



## Comparison of Clinical Response between Combine Chemotherapy 5 Fluorourasil - Platinum Based and Ifosfamid - Taxane - Platinum Based in Recurrent Nasopharyngeal Carcinoma

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### Abstract

p-ISSN: 2301-4369 e-ISSN: 2685-7898  
<https://doi.org/10.36408/mhjcm.v10i3.926>

**Accepted:** February 13<sup>th</sup>, 2023

**Approved:** August 10<sup>th</sup>, 2023

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**Background :** Recurrence of Nasopharyngeal Carcinoma (NPC) is the emergence of a tumor remission after administration of chemoradiation based on symptoms and several examinations. The combination of chemotherapy in recurrent NPC still gives good results. The combine of regimens used is still varied and not much study has been done to assess the clinical response. The objectives of this study was to compare the clinical response between administration of combination 5 Fluorouracil-Platinum based (5-FU) and Ifosfamide-taxan-platinum based (IFO) in recurrent NPC.

**Methods :** This observational study used electronic medical record (ERM) data at the ENT oncology clinic at Dr. Kariadi General Hospital for the period January 2020–January 2022. The number of samples that suited to the inclusion and exclusion criteria was 44 subjects divided into two groups of 22 subjects respectively. The chi-square test was used to assess differences in alteration of clinical symptoms, tumor mass size, neck lymph node enlargement, tumours stage reduction, and the effect of confounding factors on response to therapy in both groups.

**Results :** The highest number of patients with recurrent NPC were aged  $\geq 45$  Years old and male (75%). WHO type 3 is the most common (95.5%) and ECOG status 1 (95.5%). There was no significant difference administration of the combination of 5-FU with IFO in alteration of clinical symptoms ( $p=0.500$ ), shrink tumor size ( $p=0.347$ ), reduction of neck lymph node size ( $p=0.164$ ), and reduction tumor staging ( $p=0.347$ ). There was no relationship from confounding factors to clinical response between the administration of the two groups.

**Conclusion :** Administration of 5 Fluorouracil-platinum based combination chemotherapy did not provide a better clinical response in terms of clinical symptoms, changes in primary tumor size, neck lymph node size, and decreased tumor stage compared to the Ifosfamide-taxane-platinum based combination based on recurrent NPC.

**Keywords :** recurrent nasopharyngeal carcinoma, 5-flourouracil, ifosfamide, response to therapy.

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy of squamous cell on nasopharyngeal epithelium layer mucosa. The NPC belongs to the top five of frequent malignancies after cervix cancer, breast cancer, lymph node cancer, and cutaneous cancer.<sup>1-3</sup> NPC patients are rarely diagnosed at an early stage due to unspecific symptoms and lack of awareness from the patients about the signs and complaints. It causes patients delay to get the treatments and presented with advance stage and is a challenge in determining the modality of therapy for the patients.<sup>2,4,5</sup>

Recurrency in NPC are arising of tumors once remission-phase after administration of chemoradiation based on the symptoms and by several examinations such as nasopharyngeal endoscopy and radiological imaging.<sup>1</sup> There are several modalities used to treat the NPC, including radiotherapy, chemotherapy, brachytherapy, surgery, targeted therapy, and immunotherapy. Radiotherapy or chemotherapy use to first-line therapy in the early stages or locoregional diseases gives a 5-year survival rate of 85–90%, but 8–10% of patients fail into recurrency and distant metastasis.<sup>6-8</sup>

First-line chemotherapy of taxane and platinum-based gives good results and its can administered by adjuvant, neo-adjuvant, and concurrent.<sup>6,8</sup> However NPC with locoregional/distant metastases or recurrent cases combination two or more of chemotherapy regiments still an option as either curative or palliative therapy.<sup>6</sup> In the study, it was stated that the combination ifosfamide (IFO), 5Fluorouracyl (5FU), and Leucovorin in NPC recurrent gave an overall response rate of 44%.<sup>7</sup> The National Cancer Management Committee in 2015 published the guidelines for the management of Nasopharyngeal Cancer which states that 5-FU combination chemotherapy is an option in recurrent/metastatic NPC therapy.<sup>6</sup> Consideration of effectiveness and efficiency in the administration 5-FU and IFO is very helpful in the management of recurrent, and distant metastatic of NPC. So it is expected that patients do not drop-out of treatment caused by duration of treatment and side effects of chemotherapy drugs. Clinical response monitoring of combination 5-FU and IFO in ENT department Dr. Kariadi hospital Semarang has never been before.

Assessment of the effectiveness of NPC management determined based on re-evaluation of the symptoms, physical examination, and radiology imaging. Monitoring of clinical response assessed at least 4 weeks after complete of therapy.

In this study, the author wants to know the comparison in clinical response between 5FU-platinum based combination with Ifosfamid-platinum-based-taxane combination in recurrent NPC patients at Dr. Kariadi Hospital Semarang.

## METHODS

This study is a retrospective observational study. The data was taken from medical records at Dr. Kariadi hospital for the period January 2020 until January 2022. Samples that suited the inclusion criteria and exclusion criteria were 44 subjects. The first group were patients with recurrent NPC administered by IFO combination and the next group were patients who administered by 5-FU combination for 22 samples each groups. Inclusion criteria were patients with recurrent cases who have completed previous chemotherapy with taxane and platinum-based, NPC patients with recurrent cases who have undergone external radiotherapy, histopathology type WHO 2 and WHO 3, age 18–65 years, and patient performance status ECOG 1 or ECOG 2, have a filed medical record. While the exclusion criteria were patients with severe systemic diseases (hypertension, renal failure, diabetes mellitus, and tuberculosis), patients with a history of malignancy of other organs. Patients drop-out treatment.

The variables assessed were therapeutic response from 5-FU chemotherapy and IFO including clinical symptoms, primary tumor size, size of neck lymph-nodes enlargement, and tumour stage with confounding variables include age, gender, initial tumour stage, and histopathological type.

Clinical response assessment includes improvement of clinical symptoms. Improvement if there is improvement of the complained symptoms even though only 1 symptom, there is no improvement if there is no improvement of the complained symptoms or other new symptoms appear. Changes in the size of the primary tumor, assessed the size of the tumor remission or remains/enlarged. Changes in the size of the enlarged neck lymph-node, assessed the size of the neck lymph-node remission or remains/enlarged. Decrease in tumor stage, assessed decrease in tumor stage or still remains. Confounding variables assessed include age,  $\leq 45$  years and  $\geq 45$  years. Gender, distinguished male or female. Histopathological type, assessed by WHO 2 and WHO 3. Performance status, which is assessed ECOG 1 and ECOG 2.

Data analysis using Chi-square test using SPSS software version 25.0. This research has been ethically approved by the Health Research Ethics Committee (KEPK) No. 1227/ EC/ KEPK-RSDK/ 2022 and research approval from Dr. Kariadi Hospital No: P/02.01/I.II/ 6811/2022.

## RESULTS

The subjects obtained for the period January 2020–January 2022 which were used as research samples were obtained as follows (Table 1).

Patients with NPC recurrent is 68.2% of patients

TABLE 1  
Characteristic of subjects

Variable		Chemotherapy		Total (%)
		Ifosfamide n	5-FU n	
Age	< 45 years old	8 (57.1)	6 (42.9)	14 (31.8)
	≥ 45 years old	14 (46.7)	16 (53.3)	30 (68.2)
Gender	Female	8 (72.7)	3 (27.3)	11 (25)
	Male	14 (42.4)	19 (57.6)	33 (75)
Histopathological Types	WHO 3	21 (50)	21 (50)	42 (95.5)
	WHO 2	1 (50)	1 (50)	2 (4.5)
Performance status	Performance status	21 (50)	21 (50)	42 (95.5)
	Negative	1 (50)	1 (50)	2 (4.5)

TABLE 2  
Changes in clinical symptoms

Chemotherapy	Clinical symptoms		Total (%)	p
	Improve n (%)	None n (%)		
Ifosfamide	22 (50)	0 (0)	22 (50)	0.500 <sup>£</sup>
5-FU	21 (47,7)	1 (2,3)	22 (50)	
Total	43 (97,7)	1 (2,3)	44 (100)	

Description : <sup>£</sup>Fisher's Exact

TABLE 3  
The comparison in changes the size of the primary tumor of the nasopharynx

Chemotherapy	Nasopharyngeal Tumor		Total (%)	p
	Remission n (%)	Remain/Enlarged n (%)		
Ifosfamide	16 (36.4)	6 (13.6)	22 (50)	0.347 <sup>¥</sup>
5-FU	12 (27.3)	10 (22.7)	22 (50)	
Total	28 (63.6)	16 (36.4)	44 (100)	

Description : <sup>¥</sup> Continuity Correction

aged ≥45 years. The youngest age was 18 years old and the oldest was 65 years old. Male patients predominance than female as much as 75%. Patients with WHO histopathological type 3 are at most 95.5% and 95.5% of patients with ECOG 1 status.

Improvement in clinical symptoms there was *Ifosphamide* chemotherapy and 5-FU chemotherapy there was no difference remarkably (p = 0.500) (Table 2).

Changes in the size of the primary tumor there was *Iphosphamide* chemotherapy and 5-FU chemotherapy no remarkably difference (p = 0.347) (Table 3).

Changes in the size of the neck lymph-nodes administration of *Ifosphamide* chemotherapy and 5-FU chemotherapy found no remarkably difference (p = 0.164) (Table 4).

Decreased stage there was *Iphosphamide*

**TABLE 4**  
**The Comparison in size changes neck lymph-node**

Chemotherapy	Lymph-node enlargement		Total (%)	p
	Remision n (%)	Remain/Enlarged n (%)		
Ifosfamide	19 (43.2)	3 (6.8)	22 (50)	0.164 <sup>‡</sup>
5-FU	14 (31.8)	8 (18.2)	22 (50)	
Total	33 (75)	11 (25)	44 (100)	

Description : <sup>‡</sup> Continuity Correction

**TABLE 5**  
**Differences in tumor stage changes**

Chemotherapy	Tumor Stage		Total (%)	p
	Decrease n (%)	None n (%)		
Ifosfamide	16 (36.4)	6 (13.6)	22 (50)	0.347 <sup>‡</sup>
5-FU	12 (27.3)	10 (22.7)	22 (50)	
Total	28 (63.6)	16 (36.4)	44 (50)	

Description : <sup>‡</sup> Continuity Correction

chemotherapy and 5-FU chemotherapy was found there was no remarkably difference (p = 0.347) (Table 5).

In Our study the relationship of confounding factors such as age, sex, histopathological type, and performance status to changes in clinical response. In statistical analysis, there was no relationship of confounding factors to changes in clinical response in patients who receiving chemotherapy (Table 6).

### DISCUSSION

This study found that the IFO group there was a change in remission of primary tumor size, neck lymph-nodes size, decreased tumor stage, and improvement in clinical symptoms greater than the 5-FU group with more than 50%. Statistically there is no significant difference to the clinical response to chemotherapy IFO with 5-FU. The National Cancer Management Committee has issued guidelines for the management of nasopharyngeal cancer where the use of a combination of 5-FU and cisplatin in cases of metastasis/ recurrence as a curative treatment or as a palliative treatment. This guide notes that the side effects and toxicity of chemotherapy may cause patients to discontinue treatment or discontinue treatment.<sup>6</sup> Previous studies, the administration of chemotherapy combination of ifosfamide, 5-fluorouracil, and leukovorin gives the value of overall response rate (ORR)

reached 56% with a 1-year survival probability rate reached 51%.<sup>9</sup> other studies stated the administration of ifosfamid-doxorubicin combination chemotherapy gives results of 15% to achieve a complete response with ORR reaching 68%.<sup>10,11</sup>

Previous studies have not compared the therapeutic response between ifosfamid-taxane-platinum based with 5FU-platinum based. Several studies that explain administered chemotherapy IFO and 5-FU, both effective and give good results as chemotherapy in recurrent NPC.<sup>6</sup> Administration of IFO and 5-FU combination therapy in several studies was able to provide good response rate when side effects and drug toxicity can be controlled.<sup>10,11</sup> based on the results of this study, the selection of the type of chemotherapy ifosfamid can be a better choice by also considering the length of hospital stay and minimally side effects.

This study shows that the most age range of patients with recurrent NPC is 45 years. Previous research at Dr. Kariadi obtained the average age of NPC patients was 44 years.<sup>4</sup> peak incidence of NPC in the age range of 40–49 years.<sup>2</sup> Incidence of recurrency NPC there are not many studies that discuss it demographically, but the 5-year cumulative rate of recurrent NPC into neck regional is around 12–22%.<sup>13</sup> Incidence at a younger age are suspected to be related to genetic factors and exposure to carcinogenic substances from the environment

TABLE 6  
The relationship of confounding factors to clinical symptoms

Variable		Chemotherapy				Total (%)
		Ifosfamide		5-FU		
		n	%	n	%	
Age	< 45 years old	8	57,1	6	42,9	0.746 <sup>¥</sup>
	≥ 45 years old	14	46,7	16	53,3	
Gender	Male	14	42,4	19	57,6	0.164 <sup>¥</sup>
	Female	8	72,7	3	27,3	
Nasopharyngeal tumors	Remision	16	57,1	12	42,9	0.347 <sup>¥</sup>
	Remains/enlarged	6	37,5	10	62,5	
Lymph-node enlargement	Remision	19	57,6	14	42,4	0.164 <sup>¥</sup>
	Remains/enlarged	3	27,3	8	72,7	
Stage changes	Remision	16	57,1	12	42,9	0.347 <sup>¥</sup>
	None	6	37,5	10	62,5	
Hystopatological type	WHO 2	1	50	1	50	0.756 <sup>£</sup>
	WHO 3	21	50	21	50	
ECOG	ECOG 1	21	50	21	50	0.756 <sup>£</sup>
	ECOG 2	1	50	1	50	
Clinical symptoms	Improvement	22	51,2	21	48,8	0.500 <sup>£</sup>
	None	0	0	1	100	

Description : <sup>¥</sup> Continuity Correction; <sup>£</sup> Fisher's Exact

earlier.<sup>14-16</sup> As a prognostic factors, age is very influential on the survival rate and tolerance of chemoradiation treatment, so it can affect the recurrence factor of the disease.<sup>17</sup>

Characteristics of patients with recurrent NPC in this study 75% predominantly male This characteristic is similar to previous studies which stated that men have a higher recurrence potential than women.<sup>13</sup> Male tend to be more frequent distant metastases, thereby reducing survival rates due to genetic variation influenced by hormonal changes.<sup>14</sup> Males carried the VEGF-2578 allele gene that is associated with larger tumor size and higher tumor stage.<sup>14,18</sup>

This study patients with recurrent NPC with histopathological type WHO 3 more than WHO 2 and did not find histopathological type WHO 1. Previous studies found that the most histopathological types were WHO 3.<sup>2,4,16,19</sup> Factors that affect the NPC keratinization subtype include unhealthy lifestyles such as smoking. The research conducted by Naomi *et al* stated that there was no relationship between the degree of histopathology and the clinical stage in NPC. The study

mentioned that NPC WHO 3 sub-type most often occurs recurrences due to high-incidence factors related to endemic areas.<sup>14,20</sup>

This study did not find the relationship of several confounding factors such as age, gender, histopathology sub-type, and performance status to the assessed clinical response. In this study the dominant age above 45 years, the dominant male with the most histopathology type is WHO 3 and ECOG performance status 1. Improvement of clinical response from chemotherapy management in patients with recurrent NPC is only affected by the type of chemotherapy were administered.

## CONCLUSION

Administration of 5 fluorouracil-platinum based combination chemotherapy did not provide better clinical response of clinical symptoms, changes in primary tumor size, neck lymph-nodes size, and decreased tumor stage compared with Ifosfamid-taxane-platinum based combination on recurrent NPC. There was no association of confounding factors on clinical

response between the two groups.

### Acknowledgements

The author would like to express his gratitude to all who have supported the implementation of this study and to the reviewers who also provide corrections until the publication of this study.

### Conflict of Interest

The authors indicated no potential conflicts of interest.

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