Sys Rev Pharm 2020;11(5):587-590
A multifaceted review journal in the field of pharmacy

Increasing Neoadjuvant Chemotherapy in Nasopharyngeal Carcinoma Patients

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ABSTRACT

Nasopharyngeal carcinoma (NPC) has radiosensitive and chemosensitive properties. The lack of radiotherapy devices makes concurrent chemoradiation difficult in Indonesia. Thus, neoadjuvant chemotherapy is the most commonly given treatment option as initial management in patients with NPC. This study determined the profile of patients receiving neoadjuvant chemotherapy. This study was conducted retrospectively using secondary data derived from medical records of NPC patients treated at the Inpatient Ward, Dr. Soetomo General Hospital, Surabaya, Indonesia, from January to December 2018. Among 166 NPC patients undergoing neoadjuvant chemotherapy, there were 76.51% male and 23.49% female, and mostly were in the age group of 41-50 years. The majority of patients were with stage IVA NPC and type III histopathology. Most patients underwent 6 cycles of neoadjuvant chemotherapy. Cisplatin-Paclitaxel was the most widely used regimen, and 28.31% patients experienced regimen changes during chemotherapy cycle. The lack of radiotherapy devices causes concurrent chemoradiation which cannot be given widely to NPC patients and increases the number of neoadjuvant chemotherapy cycles, while waiting for the radiotherapy schedule.

Keywords: Nasopharyngeal carcinoma, neoadjuvant chemotherapy, chemotherapy cycle.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from epithelial nasopharyngeal mucosa easily infiltrating local tissues, metastasis, and having rapid tumor growth (1,2). Factors that play a role in the pathogenesis of NPC include Epstein Bar virus, genetic susceptibility, and environment. Epstein Bar virus also may cause gastric cancer as a coinfection similar to *Helicobacter pylori* (3,4). Radiotherapy and chemotherapy are main therapy for tumor (5). NPC is the one of disease with poor prognosis because of the position of the tumor adjacent to the skull base and vital structures (6). NPC also has radiosensitive and chemosensitive properties. Radiotherapy is the main therapeutic modality because of the highly radiosensitive nature of NPC and the location of the tumor which is difficult for surgery [1]. Single radiotherapy is recommended for early-stage NPC patients (T1, N0, M0). The incidence of NPC at an advanced stage is around 70% and has a higher risk for local recurrence and distant metastases when treated with radiation alone. The standard therapy for NPC patients with more advanced stages (T1, N1-3 and T2-T4, all N) is concurrent chemoradiation with or without adjuvant chemotherapy (7–9). The lack of radiotherapy devices makes concurrent chemoradiation difficult in Indonesia in general and in particular in Dr. Soetomo General Hospital, Surabaya. Thus, neoadjuvant chemotherapy is the most commonly given treatment option as initial management in patients with NPC [2].

Neoadjuvant chemotherapy is receiving a lot of attention because of its good compliance rate and the effect of early eradication of micrometastases. Recent clinical trials have shown that neoadjuvant chemotherapy before concurrent chemotherapy can significantly improve survival rates, progression-free survival, and distant metastasis-free survival in the management of NPC patients with an advanced locoregional disease [3]. Neoadjuvant chemotherapy regimens are given up to three times at intervals every 3 weeks (10). Another study also reveals that there is a significant decrease in viral load detected in the plasma of NPC patients following therapy (11).

Recording and data collection of NPC patients in Indonesia is still inadequate and not yet digital, and it is difficult to compare the results of treatment from several centers in Indonesia to other countries and include patients in the chemotherapy protocol in accordance with international recommendations. Adequate data collection for NPC patients is considered important (12). There is no data yet on the management of neoadjuvant chemotherapy in NPC patients at Dr. Soetomo General Hospital, Surabaya. Thus, this research was conducted. The objective of this study was to determine the profile of patients receiving neoadjuvant chemotherapy at Otorhinolaryngology-Head and Neck Surgery (ORL-HNS) Department of Dr. Soetomo General Hospital, Surabaya, Indonesia [4].

METHODS

This study was conducted retrospectively using secondary data derived from medical records of NPC patients treated at the Inpatient Ward, Dr. Soetomo General Hospital, Surabaya from January to December 2018. The study sample was all medical records of NPC patients who had undergone neoadjuvant chemotherapy and met the inclusion and exclusion criteria. The inclusion criteria were NPC patients who had undergone neoadjuvant chemotherapy with complete medical record data. The variables studied were sex, age, stages, histopathology, number of cycles, chemotherapy regimens and changes of regimens. The age group used was a 10-year interval, and the stage used the tumor node metastasis (TNM) classification system according to AJCC 7th edition. Meanwhile, histopathology uses WHO criteria. Data are presented as frequency and percentage and described descriptively.

RESULTS

From January to December 2018, 166 NPC patients underwent neoadjuvant chemotherapy at the Inpatient Ward ORL-HNS Department, Dr. Soetomo General Hospital, Surabaya. The demographic profiles of subjects are presented in Table 1. This study consisted of 127 male patients (76.51%) and 39 female patients (23.49%). The average age of patients was 46.78 years, with the youngest age range of 15 years to the oldest of 75 years old. The age group with the highest incidence of NPC was 41-50 years with 54 patients (32.53%), followed by the 51-60 years and 31-40 years age groups. The 11-20-year age group had the lowest incidence of NPC.

Table 1. Demographic characteristics of subjects

Characteristics	Frequency	Percentage (%)
Sex		
Male	127	76.51
Female	39	23.49
Age		
11 – 20 years	3	1.81
21 – 30 years	15	9.04
31 – 40 years	24	14.46
41 – 50 years	54	32.53
51 – 60 years	51	30.72
61 – 70 years	15	9.04
71 – 80 years	4	2.41

Table 2 shows the clinical characteristic of patients. The majority of patients undergoing neoadjuvant chemotherapy were patients with stage IVA (39.76%), followed by stages IVB (28.31%) and III (16.87%). There was no stage 1 in this study. Most of NPC patients in this study were found with type III histopathology at 95.18%, followed by type II (3.61%) and type I (1.2%). Most of the NPC patients in this study received 6 cycles of neoadjuvant chemotherapy (39.16%), followed by 3 cycles (19.28%), 5 cycles, and 2 cycles (11.45%).

Table 2. Clinical characteristics of patients

Characteristics	Frequency	Percentage (%)
Stage		
I	0	0
II	17	10.24
III	28	16.87
IVA	66	39.76
IVB	47	28.31
IVC	8	4.82
Histopathology		
Type I WHO	2	1.2
Type II WHO	6	3.61
Type III WHO	158	95.18
Cycles		
1	17	10.24
2	19	11.45
3	32	19.28
4	14	8.43
5	19	11.45
6	65	39.16

Cisplatin-Paclitaxel is the most used chemotherapy regimen in this study (56.28%), followed by Carboplatin-Paclitaxel (30.23%) and 5FU-Cisplatin (7.91%). The Carboplatin-Docetaxel Regimen was the least used in this study as seen in Table 3. A total of 47 patients (28.31%) experienced regimen changes during the neoadjuvant chemotherapy cycle, but most of patients underwent the same regimen from the beginning to the end of the chemotherapy cycle (71.69%).

Table 3. Profile of regimen chemotherapy

Variables	Frequency	Percentage (%)
Regimen		
Cisplatin-Paclitaxel	121	56.28
Carboplatin-Paclitaxel	65	30.23
5FU-Cisplatin	17	7.91
Cisplatin-Docetaxel	5	2.33
5FU-Carboplatin	4	1.86
Carboplatin-Docetaxel	3	1.39
Regimen replacement		
No	119	71.69
Yes	47	28.31

DISCUSSION

Our findings showed that the most NCP patients were men, and most of them were in the age group of 41-50 years. The majority of patients undergoing neoadjuvant chemotherapy were patients with stage IVA and type III histopathology. Most patients underwent 6 cycles of neoadjuvant chemotherapy, and the most widely used chemotherapy regimen was Cisplatin-Paclitaxel. The additional cycles of chemotherapy can be caused by the lack of radiotherapy devices, so patients must undergo additional neoadjuvant chemotherapy regimen while waiting for radiotherapy schedule.

The present study are consistent with study conducted in Guangzhou in 2014 consisting of 3399 men (73.4%) and 1231 women (26.6%) with the most frequent age group being 40-49 years (32.8%) and 50-59 years (25.6%) (13). Another study in 1121 NPC patients consisted of 789 men (70.4%) and 332 women (29.6%) with a peak incidence at the age of 40-49 years and more than 80% of patients diagnosed at the age of 30-59 years (12). This is consistent with reports in some literature stating that the incidence of NPC in men is two to three times higher than women. Differences between men and women may be due to differences in lifestyle (e.g. tobacco consumption) and biological factors (14). The lower incidence of NPC in women may also be influenced by the protective effect of the hormone estrogen (15).

The most age groups of NPC patients in this study were 41-50 years and 51-60 years. These results are following several studies reporting incidents in high-risk populations increased in the age group 40-49 years and 50-59 years (16,17). This is because NPC patients in high-risk populations are exposed to carcinogenic substances in the early stages of life. Nasopharyngeal carcinoma takes several decades to develop malignant cells. Thus, carcinogenic exposure in early life may have a significant effect. In low-risk populations, the incidence of NPC increases consistently with age (13,15).

The majority of patients undergoing neoadjuvant chemotherapy were patients with stage IVA, followed by stages IVB and III. The same results were reported by study in Jakarta in 2012 discovering that people with NPC in Indonesia tended to be diagnosed at an advanced stage (12). These results are slightly different from studies conducted in Guangzhou in 2014 and Seoul in 2015 showing the largest group with stage III, followed by stage IV (7,13,18). Differences in results with research abroad may be due to differences in the level of knowledge, social economy, and community behavior.

Most of NPC patients in this study were found with type III histopathology, followed by type II and type I. This is consistent with research conducted in Jakarta in 2012 (12) and Guangzhou in 2014 (13) showing that type III histopathology was most prevalent in the Southeast Asian

region and other high-risk areas. Types II and III have a higher sensitivity to chemotherapy than type I so that it can be used in therapeutic strategies and prediction of response to treatment. Type III has an incidence of up to 92% in endemic areas and is associated with Epstein Barr virus (EBV) infection in more than 90% of cases. The relationship between EBV infection and low differentiation of squamous cells or glands shows specific differentiation of NPC cells in support of latent EBV infection (19,20).

The majority of NPC patients in this study were given 6 cycles of neoadjuvant chemotherapy. This is not following the recommendations of neoadjuvant chemotherapy regimens in various literature suggesting 3 cycles of chemotherapy at intervals of 3 weeks before being given concurrent chemoradiation. As many as 28.31% of patients experienced a change of regimen during the chemotherapy cycle because, among other things, the previous regimen do not provide a satisfactory response; there are side effects of chemotherapy drugs and impaired kidney function due to cisplatin (8,18).

Cisplatin-Paclitaxel was the most widely used chemotherapy regimen in this study. This is different from the recommendations from some literature using 5FU-Cisplatin as first-line therapy for neoadjuvant chemotherapy (9,21). The choice of the Cisplatin-Paclitaxel regimen as first-line therapy is due to the lack of facilities and infrastructure in the inpatient ward, considering the 5FU-Cisplatin regimen requires a longer inpatient compared to the Cisplatin-Paclitaxel regimen with shorter stays. NCCN recommendations for NPC stage I patients are given definitive radiotherapy in the nasopharynx and elective radiotherapy in the neck area, while the treatment options in stages II-IV are concurrent chemoradiation followed by adjuvant chemotherapy, neoadjuvant chemotherapy followed by concurrent chemoradiation and concurrent chemoradiation. Several chemotherapy drug regimens can be used, including cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU and epirubicin (7).

The overall results of advanced NPC treatment have not been satisfied with a 5-year survival rate of around 53-80% for stage III and 28-61% for stage IV. Several studies have examined neoadjuvant, concurrent, and adjuvant chemotherapy. Clinical trials, meta-analyses, and systematic reviews indicate concurrent chemoradiation to be most effective in the management of NPC. Cisplatin-based chemotherapy together with radiotherapy is now the standard therapy for stage II-IVB NPC (21). However, the lack of facilities and infrastructure at Dr. Soetomo General Hospital, Surabaya, is not yet possible to do concurrent chemoradiation in NPC patients. Management given to NPC patients at Dr. Soetomo General Hospital, Surabaya, is neoadjuvant chemotherapy followed by radiotherapy only and can be followed by adjuvant chemotherapy or radiotherapy administration followed by adjuvant chemotherapy.

The benefits of neoadjuvant chemotherapy before concurrent chemoradiation have been widely studied. Neoadjuvant chemotherapy is believed to be superior to adjuvant chemotherapy in several theoretical aspects: (1) higher compliance to all chemotherapy regimens; (2) chemotherapy drug penetration into tumor tissue may decrease due to decreased circulation after radiotherapy; and (3) neoadjuvant chemotherapy can kill micrometastases before definitive local treatment (18). A meta-analysis study showed that neoadjuvant chemotherapy followed by concurrent chemoradiation or radiotherapy alone can improve overall survival rates and progression-free survival in advanced NPC patients compared to concurrent chemoradiation or radiotherapy alone (22).

The interval between neoadjuvant chemotherapy and radiotherapy also influences treatment outcomes related to overall survival and progression-free survival. Research conducted on 239 NPC patients with advanced locoregional spread found that the shorter the interval between neoadjuvant chemotherapy and radiotherapy, the better the overall prognosis associated with overall survival, failure-free survival, and distant failure-free survival rate (23). Another study involved in 668 patients found that intervals of more than 30 days between neoadjuvant chemotherapy and radiotherapy were associated with a high risk of distant failure and overall survival prognosis, especially for high N category patients (24-28).

NPC patients who received neoadjuvant chemotherapy and concurrent chemoradiation also had an increased risk of locoregional recurrence compared to those who received concurrent chemoradiation and adjuvant chemotherapy. This is caused by the severe side effects of neoadjuvant chemotherapy so that it can delay concurrent chemoradiation. The results of a meta-analysis showed that neoadjuvant chemotherapy is associated with an increased risk of hematological side effects, including leukopenia and thrombocytopenia. These acute side effects can be treated by giving growth factors (12).

CONCLUSION

Nasopharyngeal carcinoma was more common in men and the age group of 41-50 years. The majority of patients undergoing neoadjuvant chemotherapy were patients with stage IVA and type III histopathology. Most patients received 6 cycles of neoadjuvant chemotherapy, and Cisplatin-Paclitaxel was the most widely used chemotherapy regimen. The lack of radiotherapy devices causes concurrent chemoradiation to not be given widely to nasopharyngeal carcinoma patients and increases the number of neoadjuvant chemotherapy cycles while waiting for the radiotherapy schedule.

REFERENCES

1. Romdhoni AC, Herawati S, Mustikaningtyas E. Correlation Between Intracellular Heat Shock Protein 70 Expression And Cervical Lymph Nodes Enlargement In Nasopharyngeal Carcinoma. Folia Medica Indones. 2016;52(1):24–34.
2. Sudiono J, Hassan I. Epstein-Barr virus (EBV) DNA as biomaker of nasopharyngeal carcinoma diagnosis. Dent J (Majalah Kedokt Gigi). 2013;46(3):140–7.
3. Singh S, Jha HC. Status of Epstein-Barr Virus Coinfection with Helicobacter pylori in Gastric Cancer. J Oncol [Internet]. 2017/03/21. 2017;2017:3456264. Available from: https://pubmed.ncbi.nlm.nih.gov/28421114
4. Miftahussurur M, Sharma RP, Shrestha PK, Maharjan RK, Shiota S, Uchida T, et al. Helicobacter pylori infection and gastric mucosal atrophy in two ethnic groups in Nepal. Asian Pac J Cancer Prev. 2015;16(17):7911–6.
5. Savitri E, Maharis I, Kadir A, Djamin R, Mubarikaand S, Wardana T. The expression of mir-21 and mir-29c in blood plasma of nasopharyngeal carcinoma patient post-chemoradiotherapy. Indian J Public Heal Res Dev. 2019;10(10):1523–9.
6. Farhat, Asnir RA, Yudhistira A, Daulay ER, Puspitasari D, Yulius S. Evaluation of matrix metalloproteinase-9 expressions in nasopharyngeal carcinoma patients. In: IOP Conference Series: Earth and Environmental Science.

Institute of Physics Publishing; 2018.
7. Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, et al. NCCN guidelines insights: head and neck cancers, version 1.2018. J Natl Compr Cancer Netw. 2018;16(5):479–90.
8. Wang M, Tian H, Li G, Ge T, Liu Y, Cui J, et al. Significant benefits of adding neoadjuvant chemotherapy before concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a meta-analysis of randomized controlled trials. Oncotarget [Internet]. 2016 Jul 26;7(30):48375–90. Available from: https://pubmed.ncbi.nlm.nih.gov/27356743
9. Liu T, Sun Q, Chen J, Li B, Qin W, Wang F, et al. Neoadjuvant Chemotherapy with Fluorouracil plus Nedaplatin or Cisplatin for Locally Advanced Nasopharyngeal Carcinoma: a Retrospective Study. J Cancer. 2018;9(20):3676–82.
10. Zhou R, Zhu J, Chen X, Liu Y, Wang Y, Zhang T. The efficacy and safety of docetaxel, cisplatin and fluorouracil (TPF)-based induction chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a meta-analysis. Clin Transl Oncol Off Publ Fed Spanish Oncol Soc Natl Cancer Inst Mex. 2020 Mar;22(3):429–39.
11. Savitri E, Haryana MS. Expression of interleukin-8, interleukin-10 and Epstein-Barr viral-load as prognostic indicator in nasopharyngeal carcinoma. Glob J Health Sci. 2015;7(3):364–72.
12. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, et al. Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 2012 Apr;31(4):185–96.
13. Tang L-Q, Li C-F, Li J, Chen W-H, Chen Q-Y, Yuan L-X, et al. Establishment and Validation of Prognostic Nomograms for Endemic Nasopharyngeal Carcinoma. J Natl Cancer Inst. 2016 Jan;108(1).
14. Jia W-H, Qin H-D. Non-viral environmental risk factors for nasopharyngeal carcinoma: a systematic review. Semin Cancer Biol. 2012 Apr;22(2):117–26.
15. Xie S-H, Yu IT-S, Tse L-A, Mang OW, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983-2008: suggestion of a potential protective role of oestrogen. Eur J Cancer. 2013 Jan;49(1):150–5.
16. Farhat F, Daulay ER, Chrestella J, Asnir RA, Yudhistira A, Susilo RR. Correlation of P38 mitogen-activated protein kinase expression to clinical stage in nasopharyngeal carcinoma. Open Access Maced J Med Sci. 2018;6(11):1982–5.
17. Chrestella J, Farhat F, Daulay ER, Asnir RA, Yudhistira A, Nasution IA. Cyclooxygenase-2 expression and its correlation with primary tumor size and lymph node involvement in nasopharyngeal carcinoma. Open Access Maced J Med Sci. 2018;6(11):2001–5.
18. Song JH, Wu H-G, Keam BS, Hah JH, Ahn YC, Oh D, et al. The Role of Neoadjuvant Chemotherapy in the Treatment of Nasopharyngeal Carcinoma: A Multi-institutional Retrospective Study (KROG 11-06) Using Propensity Score Matching Analysis. Cancer Res Treat. 2016 Jul;48(3):917–27.
19. Tsang CM, Lo KW, Nicholls JM, Huang SCM, Tsao SW. Pathogenesis of Nasopharyngeal Carcinoma: Histogenesis, Epstein–Barr Virus Infection, and Tumor Microenvironment. In: Nasopharyngeal Carcinoma. Elsevier; 2019. p. 45–64.
20. Paiar F, Di Cataldo V, Zei G, Pasquetti EM, Cecchini S, Meattini I, et al. Role of chemotherapy in nasopharyngeal carcinoma. Oncol Rev. 2012 Mar;6(1):e1.
21. Jin T, Qin W-F, Jiang F, Jin Q-F, Wei Q-C, Jia Y-S, et al. Cisplatin and Fluorouracil Induction Chemotherapy With or Without Docetaxel in Locoregionally Advanced Nasopharyngeal Carcinoma. Transl Oncol. 2019 Apr;12(4):633–9.
22. Chen Y-P, Guo R, Liu N, Liu X, Mao Y-P, Tang L-L, et al. Efficacy of the Additional Neoadjuvant Chemotherapy to Concurrent Chemoradiotherapy for Patients with Locoregionally Advanced Nasopharyngeal Carcinoma: a Bayesian Network Meta-analysis of Randomized Controlled Trials. J Cancer. 2015;6(9):883–92.
23. Yang S, Fu X, Huang G, Chen J, Luo S, Wang Z, et al. The impact of the interval between the induction of chemotherapy and radiotherapy on the survival of patients with nasopharyngeal carcinoma. Cancer Manag Res. 2019;11:2313–20.
24. Peng L, Liu J-Q, Xu C, Huang X-D, Tang L-L, Chen Y-P, et al. The prolonged interval between induction chemotherapy and radiotherapy is associated with poor prognosis in patients with nasopharyngeal carcinoma. Radiat Oncol. 2019 Jan;14(1):9.
25. de la Torre, J. and C. Jenaro, *THE IMPACT OF JOB STRESS ON WORKERS IN CHILDREN'S CONTACT SERVICES IN SPAIN.* REVISTA ARGENTINA DE CLINICA PSICOLOGICA, 2019. **28**(4): p. 452-460.
26. Ochoa Pineda, C., et al., *SEXTING AND ITS RELATIONSHIP WITH EARLY MALADAPTIVE SCHEMES IN ADOLESCENTS.* REVISTA ARGENTINA DE CLINICA PSICOLOGICA, 2019. **28**(4): p. 461-470.
27. Cisternas Isla, C. and C. Carreno Miranda, *THE WORK OF THE PSYCHOLOGIST ON DUAL PATHOLOGY IN JUVENILE OFFENDERS.* REVISTA ARGENTINA DE CLINICA PSICOLOGICA, 2019. **28**(4): p. 471-479.
28. Prudent, C., et al., *EXPLORATORY STUDY OF FORCLUSION IN PARANOID PSYCHOSES IN A CLINICAL AND PROJECTIVE APPROACH.* REVISTA ARGENTINA DE CLINICA PSICOLOGICA, 2019. **28**(4): p. 480-486.