RESEARCH PAPER

Association Between Number of Induction Chemotherapy Cycles and Toxicity Occurrence Following Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

Nourhan Abdallah Afifi*[1], Ibraheem Malash[1], Dalia Ibraheem Hussein[1], Ghada Mohamed Abd El Salam[2], Ola Mohamed Reda Khorshid[1]

[1]*Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt*
[2]*Department of Pathology, National Cancer Institute, Cairo University, Egypt*

ABSTRACT

Background: Induction chemotherapy with TPX (docetaxel, cisplatin, capecitabine) is an emerging regimen for locally advanced head and neck squamous cell carcinoma (HNSCC). Whether a higher number of induction cycles increases toxicity burden remains unclear.

Objective: To evaluate whether the number of TPX cycles (≤3 vs. >3) is associated with the occurrence of adverse events in patients with locally advanced HNSCC.

Methods: This prospective cohort study included adult patients with newly diagnosed locally advanced HNSCC who received induction TPX every 3 weeks for 3–5 cycles. Toxicity was graded according to CTCAE v5.0. The association between the number of cycles (categorized as ≤3 cycles vs. >3 cycles) and overall toxicity occurrence was analyzed.

Results: A total of 105 patients were evaluable for toxicity. Across 364 administered cycles, 112 toxicity events of any grade were recorded (30.8 events per 100 cycles). The most common toxicities were diarrhea (8.5/100 cycles), mucositis (4.4/100 cycles), and vomiting (3.8/100 cycles). Among patients receiving ≤3 cycles, 32.8% (19/59) experienced toxicity, compared to 32.1% (15/46) among those receiving >3 cycles. The difference was not statistically significant (p = 1.00). No cumulative increase in toxicity was observed with additional cycles.

Conclusion: The number of TPX induction cycles (≤3 vs. >3) is not associated with the occurrence of toxicity. Extended treatment beyond 3 cycles does not appear to increase adverse event rates, supporting the feasibility of administering up to 5 cycles of this regimen in appropriately selected patients.

Keywords: TPX (Docetaxel, Cisplatin, Capecitabine), Squamous Cell Carcinoma

How to cite this article: Afifi NA, Malash I, Hussein DI, El Salam GMA, Khorshid OMR. Association Between Number of Induction Chemotherapy Cycles and Toxicity Occurrence Following Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma. Int J Drug Deliv Technol. 2026;16(57s): 1889-1893. DOI: 10.25258/ijddt.16.57s.190

Source of support: None

Conflict of interest: None

INTRODUCTION

Worldwide, head and neck cancer accounts for approximately 900,000 cases and over 400,000 deaths annually. Head and neck squamous cell carcinomas (HNSCC) are the most common head and neck cancer type. More than half of the patients with HNSCC present with locally advanced disease at initial diagnosis. An optimal treatment consists of multiple procedures, which include surgery, radiotherapy, and [1-3].

Depending on the localization and size of the tumor, valid options include chemoradiotherapy (CRT) or surgery followed by (chemo) radiotherapy. In some cases, induction chemotherapy (IC) is the treatment of choice [4].

There are several comparisons among different ICT regimens for resectable as well as unrespectable disease. In recent times, docetaxel, cisplatin, and 5-fluorouracil (TPF) have been increasingly used as an effective induction regimen based on the survival benefit obtained from the landmark TAX-323 and TAX 324 trial [5-7].

Capecitabine is a type of oral fluorouracil derivative metabolized to fluorouracil in tumor cells. Capecitabine combined with docetaxel and cisplatin (TPX) has been used as an alternative induction chemotherapy regimen for LAHSCC in many studies showing higher survival parameters with good tolerance [8]. So, this study aimed to evaluate whether the number of TPX cycles (≤3 vs. >3) is associated with the occurrence of adverse events in patients with locally advanced HNSCC.

PATIENTS AND METHODS

This was a prospective cohort study conducted at the Medical Oncology Department, National Cancer Institute, Cairo University. After approval from the Institutional Review Board of NCI (IRB Approval No. 2306-305-070), 110 adult patients with newly diagnosed locally advanced HNSCC were enrolled in our study from November 2022 to April 2025, all patients received induction TPX chemotherapy protocol and were followed up at medical oncology department of NCI, CU with the maximum follow-up duration extending to approximately 30 months.

. Intervention

All patients received induction TPX chemotherapy every 3 weeks: docetaxel (75 mg/m², day 1), cisplatin (75 mg/m², day 1), and capecitabine (800 mg/m² twice daily, days 1–

14). A total of 3 to 5 cycles were administered per patient based on clinical response and tolerability.

Toxicity Assessment

Toxicity was assessed after each cycle and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Any adverse event of grade 1 or higher was recorded.

Study Groups for Comparison

Patients were divided into two groups based on the number of TPX cycles received:

≤3 cycles (3 cycles or fewer)

>3 cycles (4 or 5 cycles)

Statistical Analysis

The primary outcome was the occurrence of any toxicity (all grades) during the entire induction period. The association between cycle number category (≤3 vs. >3) and toxicity occurrence was examined using the Chi-square test (or Fisher's exact test as appropriate). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

This study included 110 adult patients with a median age at diagnosis 52 years ranging from 20 to 70 years. Male patients were 71.8% of our cohort (79 patients) while 28.2% were females (31 patients). Smoking was reported in 58.2 % of our study group (64 patients) with a median daily cigarette intake of 20 and a median smoking history of 25 years. Males constituted the vast majority of smokers (88.5% in males VS 11.5% in females). Thirty eight patients (34.5%) had at least one documented comorbidity. Hypertension was the most prevalent condition, affecting 18.2% (20 patients) followed by diabetes mellitus in 13.6 % of patients (15 patients). Ten patients (9.1%) had both hypertension and diabetes mellitus, representing the most common comorbidity combination. A smaller proportion of patients had viral hepatitis (5.4%), cardiac disease (2.7%) or rheumatoid arthritis (1.8%). Among patients with comorbidities, 63.2% had only one condition, while 36.8% had multiple comorbidities. Most of our cohort (65.5%) had no documented comorbidities (Table 1).

Table 1. Patients' characteristics of the study group

Variables		N =110	%
Age/years Mean ±SD (Min-Max)		52.66±12.44(20.0-70.0)	
Gender	Female	31	28.2
	Male	79	71.8
Residence	Urban	79	71.8
	Rural	31	28.2
Marital status	Married	90	81.8
	Single	7	6.4
	Divorced	3	2.7
	Widow	10	9.1
Offspring's number		4±2(0.0-11.0)	
Menopausal status in females	Premenopausal	14	45.2
	Postmenopausal	15	48.4
	Perimenopausal	2	6.4
Smoking status	No	46	41.8
	Yes	64	58.2
Cig./day median (Range)		20.0 (4.0-60.0)	
Years of smoking median (Range)		25.0 (2.0-55.0)	
WT Mean ±SD (Min-Max)		69.0±15.0(27.0-107.0)	
HT Mean ±SD (Min-Max)		165.0±9.0(139.0-181.0)	
BSA Mean ±SD (Min-Max)		1.72±0.19(1.0-2.0)	
BMI Mean ±SD (Min-Max)		25.4±5.6(14.0-42.0)	
ECOG PS	1	98	89.9
	2	11	10.1
Comorbidities	Yes	38	34.5
	No	72	65.5
Comorbidity type	Hypertension	20	18.2
	Diabetes mellitus	15	13.6
	HCV	5	4.5
	Cardiac disease	3	2.7
	Rheumatoid arthritis	2	1.8
	HBV	1	0.9

Toxicity data were available for 105 out of 110 enrolled patients, as 5 of the 10 patients who lost follow-up before the second TPX cycle attended a follow-up visit after the first TPX cycle where toxicity occurrence was documented. A total of 364 cycles of TPX induction chemotherapy were administered in our study. Across all cycles, 112 toxicity events of any grade were recorded, corresponding to 30.8 events per 100 cycles as shown in table 2. Assessment of toxicity and grading were done according to CTCAE. The most common toxicities per cycle were diarrhea with 8.5 events per 100 cycles, Mucositis with 4.4 events per 100 cycles, vomiting: 3.8 events per 100 cycles, and anemia with 3.0 events per 100 cycles.

Severe hematologic events such as febrile neutropenia occurred at a rate of 2.2 events per 100 cycles. Notably, hand-foot syndrome, which is a characteristic toxicity associated with capecitabine, was infrequently observed, with only 0.8 events per 100 cycles, and all reported cases were mild to moderate in severity (grade 1–2). Grade 4 toxicity events occurred only once in the form of mucositis grade 4.

Table 2. Toxicity events from induction TPX across cycles (Per-cycle incidence)

Toxicity	C1	C2	C3	C4	C5	Total events	Events per 100 cycles
Diahrrea	18	9	3	1	0	31	8.52
Vomiting	8	4	2	0	0	14	3.85
Anemia	2	6	2	1	0	11	3.02
Neutropenia	4	3	2	0	0	9	2.47
Febrile neutropenia	4	2	1	0	1	8	2.2
Pancytopenia	0	1	0	0	0	1	0.27
Mucositis	7	3	4	1	1	16	4.4
Peripheral neuropathy	1	1	4	1	0	7	1.92
Tinnitus	2	1	0	0	0	3	0.82
Hand-Foot Syndrome	0	2	0	1	0	3	0.82
Elevated KFTs	0	2	0	1	0	3	0.82
Thromboembolic events	0	1	1	0	0	2	0.55
Fatigue	2	2	0	0	0	4	1.1

Among patients receiving ≤3 cycles, 19 out of 59 (32.8%) experienced at least one toxicity event. Among patients receiving >3 cycles, 15 out of 46 (32.1%) experienced at least one toxicity event. The difference was not statistically significant (p = 1.00) as shown in Table 3. No cumulative increase in toxicity severity or frequency was observed with additional cycles beyond 3.

Table 3. Relation between toxicity occurrence and number of cylces

Number of Cycles	Patients (N)	Toxicity Occurrence (n, %)	p-value
≤3 cycles	59	19 (32.8%)	1.00
>3 cycles	46	15 (32.1%)	

DISCUSSION

This study aimed to evaluate whether the number of TPX cycles (≤3 vs. >3) is associated with the occurrence of adverse events in patients with locally advanced HNSCC. The median age at diagnosis in our cohort was 52 years, with a range from 20 to 70. Our patient population lies at the younger end of the spectrum commonly reported in the global HNSCC literature. Large, pivotal induction chemotherapy trials in LA HNSCC, such as TAX 323 and TAX 324, reported median ages of 55 and 57 years, respectively, with typical ranges extending into the mid-70s [5, 9].

Similar to TAX cohorts, cohorts from major cooperative group trials in the United States and Europe often report median ages between 58 and 62 years [10, 11]. The male predominance (71.8%) in our cohort is a universal feature of HNSCC in agreement with global literature, although the male-to-female ratio in our cohort (approximately 2.5:1) is somewhat lower than the 3:1 to 4:1 ratios often reported [12].

Furthermore, smoking was documented in 58.2% of patients in our cohort which confirms tobacco as a dominant etiologic agent in our population, consistent with the classic HNSCC paradigm. However, smoking prevalence in our cohort is lower than TAX 323 trial, which exclusively enrolled patients who were smokers or had a significant smoking history [5].

In our study, TPX was generally tolerable, with a manageable toxicity profile dominated by gastrointestinal events, mostly grade 1 & 2 events. Across all 364 TPX cycles administrated in our study, 112 toxicity events of any grade were recorded, corresponding to 30.8 events per 100 cycles. The most common toxicities per cycle were diarrhea: 8.5 events per 100 cycles, mucositis: 4.4 events per 100 cycle and vomiting: 3.8 events per 100 cycles. Severe hematologic events such as febrile neutropenia occur at a rate of 2.2 events per 100 cycles. Grade 4 toxicity events occurred only once in the form of mucositis grade 4. Our toxicity analysis revealed distinctive patterns that both align with and diverge from existing literature. In contrast,

toxicity profile of our TPX regimen demonstrated dramatic advantages over the standard TPF regimens from the TAX 323 and TAX 324 trials, particularly in hematologic toxicity. While TAX 323 reported 76% grade 3–4 neutropenia and TAX 324 reported 83%, our study observed only 2.5 events per 100 cycles. Similarly, febrile neutropenia occurred in 12% of patients in both TAX trials compared to just 2.2 events per 100 cycles in our cohort. Mucositis rates also favored TPX, with severe (grade 3–4) mucositis affecting 21% of patients in the TPF trials versus 4.4 events/100 cycles (mostly grade 1-2, only 1 grade 4 event) in our TPX study. For capecitabine-specific toxicities, TPX introduced manageable hand-foot syndrome (0.8 events per 100 cycles) which was not reported with 5-FU in TPF regimens [5, 9].

Mirroring our favorable toxicity pattern, Yamouni et al. using the same induction TPX regimen noted a favorable toxicity profile, with manageable gastrointestinal and hematologic adverse events, and no grade 4 toxicities during the induction phase [13]. Also, Li et al. noted manageable hematologic and gastrointestinal toxicity with TPX with grade 3–4 hematologic toxicity in 19.3% of patients and only 1.6% experiencing grade 3–4 diarrhea [14]. Similarly, Alvarado-Muñoz et al. in a cohort of LAHNSCC patient treated with TPX regimen (paclitaxel, cisplatin and capecitabine), reported predominantly gastrointestinal (diarrhea, mucositis) and hematologic adverse events. The incidences of grade 3–4 neutropenia (18.8%) and hand-foot syndrome (12.5%) in this study is higher than rates of severe hematologic toxicity (febrile neutropenia 2.2 per 100 cycles) and minimal hand-foot syndrome (0.8 per 100 cycles) in our study. These differences may be attributable to variations in capecitabine dosing (1000mg/m2 in that study vs 800 mg/m2 in our study, both twice a day for 14 days) and choice of taxane (paclitaxel in that study vs. docetaxel in our study) [15].

CONCLUSION

The number of TPX induction cycles (≤3 vs. >3) is not associated with the occurrence of toxicity. Extended treatment beyond 3 cycles does not appear to increase adverse event rates, supporting the feasibility of administering up to 5 cycles of this regimen in appropriately selected patients.

CONFLICT OF INTEREST

All authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

REFERENCES

1. Fang Q, Li P, Qi J, Luo R, Chen D, Zhang X. Value of Lingual Lymph Node Metastasis in Patients with Squamous Cell Carcinoma of the Tongue. The Laryngoscope. 2019;129(11):2527-2530.
2. Du W, Fang Q, Wu Y, Wu J, Zhang X. Oncologic Outcome of Marginal Mandibulectomy in Squamous Cell Carcinoma of the Lower Gingiva. BMC cancer. 2019;19(1):775.
3. Cui M, Du W, Fang Q, Dai L, Qi J, Luo R. Prognostic Value of a Family History of Oral Tongue Squamous Cell Carcinoma: A Matched-Pair Study. The Laryngoscope. 2020;130(11): E605-E610.
4. Grégoire V, Lefebvre J-L, Licitra L, Felip E, group EEEgw. Squamous Cell Carcinoma of the Head and Neck: Ehns–Esmo–Estro Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. Annals of oncology. 2010;21: v184-v186.
5. Vermorken JB, Remenar E, Van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer. New England Journal of Medicine. 2007;357(17):1695-1704.
6. Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, et al. Induction Chemotherapy with Cisplatin and Fluorouracil Alone or in Combination with Docetaxel in Locally Advanced Squamous-Cell Cancer of the Head and Neck: Long-Term Results of the Tax 324 Randomised Phase 3 Trial. The lancet oncology. 2011;12(2):153-159.
7. Karabajakian A, Gau M, Reverdy T, Neidhardt E-M, Fayette J. Induction Chemotherapy in Head and Neck Squamous Cell Carcinoma: A Question of Belief. Cancers. 2018;11(1):15.
8. Iqbal H, Pan Q. Capecitabine for Treating Head and Neck Cancer. Expert opinion on investigational drugs. 2016;25(7):851-859.
9. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer. New England Journal of Medicine. 2007;357(17):1705-1715.
10. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy Plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. New England Journal of Medicine. 2006;354(6):567-578.
11. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. New England Journal of Medicine. 2010;363(1):24-35.
12. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. Journal of clinical oncology. 2011;29(32):4294-4301.
13. Yamouni M, Beldjilali Y, Benhadji K, Khellafi H, Betkaoui F, Kaid Y, et al. A Phase Ii Trial of Induction Chemotherapy with Cisplatin, Docetaxel, and

Capecitabine Followed by Concurrent Cisplatin-Radiotherapy in Advanced Nasopharyngeal Carcinoma. Journal of Clinical Oncology. 2011;29(15_suppl):5543-5543.

14. Li W-Z, Lv X, Hu D, Lv S-H, Liu G-Y, Liang H, et al. Effect of Induction Chemotherapy with Paclitaxel, Cisplatin, and Capecitabine Vs Cisplatin and Fluorouracil on Failure-Free Survival for Patients with Stage Iva to Ivb Nasopharyngeal Carcinoma: A Multicenter Phase 3 Randomized Clinical Trial. JAMA oncology. 2022;8(5):706-714.
15. Alvarado-Muñoz JF, Reyes-Morales A, Puac-Polanco V, Bruixola G, Chivalan M, Torselli S. Induction Chemotherapy with Cisplatin, Paclitaxel, and Capecitabine (Ptc) in Locally Advanced (La) Squamous Cell Carcinoma of Head and Neck (Scchn). International Journal of Radiation Oncology, Biology, Physics. 2022;112(5): e26.