ranitidine 50 mg, Inj Dexamethasone 8 mg, Inj Ondensetron 8 mg which was given through intravenous (IV) route. Tab Olanzapine 5 mg was also given per oral. Complete blood counts, Renal function tests and Serum Electrolytes were done prior to each cycle. RIFLE criteria (Table 1) was used to classify renal impairment.

During treatment, patients presenting with side effects of CCRT were adequately treated. IV Fluids were administered and also Ryle's tube was placed who were not able to take food and water orally due to mucositis

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics Software version 26.0. The level of statistical significance was set at $p<0.05$ with 95% confidence interval. Chi-square test for independence was employed to determine the statistical significance between the HNC and cervical cancer groups.

RESULTS

In the HNC arm, of the 22 patients aged ≥60 years, 18 (81%) patients developed nephrotoxicity (p=0.02). In the Ca Cervix arm, of the 16 patients aged ≥60 years, 4 (25%) patients developed nephrotoxicity(p=0.7471). In the HNC arm, all the 12 patients who had HTN (100%) developed nephrotoxicity ($p<0.05$). In the Ca Cervix arm, of 14 patients who had HTN, 4 (28%) developed nephrotoxicity (p=0.9496).

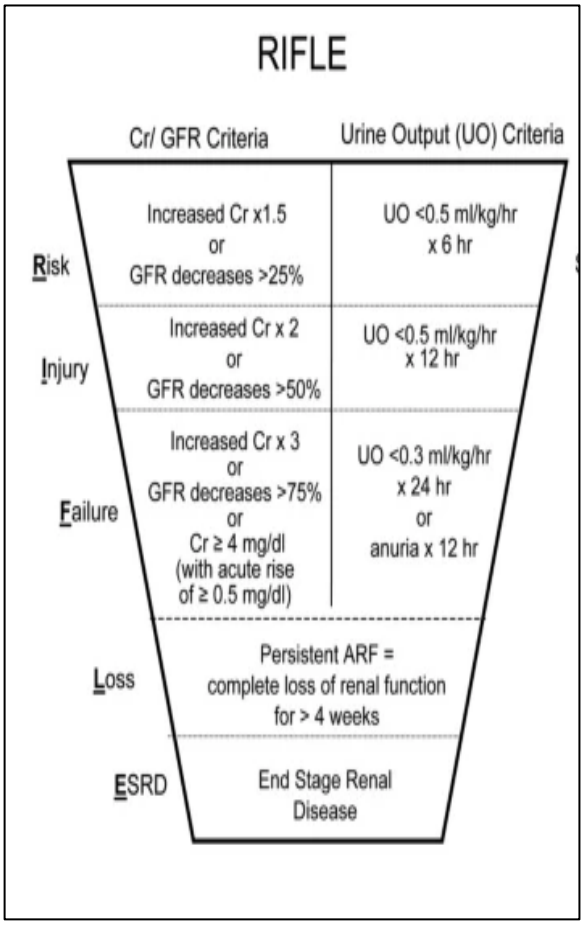

Figure 1: Criteria to classify renal impairment.

In the HNC arm, all the 12 patients who had T2DM (100%) developed nephrotoxicity (p=0.0029). In the Ca cervix arm, of the 16 patients that had T2DM, 10 (62.5%) patients developed nephrotoxicity (p=0.0002). During the course of treatment, renal impairment was seen in 32/50 patients (64%) in the HNC arm, whereas in Ca Cervix arm it was seen in only 14/50 patients (28%).

In the HNC arm, of the 34 patients who received ≥40 mg/m^2 of weekly Inj. Cisplatin, 20 patients (58.8%) developed nephrotoxicity (p=0.2662). In the Ca Cervix arm, of the 28 patients who received ≥40 mg/m^2 of weekly Inj. Cisplatin, 12 patients (42.8%) developed nephrotoxicity (p=0.0083). In both the arms 46 patients each received at least 3 or more cycles of weekly Inj. Cisplatin, of which, 28 patients (60.8%) in the HNC arm (p=0.1179) and 10 patients (21.7%) in the Ca Cervix arm (p=0.0006) developed nephrotoxicity.

Table 1: Patient characteristics.

Variables	HNC, N (%) (n=50)	CA cervix, N (%) (n=50)	P value
Age (in years)			
<60	28 (56)	34 (68)	0.29
≥60	22 (44)	16 (32)	0.474
Comorbidities			
Hypertension (HTN)	12 (24)	14 (28)	1.0
Type II diabetes mellitus (T2DM)	12 (24)	16 (32)	0.80

Table 2: Tumour characteristics.

Variables	HNC (%)	CA cervix (%)	P value
Histology			
Well differentiated SCC	6 (12)	8 (16)	0.143
Moderately differentiated SCC	34 (68)	24 (48)	0.862
Poorly differentiated SCC	10 (20)	18 (36)	1.143
Stage			
II	4 (8)	22 (44)	<0.05
III	14 (28)	26 (52)	<0.05
IV	32 (64)	2 (4)	<0.05

Table 3: Treatment and toxicity details.

Variables	HNC (%)	CA cervix (%)	P value
Chemotherapy dose (mg/m^2)			
≥40	34 (68)	28 (56)	0.29
<40	16 (32)	22 (44)	0.474
No. Of chemotherapy cycles			
≥3	46 (92)	46 (92)	1.0
<3	4 (8)	4 (8)	1.0
Nephrotoxicity (Rifle criteria)			
Risk	16 (32)	10 (20)	0.55
Injury	16 (32)	4 (8)	0.716

DISCUSSION

Concurrent chemoradiation (CCRT) has been the standard of care for majority of head and neck cancers and cervical cancers. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC) has shown 6.5% improvement in overall survival (OS) with the addition of chemotherapy to External beam radiotherapy (EBRT) compared to EBRT alone.[6] Different chemotherapy regimens have been tested but the standard treatment has been administration of 3 weekly concurrent cisplatin at the dose of 100 mg/m2. However, the most widely accepted alternative is weekly cisplatin at the dose of 40 mg/m2 which is our institutional protocol also.[14]

National Cancer Institute(NCI) of United States announced in 1999 that strong consideration should be given to addition of concurrent cisplatin based chemotherapy in patients of cervical cancer treated with radiation therapy.[10] A 2008 Cochrane review found that CCRT improved OS in cervical cancer by 6% compared to radiation alone.[7] During the initial years many chemotherapy agents were tried but Cisplatin has been the most commonly used agent for the treatment of head and neck and cervical cancers.[1] Cisplatin has been traditionally administered at a weekly dose of 40 mg/m2 for cervical cancer.[12,13]

Cisplatin reacts with two different sites on DNA to produce cross links, both intra-strand as well as inter-strand. This results in formation of DNA adducts which leads to inhibition of DNA synthesis and function and also inhibits transcription. It is a proven fact that radiation induced free radicals along with toxic platinum intermediates increases cell killing.8 Cisplatin scavenges the free electron and thus the repairable damage caused by radiation gets fixed which in turn becomes lethal for the cell.

There are many major side effects of cisplatin including ototoxicity, myelosuppression, nephrotoxicity, neurotoxicity and Gastro-intestinal toxicity.[4] Dose related and cumulative renal insufficiency, including acute renal failure, is the major dose limiting toxicity of cisplatin.[2] The

frequency of cisplatin-induced nephrotoxicity (CIN) is reported to be 28–42%.[3] Even with single dose of cisplatin infusion the rate of nephrotoxicity is reported to be about 25-35%.[11] Cisplatin is usually administered along with IV fluids and electrolyte corrections in spite of which it is capable of producing significant nephrotoxicity.

Maintaining adequate hydration is very important in preventing cisplatin induced nephrotoxicity and considered the standard method.[15,16] The incidence of nephrotoxicity might increase with subsequent increase in the number of cycles administered. There is a controversy regarding the usage of osmotic diuretics like mannitol for cisplatin induced nephrotoxicity.[9] However mannitol was not administered to any of our patients according to the institutional protocol.

In HNC, during CCRT, oral mucositis significantly increases with radiation as the treatment progresses which significantly affects the oral intake of fluids.[2] In HNC arm patients developed nephrotoxicity even when they received lower dose of cisplatin or lesser number of cycles which clearly indicates the higher risk of nephrotoxicity in HNC patients, whereas in Ca Cervix arm, the incidence of nephrotoxicity was significantly higher with increased dose and number of cycles of cisplatin. Various risk factors which are associated with Cisplatin induced AKI are older age>60 years, history of hypertension, Cisplatin dose >100 mg, hypoalbuminemia (2-3.5 g/dl).[5] In our study there was a significant association between nephrotoxicity and T2DM because irrespective of the primary site patients who had T2DM were seen to be at a higher risk of developing nephrotoxicity.

There are a few limitations in this study. The sample size is very small. Also in our study we have assessed only the acute kidney injury developed in patients. Assessment of chronic kidney injury requires a longer follow up. In addition to it, the retrospective nature of our study is a limitation. Fourth limitation is that in our area during summer, the temperature rises to about 49-500 C which could be another factor causing dehydration and AKI in addition to cisplatin related nephrotoxicity.

It is suggested that all patients of HNC should be treated with Ryle's tube feeding from the end of 2nd week onwards so that adequate hydration can be maintained.[4] In carcinoma cervix without obstructive uropathy, renal function impairment is less severe as oral intake of water and liquid is not much impaired.[4]

CONCLUSION

The incidence of nephrotoxicity is higher in patients of HNC as compared to Ca Cervix. Possible causes for the same would be oral mucositis due to radiation and also sometimes, disease site itself may cause decreased oral intake. Hence adequate hydration and frequent monitoring of renal parameters is mandatory while giving cisplatin, especially in HNC patients.

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