Original Article

A Comparative Study of Response and Toxicity between Weekly Cisplatin plus Radiotherapy Versus Weekly Carboplatin plus Radiotherapy in Locally Advanced Squamous Cell Carcinoma of Head-Neck

Mahfujul Ahmed Riad[1]

Received: 5 July 2021 Accepted: 30 July 2021
doi: https://doi.org/10.3329/jemc.v11i3.66883

Abstract

Background*: Head and neck cancers are the common cancers in developing countries. Concurrent chemoradiotherapy is the treatment of choice for locally advanced stage III to IVB squamous cell carcinoma of head and neck. Carboplatin possesses comparable treatment response and better tolerability than cisplatin.* ***Objectives****: The study has been conducted to elucidate the comparable efficacy and favorable toxicity profile of carboplatin instead of cisplatin.* ***Materials and Methods****: This study was conducted at National Institute of Cancer Research and Hospital, Dhaka from March 2018 to March 2019 over 60 patients divided into 2 groups. Group A patients received cisplatin 40 mg/ m^2 and group B patients received carboplatin AUC 2 along with 66 Gy in 33 fractions of radiation. Treatment response and toxicities was evaluated periodically.* ***Results****: Total 12 (40%) patients of arm A and 8 (26.7%) patients of arm B had complete response, 10 (33.4%) patients of arm A and 12 (40%) patients of arm B had partial response, 6 (20%) patients of arm A and 3 (10%) patients of arm B had stable disease and 2 (6.7%) patients of arm A and 7 (23.3%) patients of arm B developed progressive disease. Cisplatin showed more vomiting (57.6%), nephrotoxicity (55.2%), ototoxicity (33.9%) and neurotoxicity (35.4%). On the other hand, carboplatin showed more myelosuppression (anemia 43.6%, neutropenia 44.5% and thrombocytopenia 64.3%).* ***Conclusion****: This study concluded that, both cisplatin and carboplatin have comparable efficacy and carboplatin has favorable safety profile.*

Key words: *Head neck cancer; Cisplatin; Carboplatin; Response; Toxicity*

J Enam Med Col 2021; 11(3): 173−179

Introduction

Head and neck squamous cell carcinoma accounts for 90% of all malignant disease in the head and neck region of the body.[1] Nearly 60% of the population presents with locally advanced disease.[2] Head and neck cancers are mainly attributed to tobacco, areca nut, alcohol etc.[3]

Meta-analysis of chemotherapy on head and neck cancer demonstrated that the use of radiotherapy and concurrent chemotherapy resulted in a 19% reduction in the risk of death and an overall 6.5% improvement in 5-year survival compared to treatment with radiotherapy alone.[2]

The platinum-based (mainly cisplatin and carboplatin) concurrent chemoradiotherapy regimens can be used

1. *Assistant Professor, Department of Clinical Oncology, Enam Medical College & Hospital, Savar, Dhaka*
Correspondence *Mahfujul Ahmed Riad, Email:* mahfujulriad@gmail.com

in head and neck cancers and cisplatin has priority over the other platinum-based drugs.[1,4] Concurrent chemoradiation with cisplatin is the standard approach for definitive management of unresectable locally advanced head and neck squamous cell carcinoma not only to increase loco-regional control but also decrease distal failure.[5,6] Carboplatin, though a platinum group of drugs, is generally well tolerated compared to cisplatin. The favorable toxicity profile and similar mechanism of action make it tempting to substitute carboplatin for cisplatin.[6,7] Significant cisplatin-induced toxicities include nausea and vomiting, nephrotoxicity, mucositis, dermatitis and potentially permanent ototoxicity.[4,8] Carboplatin is a second-generation platinum-based drug, has been frequently used to replace cisplatin because of its similar mode of action, but lower rates of ototoxicity, nephrotoxicity and emesis.[4,9] The intricate anatomy and the critical functional and social roles of the head and neck region have no doubt also motivated significant efforts to identify alternatives to oncologic resection of malignant tumors in head and neck region.[10]

This study was conducted to find out a comparable treatment response and lower rate of toxicity by using weekly cisplatin versus weekly carboplatin with radiotherapy for patients with locally advanced head and neck carcinoma.

Materials and Methods

Patient population

With the institutional ethical committee permission, the study was conducted in the department of Radiation Oncology, NICRH, Dhaka, Bangladesh for a period of one year from 30th March 2018 to 29th March 2019 over 60 patients. We only included patients with age range of more than 30 to less than 70 years having KPS of more than 70 with histologically proven squamous cell carcinoma of head and neck belonging to AJCC prognostic stage group of III to IVB. We excluded patients with primary tumors of nasopharynx, salivary glands, nasal cavity, paranasal sinuses, and unknown primaries or patients with non-squamous cell carcinomas. We also excluded patients who were treated previously with chemotherapy and/or radiotherapy, having multiple synchronous malignancies, recurrent disease, kidney and liver diseases.

Pretreatment evaluation

Complete history was taken from all patients, physical examination, necessary laboratory investigations, imaging studies (contrast enhanced CT scan) and fitness evaluation with Karnofsky performance score were done.

Chemotherapy

We administered weekly cisplatin at 40 mg/m^2 intravenously in 30 patients of Arm A as an outpatient basis along with adequate pre- and post-hydration, mannitol support. Rest of the 30 patients who belonged to Arm B received weekly carboplatin at AUC 2 (area under curve-2) intra-venously using Calvert formula.

Radiotherapy schedule

All patients received external beam radiotherapy of 66 Gy in 33 fractions, 5 days in a week in two-dimensional treatment planning with parallel opposed fields using Linear Accelerator. The target treatment volume included primary tumor with adequate margins and regional cervical lymph nodes. Level IV cervical lymph node was treated with a separate low anterior neck field. The spinal cord was spared after 44 Gy and if there was level V lymph node metastasis, it received electron therapy with appropriate energy (MeV) after field size reduction and the gap between photon and electron field was 0.5 cm.

Response and toxicity evaluation

Response was assessed every six weeks for four times after completion of concurrent chemoradiotherapy at Oncology outpatient department by symptom evaluation, clinical examination, Fiber Optic Laryngoscopy (FOL), and contrast-enhanced CT scan of head and neck. Treatment response was assessed in the light of RECIST (Response Evaluation Criteria in Solid Tumors) criteria 1.1. Toxicity was observed according to RTOG radiation morbidity criteria through clinical examinations, hematological and biochemical investigations and assessed weekly for the whole period of concurrent chemoradiotherapy and then every six weeks for four times.

Data collection and statistical analysis

After collection of all information, these data were checked, verified and edited for a finalized result. Continuous data were presented as mean±SD while categorical data were presented as frequency and percentage. For these values 95% confidence intervals were calculated. After editing and coding, the coded data were directly entered into the computer and processed and analyzed with the help of SPSS for windows software version 16.0 and Microsoft Excel 2007. To see the association between various variables chi-square test, Fisher's Exact test and t-test were used. P value of 0.05 or less was considered as significant.

Results

The mean age of the arm A patients was 54.30 (SD±6.69) years and that of Arm B patients was 51.56 (SD±10.23) years. Among 60 patients 81.67% were male and 18.33% patients were female. Most of the patients were farmers by profession in both groups, 12% and 11% respectively. Most of the patients in both arms were of low socio-economic background with 66.67% and 60% respectively.

Table I shows arm A patients retained their pre-treatment symptoms more than arm B patients among the study populations. In assessing dysphagia, throat pain, hoarseness of voice and dyspnea, we found that p-values were more than 0.05 that is statistically non-significant. Response assessment also revealed statistical non-significant difference in the treatment outcome comparing arm A and B (p= CR 0.412, PR 0.789, SD 0.472, PD 0.145 respectively).

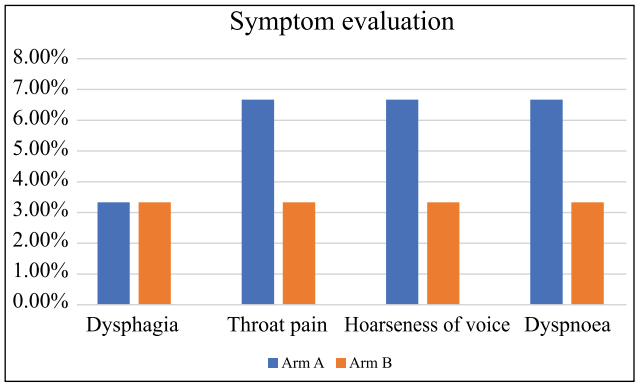

Fig 1. Comparison of symptom of Arm A and B patients in percentage through Bar chart

Table II: Comparison of toxicities between arm A and arm B patients

Toxicities	Arm A	Arm B
Anemia	35.2%	43.6%
Neutropenia	37.6%	44.5%
Thrombocytopenia	61.3%	64.3%
Vomiting	57.6%	53.9%
Diarrhea	54.8%	55.2%
Ototoxicity	33.9%	11.2%
Neurotoxicity	35.4%	12.1%
Nephrotoxicity	55.2%	33.3%
Skin reaction	62.7%	59.4%

Table I: Clinical outcomes: symptom and response evaluation

		Arm A (cisplatin + Radiotherapy)	Arm B (carboplatin + Radiotherapy)
Assessment of symptoms	Dysphagia (at 4th follow-up)	3.33%	3.33%
	Throat pain (at 4th follow-up)	6.67%	3.33%
	Hoarseness of voice (at 4th follow-up)	6.67%	3.33%
	Dyspnea (at 4th follow-up)	6.67%	3.33%
Assessment of response	Complete response	40%	26.7%
	Partial response	33.3%	40%
	Stable disease	20%	10%
	Progressive disease	6.7%	23.3%

* CD=complete response, PR=partial response, SD=stable disease, PD=progressive disease

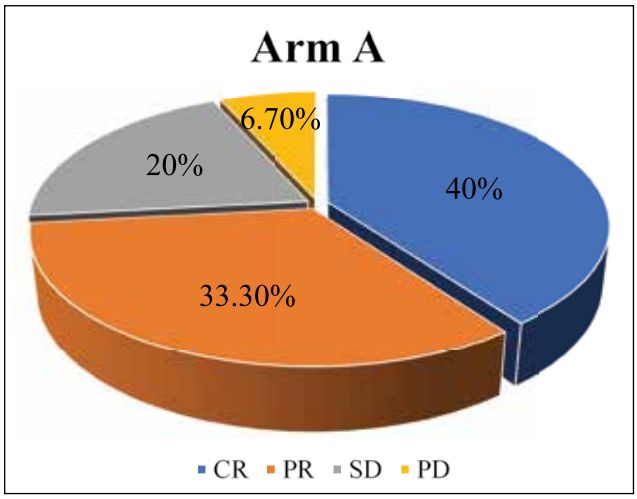

Fig 2. Distribution of treatment response of Arm A patients in percentage through pie chart

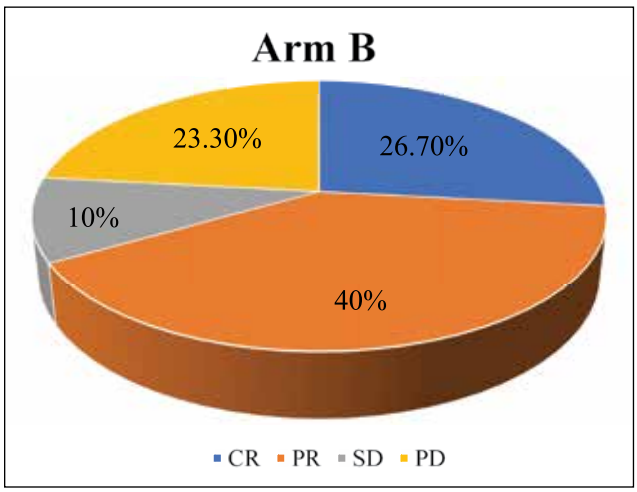

Fig 3. Distribution of treatment response of Arm B patients in percentage through pie chart

Table II shows that anemia, neutropenia and thrombocytopenia are more prevalent in arm B patients than in arm A patients; but not statistically significant (p=0.47, 0.63, 0.39 respectively). Cisplatin group showed more incidence of vomiting compared with carboplatin though there was no statistically significant difference (p=0.35) in this regard. Arm A patients had developed more ototoxicity, neurotoxicity and nephrotoxicity than arm B patients with statistically significant difference in post-treatment follow-up visits (p=0.01,0.01,0.03 respectively). Skin reaction was pronounced in the cisplatin group than in the carboplatin group with p value of 0.63.

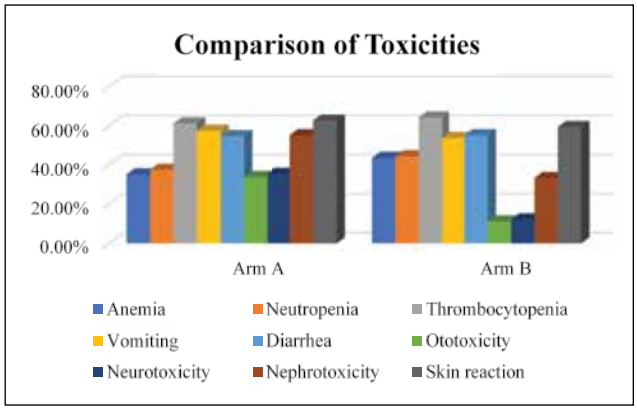

Fig 4. Comparison of toxicities of Arm A and B patients in percentage

Discussion

Cisplatin weekly with radiation is the standard agent however it causes nausea, vomiting, nephrotoxicity, mucositis, dermatitis and potentially permanent ototoxicity.[4] Moreover, Cisplatin has prolonged infusion time with monitoring of vigorous pre- and post-hydration and adequate potassium and magnesium replacement.[11,12] Carboplatin, though a platinum analogue having less nausea, vomiting, nephrotoxicity, ototoxicity and well tolerated by the patients but causes myelosuppression.[13] Phase II studies of Carboplatin-based concurrent chemoradiotherapy showed CR rates of 65%–70%, similar to those seen with Cisplatin.[14]

In this study the patients of both arms were assessed with several symptoms like dysphagia, throat pain, hoarseness of voice, dyspnea and compared with pretreatment status. At 4th follow-up more than 95% patients in both arms resolved dysphagia with no statistically significant difference in both arms (p>0.05). In case of other symptoms like throat pain, hoarseness of voice and dyspnea, more than 90% patients resolved their symptoms in both the arms at 4th follow-up with no significant difference as well (p>0.05).

While assessing anemia toxicity, 35.2% of arm A patients and 43.6% of arm B patients had anemia during the course of follow up. 37.6% and 44.5% patients developed neutropenia in arm A and B respectively. 61.3% of arm A and 64.3% of arm B patients had thrombocytopenia. In all cases p-values were more

than 0.05. Several studies found more hematological toxicity with Carboplatin than Cisplatin.[4,7,15] Though in my study no statistically significant difference was found between both the arms in terms of hematological toxicity but more patients developed anemia, neutropenia and thrombocytopenia in Carboplatin than Cisplatin group.

57.6% patients of arm A and 53.9% patients of arm B were found to have vomiting throughout the follow-up with no statistical significance difference in p-values but cisplatin group patients showed more vomiting than carboplatin group. Two studies found incidence of grade 3 nausea and vomiting was profound in Cisplatin arm than Carboplatin arm with statistically significant difference.[4,6,7] In my study with low dose Cisplatin and Carboplatin found more vomiting in Cisplatin group than Carboplatin group.Patients of both the arms had diarrhea but there was no statistically significant difference between both arms. One of the major toxicities of Cisplatin is neurotoxicity. 35.4% of arm A patients and 12.1% patients of arm B patients developed neurotoxicity of different grade with statistically significant difference (p=0.01). One study revealed Cisplatin upon cumulative dose of 300mg/m^2, 30–50% patients developed irreversible neurotoxicity.[8] Though low dose of Cisplatin has been used in my study, patients of arm A had more neurotoxicity than arm B with statistically significant difference.

Assessment of ototoxicity is an important aspect of this study. 33.9% patients of arm A and 11.2% patients of arm B developed ototoxicity though the entire follow-up(p=0.01).Ototoxicity was also found dose dependent in one study and irreversible while using Cisplatin.[8] In my study with low dose Cisplatin, ototoxicity had developed though in a smaller number of patients but more pronounced in arm A than Arm B with statistically significant difference.

Cisplatin and carboplatin both are excreted through kidney and may cause nephrotoxicity. 55.2% patients of arm A and 33.3% patients of arm B developed nephrotoxicity with statistically significant difference (p=0.03). Meta-analysis comparing cisplatin and carboplatin based regimen in locally advanced squamous cell carcinoma of head-neck and Chemoradiation in locally advanced nasopharyngeal cancer comparing cisplatin and carboplatin also found statistically significant difference in renal impairment with cisplatin.[4] Skin reactions occurred in the both the group of patients. 62.7% patients of arm A and 59.4% patients of arm B had skin reaction. Here p values are more than 0.05 and are not statistically significant. One study also observed no statistically significant difference in grade 3 skin reactions in both cisplatin and carboplatin group.[4] The response was summarized and found that 40% patients of arm A and 26.67% patients of arm B had complete response. 33.3% patients of arm A and 40% patients of arm B developed partial response. 6 patients of arm A and 3 patients of arm B had stable disease. Disease progressed in 6.67% patients of arm A and 23.33% patients of arm B. Though it seems overall response is higher in arm A, but p values are 0.412, 0.789, 0.472 and 0.145 for complete response, partial response, stable disease and progressive disease respectively for arm A and B, that means the difference of responses in between the arms are statistically not significant**.** A SEER-Medicare Analysis also found no statistically significant difference in 2-year OS between cisplatin and carboplatin-based chemotherapy (P = .360).[15] Another meta-analysis found no difference in response rate. Cisplatin tends to be more active systemically than carboplatin, without statistically significance; 5-year survival rate: 30 and 27%, respectively (p = 0.33). Despite the trend to improved outcomes in using cisplatin, carboplatin is also active and can be a reasonable option to treat patients.[16] The Laryngoscope VC 2017 The American Laryngological, Rhinological and Otological Society studied 44 patients comparing cisplatin and carboplatin for stage III to stage IVB squamous cell carcinoma of head and neck in term of response and toxicity and result of the study revealed that definitive CCRT with carboplatin for locally advanced squamous cell carcinoma of head and neck was well tolerated and demonstrated comparable results to CCRT with cisplatin.[17] Another non-inferiority trial comparing cisplatin and carboplatin as chemoradiotherapy agents in locally advanced nasopharyngeal carcinoma concluded that the treatment efficacy of carboplatin arm is not different

from the standard regimen.[18] Article published in Japanese Journal of Clinical Oncology in 2015 assessing safety and efficacy of concurrent carboplatin plus radiotherapy in locally advanced head and neck cancers in 25 patients and found that concurrent carboplatin plus radiotherapy is tolerated and may be an option in treating locally advanced squamous cell carcinoma of the head and neck patient's ineligible for treatment with cisplatin.[19] Carboplatin is currently in the WHO Essential Medicines List for Adults (2013, 18th Edition). Next to carboplatin in the WHO List is a symbol that states that the listing of the drug indicates "similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines.[20]A prospective study was conducted where in a total of 40 patients with stage III and IV squamous cell carcinomas of oral cavity, oropharynx, hypopharynx and larynx were enrolled. After completion of concurrent chemoradiation with carboplatin, 65% of patients had complete response at the primary and regional sites, and 35% of patients had a partial response of whom 23% underwent neck dissection and 5% of them underwent salvage surgery at the primary site. At the end of one year there were six deaths and four recurrences and 70% were free of disease. Concurrent chemoradiation with carboplatin provided good locoregional control for locally advanced head and neck cancers.[21]

This study concludes that concurrent chemoradiotherapy with cisplatin and carboplatin has comparable efficacy in the treatment of locally advanced head and neck cancer. Carboplatin has relatively low toxicity profile than cisplatin and may be used concurrently with radiotherapy as an alternative chemotherapy agent in locally advanced head and neck squamous cell cancer treatment.

References

1. Devita VT, Lawrence TS, Rosenberg SA, editors. Devita, Hellman & Rosenberg's Cancer: Principles and Practice of Oncology. 11th edn. New York: Lippincott Williams & Wilkins, 2019: 536–542.
2. Perez CA, Bradly LW. Principles and practice of radiation oncology. 7th edn. Philadelphia: Lippincott Williams & Wilkins, 2019: 885.
3. Joshi P, Dutta S, Chaturvedi P, Nair S. Head and Neck Cancers in Developing Countries. Rambam Maimonides medical journal 2014; 5(2): 1–6.
4. Guan J, Li Q, Zhang Y, Xiao N, Chen M, Zhang Y et al. A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). Oncotarget 2016; 7(6): 7110–7119.
5. Maghous A, Marnouche E, Loughlimi H, Rais F, Benhmidou N, Adanl-Lfe N et al.Evaluation of Cisplatin Induced Toxicity in Head and Neck Cancer and Cervical Cancer During Concurrent Chemoradiotherapy. Experience of National Institute of Oncology in Morocco. J Cancer Sci Ther 2017; 9(1): 314–318.
6. Dutta S, Ghorai S, Choudhury KB, Majumder A. Radical treatment of locally advanced head and neck cancer with concurrent chemoradiation-cisplatin versus carboplatin: A randomized comparative phase III trial. Clin Cancer Investig J 2013; 2: 122–127.
7. Wilkins AC, Rosenfelder N, Schick U ,Gupta S, Thway K, Nutting CM et al. Equivalence of cisplatin and carboplatin-based chemoradiation for locally advanced squamous cell carcinoma of the head and neck: A matched-pair analysis. 2013; 49(6): 615–619.
8. Ahn MJ, D'Cruz A, Vermorken JB, Chen JP, Chitapanarux I, Dang HQ et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. 2016; 53: 10–16.
9. Bruce A. Chabner, Dan L. Longo. Harrison's Manual of Oncology.2nd edn. New York: Mc Graw Hill Education, 2014: 70.
10. Morris ZS, Mohindra P, Kruser TJ. Combined Chemoradiation Therapy in the Treatment of

Squamous Cell Carcinoma of the Head and Neck—An Evolving Paradigm. Oncology & Hematology Review 2013; 9(2): 115–121.

11. Khalif NS, Rixe O, Skeel RT. South Asian Edition of Skeel's Handbook of Cancer Therapy. 9th edn. Philadelphia: Lippincott Williams &Wilkins, 2016: 112.

12. Chu E, DeVita VT. Physicians' Cancer Chemotherapy Drug Manual.19th edn. Burlington: Jones and Bartlett Learning, 2019: 90.

13. Denis A. Casciato, Mary C. Territo. Manual of Clinical Oncology. 7th edn. Philadelphia: Lippincott Williams &Wilkins, 2012: 64–65.

14. Noronha V, Sharma V, Joshi A , Patil VM, Laskar SG, Prabhash K. Carboplatin-based concurrent chemoradiation therapy in locally advanced head and neck cancer patients who are unfit for cisplatin therapy. Indian J cancer 2017; 54(2): 453–457.

15. Amini A, Eguchi M, Jones BL, Stokes WA, Gupta A, McDermott J et al. Comparing outcomes of Concurrent chemotherapy regimens in patients 65 years old or older with locally advanced oropharyngeal carcinoma. Cancer 2018; 124(22): 4322–4331.

16. JrP NA, Tadokoro H, Silva GF da, Landgraf MM, Barreto CMN, Filardi BA et al. Definitive chemoradiotherapy for squamous head and neck cancer: cisplatin versus carboplatin?A meta-analysis; 2016; 12: 68

17. Nagasaka M, Zaki M, Issa M, Kim H, Abrams J, Sukari A. Definitive Chemoradiotherapy with Carboplatin for Squamous Cell Carcinoma of the Head and Neck. Laryngoscope 2017; 127(10): 2260–2264.

18. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, Sumitsawan Y, Tharavichitkul E, Sukthomya V et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. European journal of cancer 2007; 43(9): 1399–1406.

19. Hamauchi S, Yokota T, Onozawa Y, Ogawa H, Onoe T, Kamijo T et al. Safety and efficacy of concurrent carboplatin plus radiotherapy for locally advanced head and neck cancer patient's ineligible for treatment with cisplatin. Japanese journal of clinical oncology 2015; 45(12):1116−1121.

20. Union for International Cancer Control, Review of Cancer Medicines on the WHO List of Essential Medicines; 2014: 6.

21. Lasrado S, Moras K, Pinto GJ, Bhat M, Hegde S, Sathian B et al. Role of concomitant chemoradiation in locally advanced head and neck cancers. Asian Pac J Cancer Prev 2014; 15(10): 4147−4152.