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Comparison of IL-6 and TNF-Alfa Serum Levels in Pre and Post Radiotherapy Nasopharyngeal Carcinoma Patients at the NTB Provincial Hospital

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Background: *Nasopharyngeal carcinoma is often found in Asia, especially in South and Southeast China, with Indonesia being the fourth most common malignancy after breast cancer, cervical cancer, and lung cancer. NPC can generally be diagnosed only in the late stages, so it can increase morbidity and mortality. One of the recommendations for therapy for NPC is radiotherapy, but radiotherapy still fails due to a chronic inflammatory process involving several inflammatory cytokines such as IL-6 and TNF-Alfa . Cytokines play a role in various signaling pathways that can lead to increased proliferation, migration, invasion, angiogenesis, and inhibit apoptosis and even have an effect on resistance to therapy in many cancer cells, especially NPC.*

Objective: *A good understanding of this pro-inflammatory cytokine, is expected to improve the prognosis in NPC patients in the future, knowing serum levels of IL-6 and TNF-Alfa pre and post-radiotherapy.*

Method: *This is a preliminary study or literature study before the main study is conducted. Sources include scientific journals accessed through an online portal, namely NCBI.*

Result and Discussion: *Poor prognosis in NPC patients with high serum levels of IL-6 and TNF-Alfa .*

Conclusions: *The higher the levels of IL-6 and TNF-Alfa in post-radiotherapy NPC patients, the worse the condition is because these pro-inflammatory cytokines can activate various signaling pathways.*

Keyword : Carcinoma nasopharynx; TNF-Alfa ; IL-6; Pre and Post Radiotherapy;

Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy in the epithelial cells of the nasopharynx. The incidence of NPC is very rare in America and Europe, with an incidence rate of less than 1 case per 100,000 population (PNPK NPC, 2017). In contrast, NPC is often found in Asia, especially in South and Southeast China with an incidence of 40-50 cases per 100,000 population. Meanwhile, Indonesia is ranked the fourth most common malignancy after breast cancer, cervical cancer, and lung cancer (Audina et al., 2019). Around 6.2/100,000 cases were found with a total of about 13,000 new cases every year (PNPK KNF, 2017). It is very important to make an early diagnosis of NPC because the cure rate will be higher if it is treated at an early stage. However, only 10% of cases can be diagnosed at an early stage so that in general NPC patients come in an advanced stage (Deviana, Rahaju, & Maharani, 2016)

The recommended therapy for NPC according to the National Guidelines for Medical Services (PNPK) for Nasopharyngeal Cancer is definitive curative radiotherapy as a single therapy modality for T1N0M0 NPC, concurrent with chemotherapy (chemoradiation), while for advanced NPC palliative radiotherapy can be given. The target of radiotherapy is to damage the DNA in the nucleus of carcinoma cells which will result in damage or decreased ability to proliferate. As described above, the majority of NPC patients are diagnosed at an advanced stage, this causes 85% of the sufferers to die (Kadir, Retnowati, Akil, & Usman, 2018). Despite advances in radiotherapy, the presence of metastases in NPC is the cause of radiotherapy failure. One of the causes of metastasis is chronic inflammation of the NPC, the presence of this inflammation causes an increase in the immune response in the tumor and has an effect on the response to therapy. Through the activation of NF-kappaB and the STAT3 pathway, 5-8F cell colonies in NPC can induce the production of pro-inflammatory cytokines, namely TNF-Alfa , IL-6, and IL-8. The activation of pro-inflammatory cytokines certainly involves the role of macrophages which function to secrete more pro-inflammatory cytokines and result in massive proliferation of 5-8F cell colonies in NPC (Ke et al., 2016)

This study will discuss more about pro-inflammatory cytokines, namely IL-6 and TNF-Alfa which are known to have IL-6 signaling pathways starting from binding to IL-6R which is an IL-6 receptor and this binding will result in dimerization and phosphorylation of gp130 which then will activate several pathways such as JAK (Janus Tyrosine Kinase). This IL-6 signaling mechanism is considered to contribute to increased proliferation, migration, invasion, angiogenesis, and inhibits apoptosis, and even has an effect on resistance to therapy in many cancer cells, especially NPC. Meanwhile, TNF-Alfa also plays a role in various tumor growth processes such as activation of cancer genes and tumor metastasis (Asnir, Yudhistira, Susilo, Daulay, & Chrestella, 2018). In its role as a tumor metastatic factor, TNF-Alfa can stimulate cell motility through activation of the JNK signaling pathway which will then increase cell invasion (Song, 2013). Several studies discussing malignant tumors said that the higher the levels of IL-6 and TNF-Alfa , the worse the prognosis and vice versa. This also applies to NPC patients who have received radiotherapy, if the levels of IL-6 and TNF-Alfa are high after radiotherapy, this means that there is a poor response to radiotherapy (Song et al., 2013)

Therefore, it is necessary to have a better understanding of IL-6 and TNF-Alfa and their relation to radiotherapy to find out whether radiotherapy can improve the prognosis in NPC patients and in the future it is hoped that IL-6 and TNF-Alfa can be

one of the modalities.

One of the therapies in NPC patients is the administration of anti-IL-6R antibodies to prevent and inhibit NPC metastases and use TNF-Alfa as a biomarker to evaluate the inflammatory status of NPC patients.

Method

This article is a preliminary study or literature study before the main study is conducted. Sources include scientific journals and are based on government guidelines or related agencies. Search sources with the keywords "Carcinoma Nasopharynx" "Pre and Post Radiotherapy" "serum level" "IL6" and "TNF-Alfa" were conducted at the Nation Center for Biotechnology Information or NCBI and found as many as 20 sources based on these keywords.

Research Result

Nasopharyngeal carcinoma is a squamous cell carcinoma which is characterized by the presence of malignant tumors that arise in the epithelial cells that cover the surface and lines of the nasopharynx (Brennan, 2006). The location of the nasopharynx is at the back between the nose and throat. The boundaries of the nasopharynx are the choana at the front, the spine to the back, the opening of the auditory tube on the side, while the sphenoid sinus is found at the top. This nasopharyngeal carcinoma originates from the lateral wall of the nasopharynx, namely the Fossa of Rosen Müller (FOR) which is behind the torus tubarius. The anatomical boundaries of the FOR are, on the front are the eustachian tube and levator palatine muscle, on the back is the nasopharynx wall, and on the side is the tensor veli palatin muscle. In populations where nasopharyngeal carcinoma is common, such as in China where some patients with nasopharyngeal carcinoma are asymptomatic and have EBV antibody titers, it was found that when initial screening for nasopharyngeal carcinoma using a CT scan was performed, there was an asymmetry and a blunt surface on the FOR. The presence of malignant tumors in the nasopharynx can spread from the FOR to the outside of the nasopharynx to the skull base, posterosuperior, lateral wall, palate, oropharynx, and can metastasize to lymph nodes (Petersson, 2015)

Etiology and Risk Factors

The viral cause of nasopharyngeal carcinoma is the Epstein–Barr virus (EBV), while the non-viral risk factors for the occurrence of NPC are not known with certainty. However, some studies suggest that alcohol consumption, smoking, high intake of preserved (salty) foods, and fermented foods with high nitrosamines are said to be risk factors for NPC. In addition, environmental factors such as exposure to wood dust, heat, chemical fumes, and incense smoke are considered to have carcinogenic properties because they contain polycyclic aromatic hydrocarbon compounds.

Genetic factors are also considered to play a role in the occurrence of NPC, several studies have linked the HLA antigen locus to an increased incidence of NPC. Certain HLA loci are associated with susceptibility to NPC, for example, in China, which is the largest population of NPC patients, alleles A2 and B46 were found to increase the risk of NPC.

The transformation of EBV infection into a malignancy is the result of a combination of several factors that consistently or widely cause NPC, such as environmental factors such as diet, gender, and genetics, which are considered the most common etiology of NPC. Meanwhile, other factors such as air and soil are considered as inconsistent factors causing NPC. Based on the explanation above, it is important to note that the presence of early EBV infection and chronic viral reactivation are the main etiology of NPC. However, based on available data, it was found that around 100% of children in Indonesia aged 5 years were carriers of EBV. This means that NPC is a multifactorial disease with risk factors as mentioned above (Nasional, 2017)

A. Pathophysiology

As explained in the etiology section, NPC is a multi-factorial disease that can be caused by one of the genetic factors. In populations with a high risk of NPC found genetic mutations on chromosomes 3p and 9p, even these mutations occurred before infection. EBV due to exposure to carcinogens such as nitrosamines in salted fish as well as people's lifestyles in populations at high risk of NPC trigger this. The presence of these predisposing factors increases the risk of faster growth of EBV infection and rapid change into premalignant NPC epithelium (Tsao, Tsang, & Lo, 2017)

In the early phase of NPC growth, an antibody response to the EBV virus antigen was found, precisely in the lytic cycle. This is because EBV targets B cells and epithelial cells, but the mechanism of infection in epithelial cells has not been further elucidated. While the mechanism of infection in B cells occurs when the gp350 protein on the surface of the viral membrane (*viral envelope*) binds to CD21/CR2 on the surface of B cells. In addition to its role in activating the immune response, binding to CD21 can increase the occurrence of dysplasia in the nasopharyngeal epithelium.

An explanation of the degree of dysplasia, either mild or severe dysplasia can be seen in the graph below.

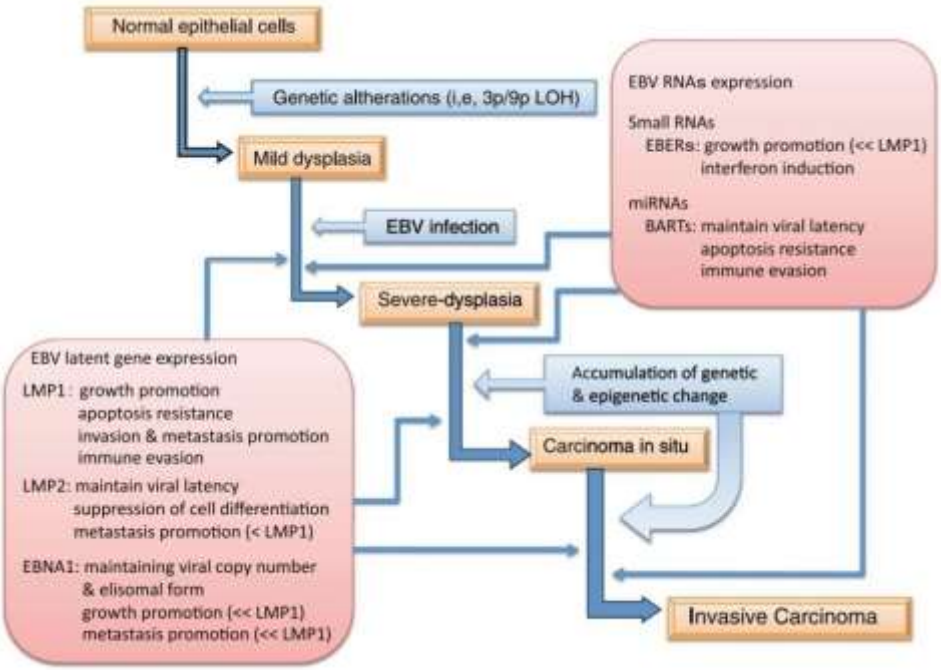

Figure 1.1. The role of EBV RNA and latent EBV genes in the transformation of normal epithelial cells into invasive carcinoma (Yoshizaki et al., 2013)

The chart is a brief description of the progression from normal epithelium to mild dysplasia. The change from mild dysplasia to severe dysplasia involves several mechanisms involving latent EBV genes such as LMP1 which act for invasion and metastasis, resistance to apoptosis and growth promotion. LMP2 functions to suppress cell differentiation, metastasis and maintain viral latency. In addition to LMP1 and LMP2, the latent EBV gene expressed is EBNA1 which functions for the growth of NPC cells. EBV RNA expression also plays a role in the pathogenesis of NPC, such as EBERs that contribute to NPC cell growth and induce interferon. MicroRNAs such as BARTs also maintain viral latency, resistance to apoptosis and *immune evasion*. BARTs and EBERs also play a role in the change to severe dysplasia, to the occurrence of genetic and epigenetic changes that result in carcinoma in situ and can develop into invasive carcinoma (Yoshizaki et al., 2013)

Further explanation of the pathogenesis of NPC can be seen in the image below.

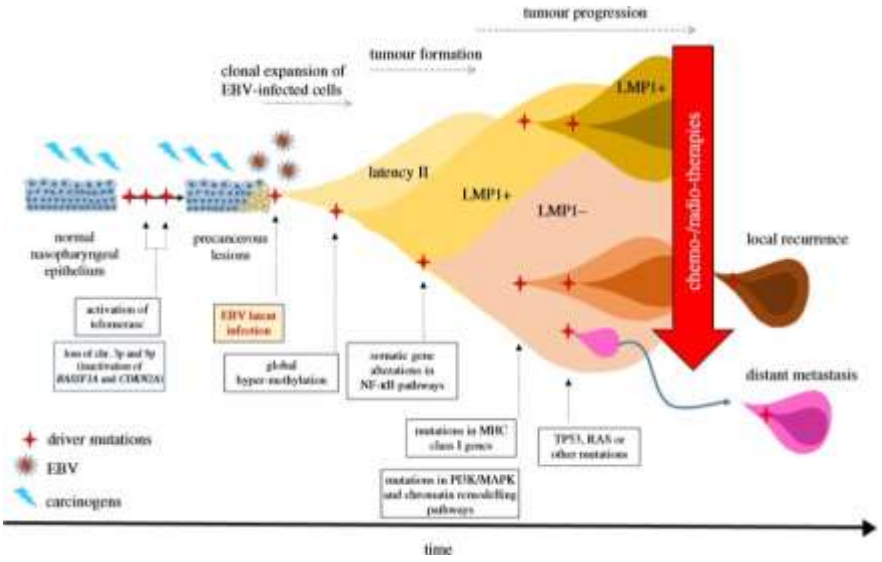

Figure 1.2. EBV infection and progressive genomic changes in NPC (Tsao et al., 2017)

The picture above explains from the beginning the pathogenesis of NPC, starting with frequent and prolonged exposure to carcinogens such as nitrosamines, which can cause mutations in DNA, for example in RASSF1A and p16 on chromosomes 3p and 9p, which are active genes for growth suppression. on tumor cells. These mutations may result in mild dysplasia of or precancerous lesions of epithelial cells.

Changes in the lytic cycle to latent are caused by persistent EBV infection resulting in the expression of latent genes such as EBNA1, LMP1, LMP2A, EBERs, and BARTs that cause extensive hypermethylation. In addition, LMP1 can activate the NF-kB signaling pathway that can stimulate genetic mutations, such as somatic mutations in TP53, RAS and other genes that can help distant metastases and an increase in recurrence even after chemotherapy or radiotherapy in NPC patients. (Tsao et al., 2017)

B. IL-6 and Nasopharyngeal Carcinoma

When inflammation occurs, a tumor microenvironment is formed in which there are many macrophages that can secrete inflammatory cytokines and can then trigger the process of tumorigenesis. One of the cytokines secreted is IL-6 and is said to be the main inflammatory cytokine in the process of tumorigenesis. IL-6 is thought to be modulated by exosomes which are vesicles that can contain various kinds of molecules so that these exosomes can *cross-talk* between the tumor microenvironment and host cells. The mechanism used is by transmitting signals from cancer cells to host immune cells. These tumor exosomes can also modulate tumor immunity by enhancing opsonization, inducing and even suppressing immunity. Exosomes can form tumor immunity by secreting immunomodulating exosomes and proteins to T cells, thereby preventing differentiation in Th1 cells

(Wang, 2020). In addition to exosomes, IL-6 is also modulated by the main oncogene of NPC, LMP1 which is known to activate various signaling pathways that can then play a role in the regulation of the expression of proteins, cytokines, and chemokines that can modulate cell growth and migration. . LMP1 can activate IL-6 via NF-kB signaling.

After IL-6 is secreted, IL-6 can then activate STAT-3 by binding to the IL-6 receptor, IL-6R. This binding of IL-6 with its receptor will trigger the dimerization and phosphorylation of STAT3 through the JAK signaling pathway. Activation and increase in the number of STAT3 in NPC are influenced by the amount of IL-6 because STAT3 can be activated due to abnormal paracrine/autocrine signals from IL-6. So the more the number of IL-6 means the worse the patient's prognosis. IL-6, besides being able to activate STAT3, IL-6 can also increase EMT (*Epithelial Mesenchymal Transition*) so that the strength to stick between one cell and another decreases so that transfer or migration can occur by infected cells and invade organs that have healthy cells. STAT3 activation also indicates a change from the lytic phase to the latent phase, because STAT3 can increase the expression of MMP-9 which plays a role in lymph node metastasis, while the higher the expression of MMP-2, the lower the patient's survival. So that the higher the level of IL-6 in NPC patients, the worse the situation. Therefore, IL-6 can be found in large numbers in NPC patients with distant metastatic stages (Soehartono, Prasetyo, Surjotomo, & Yudhanto, 2019)

C. TNF-Alfa and Nasopharyngeal Carcinoma

TNF-ALFA can be found in both physiological and pathological processes, this cytokine has a role in regulating homeostasis. TNF-Alfa can be classified into cytokines that support the inflammatory process (a *pro-inflammatory cytokine*), in addition to TNF-Alfa other cytokines such as IL-15, IL-17, IL-23 also include *pro-inflammatory cytokines*. While the cytokines that prevent inflammation (*anti-inflammatory cytokines*) are IL-4, IL-10, IL-13, and TGF-β (Nurdiansah, 2013). TNF-Alfa is a pleiotropic cytokine or cytokine that has effects on cells depending on the type of tumor, concentration, and duration of exposure. As well as the presence of chemokines and cytokines in the tumor microenvironment. So that in some cancer cells, two roles of TNF-Alfa were found, namely as a *pro-inflammatory cytokine* or *anti- inflammatory cytokine*, for example in *Lewis lung carcinoma* TNF-Alfa α plays a role in inhibiting growth and metastasis (Yu et al., 2019)

TNF-Alfa is a cytokine that is secreted by a number of cells such as NK cells, T cells, B cells, macrophages, neutrophils, and tumor cells. TNF-Alfa α functions for growth, differentiation, and increases the invasion and migration of cancer cells. TNF-Alfa has a special role in the acute inflammatory process that is modulated by macrophages in the phase of *innate immunity*. The Association of *Toll-like receptor* (TLR) on macrophages then induces the activation and produces TNF-ALFA α which then makes these macrophages become master cells that produce TNF-ALFA (Yu et al., 2019)

TNF-Alfa binding to its receptor, TNFR1 activates various signaling pathways and produces various effects of TNF-Alfa α/TNFR1 so that it can stimulate lymphatic endothelial cell activity which will result in tumor metastasis and lymphangiogenesis. Therefore, through the binding of TNF-Alfa α to its receptors and effects on lymphatic tissue, TNF-Alfa α has an important role in cancer metastasis. In addition, TNF-Alfa can activate COX-1 and COX-2 by activating several signaling pathways such as NF-kB, PEA3, and AP-1 which are active because of the COX-2 promoter which will bind to the transcription complex of these signaling pathways. In the early phase, COX-2 will increase above normal, and during the growth of cancer cells, COX-2 expression will be more and more expressed so that this can link COX-2 as a factor for tumor invasive growth (Nurdiansah, 2018). Through the C- Jun-N-Terminal Kinase (JNK) signaling pathway, TNF-Alfa α can regulate the expression of c-IAP2 (*Inhibitor of Apoptosis Proteins*) which, when these IAPs are active, will activate caspases to inhibit cell apoptosis. In addition, IAPs function to influence the inflammatory process, cell migration, invasion, and metastasis.

Clinical Manifestations

Symptoms that arise in NPC patients are divided into four main categories, namely:

1) Masses in the nasopharynx can cause epistaxis, obstruction and *discharge.*
2) Eustachian tube dysfunction and can lead to decreased hearing and tinnitus
3) Disorders of cranial nerves 5 and 6 that manifest clinically as facial pain, diplopia, headache and paresthesias
4) Mass in the neck (Petersson, 2015)

With the above symptoms, it shows that NPC can extend inside or outside of the nasopharynx either on the other lateral wall or towards the posterosuperior to the skull base, even the nasal cavity and oropharynx. Therefore, the symptoms found in the primary tumor are nasal regurgitation due to paresis of the soft palate, decreased hearing ability, obstruction/bleeding in the nasal cavity and producing *nasal twang* or nasal sounds and other symptoms. The higher the NPC stage, it can trigger metastases to lymph nodes and even distant metastases to other organs such as bones, lungs, and *liver*, although rarely (Brennan, 2006)

The emergence of these symptoms is due to the difficulty of detecting NPC at an early stage due to a hidden location in the nasopharynx and can occur due to a misdiagnosis because some of the symptoms of infection in the respiratory tract are similar to NPC and low awareness of NPC in health workers is one of the factors that affect NPC. This makes NPC detectable only at an advanced stage. In Indonesia, the most common clinical manifestations are:

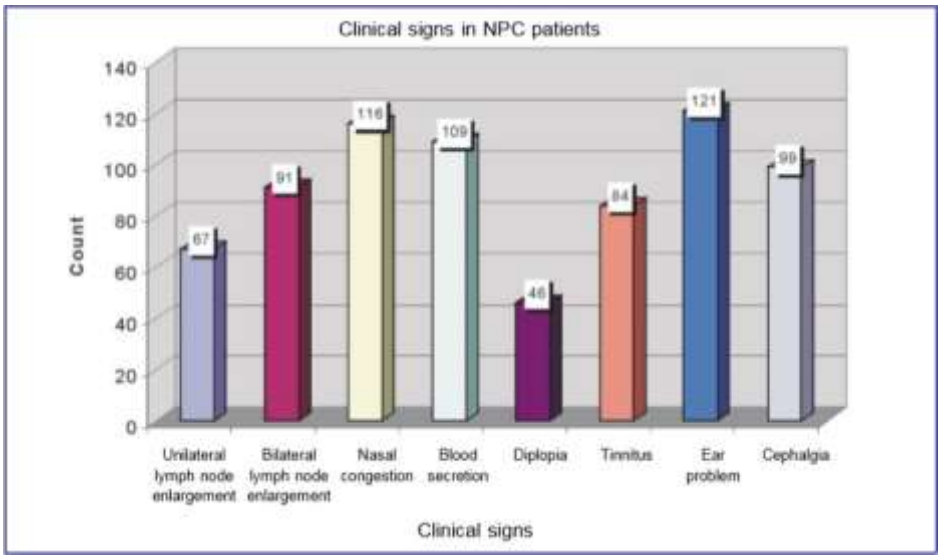

Figure 1.2 Clinical manifestations of NPC patients in Indonesia

The graph is a clinical manifestation of NPC patients, data were taken from 733 patients with a total of 1121 patients. From the graph the most symptoms felt were symptoms in the ears, nose, and throat. Although these symptoms appear in the initial phase, both patients and doctors only take it seriously if there is already a dilation of the lymph nodes which is an advanced phase of NPC (Nasional, 2017)

Diagnosis

diagnosis of NPC is based on history, physical examination, and investigations. Data obtained through anamnesis in the form of symptoms felt by patients such as symptoms in the nose, ears, nerves, and other symptoms. As stated in the clinical manifestations section, the physical examination carried out is a nasopharyngoscope or posterior rhinoscopy (Nasional, 2017). While the general examination can be done by:

1) Complete blood count
2) Examination of creatinine, electrolytes, liver function, liver, etc.
3) Cranial nerve neurologic examination
4) CT scan or MRI of the head and neck area as well as to the back below the clavicle to see the expansion in the surrounding area and see the primary tumor
5) Biopsy, to determine the diagnosis of NPC, an Anatomical Pathology examination is carried out and the results will be a definite diagnosis. Meanwhile, if only a Fine Needle Aspiration Biopsy (BAJH) is performed, the result will be an uncertain diagnosis. The purpose of a biopsy is to see the degree of differentiation and the type of malignancy (Nasional, 2017)
6) Photothorax
7) *Bone scintigraphy* to see the invasion/metastasis of cancer in bone (Brennan, 2006)

After carrying out supporting examinations, a definite diagnosis will be determined using the WHO criteria, namely:

a) *Keratinizing squamous cell carcinoma* (WHO Type I):
b) Non-keratinizing squamous cell carcinoma /*non-keratinizing carcinoma*: Has two cell types namely, differentiated (WHO type 2) and undifferentiated (WHO type 3) cell types.

The staging of nasopharyngeal carcinoma uses an agreement made by the *American Joint Committee on Cancer* (AJCC) edition VIII (2018) which includes staging based on the primary tumor and its size and how widely the tumor spreads or commonly known as the TNM division (Primary tumor, regional lymph nodes, distant metastases).

Management

Treatment for NPC patients can be symptomatic therapy, chemotherapy, radiotherapy, or a combination of both. In addition, the prevalence of NPC patients who experience nutritional disorders is quite high, so that nutritional support is needed for NPC patients in order to maximize the therapeutic effect. Before therapy is given, several examinations such as neurological, dental, and eye examinations should also be performed.

a. Radiotherapy

is one of the methods of NPC therapy which is divided into two types, namely definitive curative and palliative. Each of these types of radiotherapy can be given according to the stage of the NPC patient.

- **Definitive Curative Radiotherapy**

Radiotherapy can be given to all stages of NPC, both stage I, II, III, and even local stage IV. This radiotherapy targets the primary tumor, lymph nodes (KGB), neck, and supracavicular. NPC with T1N0M0, radiotherapy is the sole treatment option. While T1N1-3, T2-T4 N0-3 are based on the TNM NCCN category, the therapy given is radiotherapy together with chemotherapy. Radiation is performed in the area of the primary tumor that has the potential for regional and supraclavicular gland spread.

- **Palliative Radiotherapy**

In contrast to definitive curative radiotherapy, palliative radiotherapy is used when definitive curative therapy can no longer be performed, which means the patient is at an advanced stage, usually performed on patients with indications of pain due to distant bone metastases. Radiotherapy is usually given in conjunction with chemoradiation.

b. Chemotherapy

Chemotherapy is usually combined with radiotherapy. The use of chemotherapy is used as a *radiosensitizer* by giving *platinum based* 2.5 – 3 hours before radiotherapy at a dose of 30-40 mg/m^2, given 6 times once a week. Chemotherapy is often given to patients T2 – T4 and N1 – N3. Dosage in chemotherapy is divided into two, namely, *adjuvant* and *neo-adjuvant*. Patients with N3 >6 cm are usually given the full dose of both types of chemotherapy. In NPC with systemic metastases or recurrent cases, cisplatin + RT is given and can be added with cisplatin / 5 FU as adjuvant chemotherapy (PNPK, 2017).

c. Symptomatic Therapy

Complaints of nausea, vomiting, anorexia, are common complaints found in NPC patients. These complaints can be reduced by giving symptomatic therapy. Other symptoms that can appear are pain in the oral mucosa so that when swallowing or chewing it can cause an uncomfortable feeling. These symptoms arise as a side effect of radiotherapy. Symptomatic therapy options for these symptoms can be given as an adstringent as a mouthwash and can be given 3-4 times a day (PNPK, 2017).

d. Nutritional Support

Malnutrition conditions are often found in NPC patients, in addition to conditions such as nausea, vomiting, mucositis, diarrhea, and others can be found after therapy. Therefore, NPC patients must receive nutritional support, because if NPC patients are malnourished, this condition can have an impact on the response to therapy given to NPC patients. Screening can be done as soon as the patient is diagnosed with NPC. Screening is done by examining the weight, TB, BMI, and nutritional disorders in patients. Then after NPC patients diagnosed with malnutrition at the time of screening were immediately given treatment to meet the nutritional needs of these patients. The treatment given to NPC patients, especially those undergoing radiotherapy or chemotherapy, is to provide adequate daily needed nutrition. Energy needs in NPC patients can be done with theformula *rule of thumb*. However, 25-30 kcal/g can be given if individual calculations are not carried out (PNPK, 2017).

e. Complications

NPC patients or *survivors* cancerwho have received therapy for a long time may experience the side effects of chemotherapy and radiation due to frequent and repeated exposure. Side effects of radiotherapy are carotid artery stenosis, osteoradionecrosis, and temporal lobe necrosis. Cisplatin used in chemotherapy can also cause ototoxicity. One of the clinical manifestations of NPC is chronic dysfunction of the Eustachian tube which can then lead to complications, namely cranial nerve paralysis and hearing problems. In addition, the risk of developing into secondary malignant tumors can also occur (Petersson, 2015)

f. Prognosis

Prognosis in NPC patients depends on the stage and therapy given to these patients. Patients with stage I NPC are given radiotherapy and it is the main treatment option. Stage II, radiotherapy can also be given in conjunction with chemotherapy. While in stage III, chemoradiation was given and was able to increase the percentage of survival for NPC patients to 30% compared to only radiotherapy alone. In IVA/B patients, chemoradiation is given, but if the patient has reached stage IV, the prognosis for that patient is low (Petersson, 2015)

Conclusion

Nasopharyngeal carcinoma is a malignant tumor that arises in the epithelial cells that cover the surface and line of the nasopharynx. Generally, the symptoms of nasopharyngeal carcinoma are found at a late stage, this is due to its hidden location and the possibility of errors in diagnosis because the symptoms of carcinoma are similar to the symptoms of respiratory tract infections. In nasopharyngeal carcinoma, there is a chronic inflammatory response that involves many processes, including pro-inflammatory cytokines, namely IL-6 and TNF-Alfa which can activate various signaling pathways so that it can worsen the patient's prognosis.

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