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ASSESSMENT OF UNWANTED EFFECTS OF CONCURRENT CHEMORADIOTHERAPY FOR NASOPHARYNGEAL CARCINOMA, AT THE NATIONAL OTORHINOLARYNGOLOGY HOSPITAL OF VIETNAM, FROM 2019 TO 2023

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ABSTRACT

Purpose: *Assessment of the unwanted effects of concurrent chemoradiotherapy for nasopharyngeal carcinoma.*

Subjects and methods: *A retrospective combined prospective study and description of 53 patients with stage II-IVA nasopharyngeal carcinoma, treated with concurrent chemoradiotherapy by the cisplatin regimen on days 1, 22 and 43 at the National Otorhinolaryngology Hospital of Vietnam from 2019 to 2023.*

Results: *The incidence of grade 3 toxicity on the hematopoietic and non-hematopoietic systems, and late complications occurred at a low rate. Specifically: toxicities of leukopenia and granulocytopenia at grade 3 were 17.0%, and 7.5% respectively; toxicity: dermatitis, mucositis, and, nausea at grade 3 were 3.8%, 18.9%, and 5.7%, respectively. Late complications of xerostoma and skin fibrosis at grade 3 were 18.9% and 1.9%, respectively.*

Keywords: Nasopharyngeal carcinoma, unwanted effects, response rate.

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1. INTRODUCTIONS

According to the cancer treatment guidelines of the National comprehensive cancer network (NCCN) and the European society for Medical Oncology (ESMO), stage I of nasopharyngeal carcinoma (NPC) is usually treated with radiotherapy alone, resulting in an overall survival benefit of over 90% at five years. For stage II-IVB, concurrent chemoradiotherapy, either in combination with additional chemotherapy or not, is recommended as the standard regimen for the treatment of locally advanced NPC. This regimen has shown a good response to treatment and effective local control while reducing the rate of distant metastasis [1] [3]. In Vietnam, over 90% of cases of NPC are undifferentiated, which responds well to both chemotherapy and radiotherapy. Currently, concurrent chemoradiotherapy is the standard treatment for locally advanced NPC [3].

The National Otorhinolaryngology Hospital of Vietnam has been implementing combined chemoradiotherapy for NPC patients since 2019. However, there have been no studies evaluating the unwanted effects of this method. We conducted this study to evaluate the unwanted effects of concurrent chemoradiotherapy in NPC patients at the National Otorhinolaryngology Hospital of Vietnam from 2019 to 2023.

2. SUBJECTS AND METHODS

2.1. Subjects

53 patients diagnosed with stage II-IVA NPC who underwent concurrent chemoradiotherapy by the Cisplatin regimen on days 1, 22, and 43, at the Center for Oncology and Head, Face and Neck Surgery, National Otorhinolaryngology Hospital of Vietnam, from 2019 to 2023.

- Inclusion criteria: Patients aged 18-70 years, performance status (PS) < 2; the patients were diagnosed and treated for the first time, with no contraindications for concurrent chemoradiotherapy; patients with complete medical records (sufficient

information on post-treatment condition through regular follow-up and/or survey responses); patients agreed to participate in the study.

- Exclusion criteria: patients did not comply with treatment principles; the presence of other contraindicated concomitant diseases for chemotherapy (cardiovascular disease, liver, kidney problems); psychiatric disorders or inability to self-report according to the questionnaire.

- Study design: retrospective combined prospective and descriptive study.

- Sampling method: conventional random sample.

- Research methods: selection of qualified patients, data collection from medical records (retrospective), or recording information in sample medical records (prospective). The treatment course was clearly explained to the patients and they voluntarily accepted the standard treatment regimen.

2.2. Methods

- Evaluation criteria:

+ Treatment response assessment according to RECIST:

Response evaluation	RECIST
Complete response (CR)	Complete disappearance of all lesions, lasting for at least 4 weeks, with no appearance of new lesions.
Partial response (PR)	Lesions reduced by > 30% in size, with no appearance of new lesions for at least 4 weeks.
Stable Disease (SD)	Lesion size reduced < 30% or an increased < 20%.
Disease progression (PD)	Lesion size increased > 20% or the appearance of new lesions.

+ Toxicity to the hematopoietic system, liver, and kidneys:

Organ suffered toxicity	Toxicity grade				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
White Blood Cells (G/l)	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	< 1.0
Platelets G/l	> 150	75-149	50-74.9	25-49.9	< 25
Hemoglobin (g/l)	≥ 12	9.5-11.9	7.5-9.4	5-7.4	< 5
Neutrophils (G/l)	≥ 2.0	1.5-1.9	1.0-1.4	0.5-0.9	< 0.5
ALT/AST	≤ 1.25 times the normal	1.26-2.5 times the normal	2.6-5 times the normal	5.1-10 times the normal	> 10 times the normal
Creatinin	≤1.25 times the normal	1.26-2.5 times the normal	2.6-5 times the normal	5.1-10 times the normal	> 10 times the normal
Urea	≤1.25 times the normal	1.26-2.5 times the normal	2.6-5 times the normal	5.1-10 times the normal	> 10 times the normal

+ Toxicity to the non-hematopoietic systems:

Symptom	Toxicity grade				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	None	1 time/24 hours	2-5 times/ 24 hours	6-10 times/ 24 hours	> 10 times/24 hours or required nurturing outside the digestive tract
Stomatitis	None	Painful rash or mild ulcers	Painful rash or ulceration, can eat	Painful rash edematous unable to eat	Required nurturing outside the digestive tract or comprehensive support
Dermatitis	None	Erythema	Dry peeling, burning, itchy skin	Blistering pyorrhea, ulcers	Exfoliative dermatitis, and necrosis required surgical intervention

+ Chronic radiation complications according to RTOG (Radiation Therapy Oncology Group):

Organ	Toxicity grade				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin fibrosis	Normal	Asymptomatic	Mild fibrosis (elasticity retained)	Moderate fibrosis (loss of elasticity)	Severe fibrosis (thickened, rigid skin, affecting neck movement)
Xerostomia	Normal	Mild erostomia, Sensation retained	Moderate xerostomia, reduced sensation	Severe xerostomia, loss of sensation	Fibrosis
Trismus	Normal	Limited a little	Difficulty eating, the distance between dental arches 1-2 cm	Very difficult to eat, distance between dental arches 0.5-1 cm	Oral feeding is not possible, distance between dental arches < 0.5 cm

- Data Processing: analyzed and processed using statistical software SPSS 20.0 and STATA 10.0.

3. RESULTS

Table 1. Distribution of patients by age and gender (n = 53)

Characteristics		Patient	Rate %
Age	18-29 years	6	11.3
	30-39 years	9	17.0
	40-49 years	16	30.1
	50-59 years	11	20.8
	≥ 60 years	11	20.8
Gender (Male/Female)		1.9/1	
illness onset time	< 3 months	38	71.7
	≥ 3-6 months	13	24.5
	> 6 months	2	3.8
Disease Stage	II	22	41.5
	III	29	54.7
	IVA	2	3.8
Histopatho- logical characteri-stics	Undifferen-tiated adenomatous carcinoma	49	92.5
	Other Cancers	4	7.5

The average age of patients was 46.8 ± 10.3 years, most common in the 40-49 age group (30.1%). Male/female ratio = 1.9/1. A majority of patients had a time from detection to hospitalization of less than three months (71.7%), were in stage II (41.5%) and III (54.7%), and had undifferentiated NPC (92.5%).

Table 2. Acute hematologic toxicity (n = 53)

Toxicity	0	1	2	3
Leukope-nia	20 (37.7%)	6 (11.3%)	18 (34.0%)	9 (17%)
Neutrope-nia	29 (54.7%)	15 (28.3%)	5 (9.4%)	4 (7.5%)
Anemia	35 (66.0%)	17 (32.1%)	1 (1.9%)	0
Thrombocytope-nia	47 (88.7%)	4 (7.5%)	1 (1.9%)	0

Most common was grade 2 leukopenia (34.0%), grade 1 neutropenia (28.3%), grade 1 anemia (32.1%), and grade 1 thrombocytopenia (7.5%). No cases of grade 4 hematologic toxicity observed.

Table 3. Acute non-hematologic toxicity (n = 53)

Toxicity	0	1	2	3
Dermatitis	0	22 (41.5%)	29 (54.7%)	2 (3.8%)
Mucositis	0	8 (15.1%)	35 (66.0%)	10 (18.9%)
Nausea	24 (45.3%)	10 (18.9%)	16 (30.2%)	3 (5.7%)
AST/ALT	50 (94.3%)	0	1 (1.9%)	2 (3.8%)

100% of patients experienced dermatitis and mucositis, predominantly grade 2 dermatitis (54.7%) and grade 2 mucositis (66.0%). Nausea occurred in 54.7% of patients at various grades. No grade 4 non-hematologic toxicity cases observed.

Table 4. Late complications (n = 53)

Complications	Grade 0	Grade 1	Grade 2	Grade 3
Xerostoma	3 (5.7%)	19 (35.9%)	21 (39.6%)	10 (18.9%)
Skin fibrosis	25 (47.2%)	17 (32.1%)	10 (18.9%)	1 (1.9%)
Trismus	42 (79.2%)	10 (18.9%)	1 (1.9%)	0
Fatigue	42 (79.2%)	10 (18.9%)	1 (1.9%)	0
Pain	40 (75.5%)	11 (20.8%)	2 (3.7%)	0
Hearing reduce	24 (45.3%)	15 (28.3%)	14 (26.4%)	0
Sonitus	28 (52.8%)	15 (28.0 %)	10 (18.9%)	0
Dysphagia	24 (45.3%)	27 (50.9%)	2 (3.7%)	0
Caries	14 (26.4%)	15 (28.3%)	24 (45.3%)	0
Peripheral merve injury	47 (88.7%)	6 (11.3%)	0	0
Cervical myelitis	52 (98.1%)	0	1 (1.9%)	0
Jaw bone mecrosis	51 (96.2%)	2 (3.7%)	0	0

Most patients experienced xerostoma complications (94.3%), of which grade 2 xerostoma was the most common (39.6%). Skin fibrosis was observed in 52.8% of patients, mainly grade 1 (32.1%). 18.8% of patients had trismus complications, primarily grade 1 (18.9%). There were no cases of grade 4 late complications observed.

4. DISCUSSIONS

- Regarding age: In the studies, NPC occured at any age. According to Wei (2010) of China, which has one of the highest NPC incidence rates globally, the incidence increases rapidly in the age group of 20-29 years and peaks in the age group of 60-64 years [4]. In countries with average disease risk (such as Vietnam, Thailand, Malaysia), NPC is frequently observed in middle-aged people (45-60 years) [5].

- Regarding gender: Our study found a male-to-female ratio of NPC patients was 1.9/1 (table 1). This ratio was lower than some domestic studies, such as Ngo Thanh Tung (2.7/1) [5] and Le Chinh Dai (2/1) [6]. Other studies showed a male-to-female ratio ranging from 2/1 to 3/1 [4]. This difference in the gender ratio of disease may be due to women being concerned about their health, and detecting the diseases earlier than men.

- Regarding illness onset time: in many studies, NPC patients often present to the hospital within 3-6 months from the onset of symptoms (as in the 2015 study by Ngo Thanh Tung, in which the percentage of patients hospitalised within 3-6 months of the first symptom onset was 31.1%; within 7-12 months was 32.2%, and less than three months was 24.3%) [5]. In our study, 71.7% of patients had a duration of illness of less than three months (Table 1). It was consistent with the fact that the National Otorhinorarynology hospital of Vietnam has leading experts that allow early detection of lesions compared to other studies.

- Regarding disease stage: 41.5% of NPC patients were in stage II, 54.7% in stage III, and 43.8% in stage IV (these stages were non-metastatic). We conducted a short-term follow-up, and only one patient with stage IV experienced distant metastasis (multifocal bone and liver) and received symptomatic chemotherapy. The later the stage of NPC, the higher the rate of early distant metastasis.

- Regarding histopathological characteristics: Vietnam is located in Southeast Asia, an area with a relatively high incidence of undifferentiated NPC (about 80-90%). Ngo Thanh Tung's study in 2015 found this rate to be 92.9%, similar to our study (92.5% undifferentiated NPC) [5].

- Regarding toxicity of concurrent chemoradiotherapy:

+ Hematologic toxicity assessment: In various studies with concurrent chemoradiotherapy with cisplatin administered in the first and third weeks, grade 3 and 4 toxicity tends to be lower in the third week (as observed in Tao's study in 2014, with rates of leukopenia, anemia, and thrombocytopenia in the first week at 8.2%, 2.7%, 6.8%, and in the third week 6.2%, 0%, 3.7%; with p-values of 0.312, 0.233, 0.583) [7].

Our results were consistent with Tao's study (the rates of grade 3 and 4 toxicity were lower than those of other grades: 62.3% of patients experienced leukopenia, with grade 2 being 34.0%, grade 3 being 17.0%, and there was no cases of grade 4 reduction; 45.3% of patients experienced neutropenia, with grade 1 at 28.3%, grade 2 at 9.4%, grade 3 at 7.5%, and; 34.0% of patients experienced anemia - with grade 1 at 32.1%; 9.4% of patients experienced thrombocytopenia, with grade 1 reduction at 7.5%).

+ Non-hematologic toxicity assessment: we encountered three cases of grade 2 and 3 toxicity on the liver (5.7%), and no cases of toxicity on the kidneys (Table 3). Other studies on NPC patients also reported low toxicity rates, such as study by Su (2016), which used weekly and three-weekly cisplatin, which found grade 3 and 4 liver toxicity at 16.1% and renal toxicity at 4.9% [8]. Our results showed that 100% of patients had grade 1 to 3 dermatitis (54.7% at grade 2 and 3.8% at grade 3), and no patient had grade 4 dermatitis (table 3). All patients had mucositis, with 66.0% at grade 2 and 18.9% at grade 3, and no patient had grade 4 mucositis (Table 3).

Compared to other studies, we found these rates were equivalent (such as Kim's study, which found grade 3 mucositis toxicity at 3.2%) [9]. Patients may be examined and detected early for mucositis, simultaneously receiving early treatment, resulting in fewer severe cases reported later. We found 54.7% of patients experienced nausea, predominantly at grades 1 and 2 (18.9% and 30.2%, respectively); grade 3 nausea accounted for only 5.7%, and no cases of grade 4 nausea were observed (Table 4); this is similar to Dang Huy Quoc Thinh's study (with 26.8% of patients having grades 1 and 2 nausea) [10].

Most patients experienced complications of xerostoma (94.3%), with grade 2 xerostoma being the most common (39.6%). 52.8% of patients had complications of skin fibrosis (52.8%), with grade 1 skin fibrosis being the most common (32.1%). 18.8% of patients had trismus, mainly at grade 1 (18.9%). There were no cases of grade 4 late complications.

5. CONCLUSIONS

The concurrent chemoradiotherapy treatment for NPC by the cisplatin regimen on days 1, 22 and 43 showed a rate of grade 3 toxicity on the hematopoietic system and non-hematopoietic system; late complications were at a low rate, with no cases showing grade 4 toxicity or late-stage complications.

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