Review Article

Current Cytotoxic Agents and Novel Therapy for Metastasis Nasopharyngeal Cancer

Pravinkumar V. Ingle, Sellam A/P R. Elangovan, Chow Li Yuet, Connie Tang Tung Ai, Yap Wei Yee, Nur Farah Ain Binti Mod Omar, Lee Jia Yin, Lai Yi Yan, Leong Wai Ching

International Medical University, No. 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia.

ABSTARCT

Nasopharyngeal carcinoma (NPC) is uncommon, but with the highest propensity to metastasize to distant sites, including lymph nodes in the neck or even breasts in certain cases. Genetic factors, environmental factors as well as the Epstein-Barr virus (EBV) may contribute to NPC occurrence. With this, computerized tomography (CT) scan, positron emission tomography (PET) scan, Magnetic resonance imaging (MRI), chest X-ray and fine needle aspiration are used to detect the NPC, depending on the metastatic condition of the primary tumor. At advanced NPC, the standard first-line treatment is the doublet chemotherapy with combination of platinum-fluorophrimidines, platinum-taxanes, platinum-gemcitabine, followed with the monotherapy for patients progressing after first-line platinum therapy. Several common chemotherapy-induced side effects observed in patients with metastatic NPC such as mucositis, nausea and vomiting as well as diarrhea. Patients received radiation therapy and chemotherapy experienced complications, including brain injury, trismus, hearing loss or xerostomia and radiation-related cranial nerve palsy. There is no prevention for metastatic NPC, however, non-metastatic NPC can be prevented by early detection and vaccination for Epstein-Barr virus.

Keywords: Nasopharyngeal cancer, metastasis, platinum-based chemotherapy, lobaplatin

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***Address for correspondence**
Dr. Pravinkumar V. Ingle,
International Medical University, No. 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia.
E-mail: PravinkumarVi@imu.edu.my, dr.pvingle@rediffmail.com

INTRODUCTION

Nasopharyngeal cancer (NPC) is very rare head and neck cancer where there is not even one case for every 100,000 people every year. [1] Nevertheless, the incidence is higher in certain parts of Asia, especially Guangzhou, China. [1-3] This means; ethnic Chinese are the most affected with NPC. [2-4] Besides, ethnic groups with rates reported to be intermediate to high include Eskimos, Polynesians, and the indigenous Mediterranean population. [2,3] Male is more prone to get NPC compared to female. In the United States, the age range of 60-year-old group is dominant to get the disease. [1-3] In children, the median age of development of NPC is 13 years. [3] It is a rare tumor in children. It usually begins in the nasopharynx, the upper throat side behind the nose and close to the base of the skull. It is a box-like chamber around 1.5 inches on every corner. It lies just above the soft part of the roof of the mouth (soft palate) and just in back of the nasal passages. [1] Squamous cells in the nasopharynx are usually where the NPC starts. [4]

It's hard to detect NPC since the symptoms are identical to other, less severe conditions. In addition, majority of NPC patients doesn't show any symptoms just before the cancer extents to a later phase. Around 60 - 75% of NPC patients complain of a painless neck lump, possibly caused by a swollen lymph node. The lumps may appear on both sides of the neck towards the back, but they are not tender or hurtful. Blood in the saliva is another typical symptom of NPC. Other symptoms include trouble breathing or speaking, sore throat, nasal blockage, nosebleeds, hearing problem, pain or ringing in the ear, double vision and headaches. [1,5,6]

There are several aspects involved in the prognosis of the NPC which are the stage of the cancer, type of NPC, the size of the tumor and the patient's age as well as general health. For stage I and II, 5-year survival rates of 80% and higher in patients treated with radiation alone. On the other hand, stage III or IV NPC patients who received chemoradiation have a 5-year overall survival rate of about 70%. The CRT use for stage III and IV patients has shown improvements in local and regional control, but distant metastasis remain the major failure leading to death in NPC patients. [3,5]

Generally, 50% of people diagnosed with NPC can survive up to five years or more after diagnosis. Survival rates are higher in the younger population, but lower in elderly. About 70% people below 45-year-old, and 35% people aged 65 to 74, will get through for five years or further after being diagnosed with NPC. [3,5]

Risk Factors

Studies have discovered few risk factors that are believed to be associated with the development of NPC are genetic and environmental factors and EBV.

1. Genetic

A person's genes may affect their risk for NPC. Some evidence demonstrates that individual with certain inherited tissue types are more prone to get this cancer. Family clusters with NPC are not surprising. The risk of NPC in a first-degree family member could be as high as eight times that of the general population. 15.5% cases of NPC reported that the patients had a first-degree relative with NPC. Having siblings who's had the condition, raising the likelihood of getting NPC compared to parents and children. The existence of such family clusters may be due to common genetic factors, shared environmental factors, or combination of these. [1-3, 5]

2. Environmental Factors

The most typical environmental factor related to NPC is diet, and it has been suggested that high intake of salt-cured fish and meat are associated with NPC. When cooking salt-cured foods, chemicals released in steam may get into the nasal cavity, raising the possibility of NPC. Being exposed to these chemicals during early age may increase the risk even further. Besides, inadequate intake of fresh fruit, carotene or fiber appear to be associated with an increased risk. Some researchers have shown that smoking may contribute to the growth of cancer, specifically the keratinizing type. Also, a study in 2009 shows that there's a connection between heavy drinking to this type of cancer. Nevertheless, it is hard to specify a certain food or other environmental agent as the only element superior to oncogenesis due to the presence of other confounding factors. [1-3, 5]

3. Epstein-Barr Virus (EBV)

EBV is a pervasive herpesvirus that is the causative agent of acute infectious mononucleosis and is associated with NPC. Infection with EBV plays a significant role in the etiology of NPC since the majority of NPC patients are presented with the virus in their blood. Based on DNA studies, the tumors appear to arise from a single cell that is infected with EBV, and positive EBV serology supports the diagnosis. However, the relationship between EBV infection and NPC is complicated and not yet fully understood. EBV infection alone is not sufficient to cause NPC due to the fact that infection with this virus is very common and this cancer is unlikely. A person's genes also may affect how the body reacts with EBV, which automatically may affect how EBV contributes to the NPC. Most people with EBV will not develop nasopharyngeal cancer. [1-3,5]

Diagnosis

The main diagnosis for metastatic nasopharyngeal cancer are imaging tests which includes Computerized Tomography (CT) Scan, Positron Emission Tomography (PET) scan, Magnetic Resonance Imaging (MRI) and Fine Needle Aspiration Biopsy (FNA). [1,6,7] Currently, there is no standard diagnosis procedure for metastatic cancer because it depends on the extent of metastases, predisposing symptoms and the size of primary tumor. [7]

1. Computerized tomography (CT) scan

A CT scan utilizes X-rays to construct detailed cross-sectional images of the body. CT scanning is conducted at the head and neck region to inspect the size of the tumors and to identify any enlarged lymph nodes in the neck. This is especially useful as the occurrence of metastasis is related to tumor size (T) and lymph-node involvement (N), and is most frequent in T3-4 or N2-3 tumor and in patients presenting with the Undifferentiated Carcinomas Nasopharyngeal Type. [4,8] A thoraco-abdominal CT can be used to identify any signs of cancer metastases in the chest and abdomen area. [1,4,6,7]

2. Positron emission tomography (PET) scan

The PET scan is used to clarify the results from a CT scan and is sometimes used in combination with CT where the results of a PET is further analysed using a more detailed CT scan. It is conducted by scanning and observing the radioactive areas in the body after radioactive sugar, fluorodeoxyglucose (FDG) is injected intravenously. Since cancer cells are highly proliferative, they tend to absorb higher amounts of sugar compared to normal cells and appear brighter in the scanned image. Even though the results of PET are not as refined as CT or MRI scans, it provides a general image for the

entire body. This is especially useful when the site of cancer spread is unknown or to identify any cancer spread to the lymph nodes as well as to clarify any suspicion of cancer observed in a Chest X-ray scan test. [1,4,7]

3. Magnetic resonance imaging (MRI)

The MRI scan operates on a combination of radio waves and magnetic fields to build up images of tissues and organ structures. MRI scans are one of the important diagnostic tool in identifying metastatic cancer that might have spread to the bones especially at the base of the skull. Also, MRI scan provides precise images of the soft tissues in the nose and throat. [1,4,6,7] **4**. **Fine needle aspiration biopsy**

Apart from that, fine needle aspiration (FNA) biopsy is used to detect any cancerous lump in or near the neck that originates from nasopharyngeal cancer cells. Drops of fluid containing cells and tiny fragments of tissue is extracted using a hollow needle attached to a syringe, which are then examined under a microscope to test for any cancerous signs. This method is utilized if a patient with known nasopharyngeal cancer experiences lymph node swellings in the neck area. [1]

Management

Nasopharyngeal carcinoma (NPC) is chemo sensitive and radiosensitive. It is normally treated with radiation therapy and chemotherapy either alone or in combination. Metastasis is the advanced stage of NPC where the patients should be treated with systemic chemotherapy, which aims to control the disease and prolong the survival rate. [9] Platinum-based chemotherapy is recognized as first-line treatment for metastatic nasopharyngeal carcinoma (NPC).

A) The Standard First-line Chemotherapy Regimen-Doublet Chemotherapy

The standard first-line chemotherapy regimen for the patient with metastatic NPC comprises chemotherapy with platinum doublets of drugs such as fluorouracil, gemcitabine and paclitaxel together with cisplatin or carboplatin. [9]

1. Platinum and Fluoropyrimidines Combination

Platinum and fluorouracil combination therapy is the most popular among all the other doublet regimens. This regimen gives a good response rate and even found to be effective in patients who had received prior chemotherapy. The toxicity profile is generally favourable with mild immunosuppression and peripheral neuropathy. [10] The major limitation of cisplatin-fluorouracil regimen is that it shown to have short duration of response in many studies and the requirement of deep vein catheterization with the admission to hospital. [11] Cisplatin-induced nephrotoxicity and ototoxicity were the main concern and this has limited its use. Carboplatin, the analogue of cisplatin has been used as a substitute of cisplatin due to the advantage of reduced nephrotoxicity and allows outpatient treatment. [10,12] However, carboplastin was shown to be more toxic to bone marrow. A retrospective Malaysian study in 2013 reported the combination of carboplastin with fluorouracil was not inferior to cisplatin-fluorouracil doublet combination in term of median survival. [13]

2. Platinum and Taxane Combination

Another combination is platinum and taxane combination. Platinum includes cisplatin and carboplastin whereas taxanes includes are docetaxel or paclitaxel. This combination of platinum and taxane have demonstrated high activity in recurrent and metastatic squamous cell carcinomas of the head and neck. [14,15]

a) Cisplatin and Docetaxel

Chua DTT. et al. reported that the response rate is higher, at least in chemonaïve patients and this combination is shown to be active in metastatic NPC, the efficacy in term of response rate is shown to be poor in a phase II trial carried out by McCarthy et al. [14] High incidence of Grade 3/4 neutropenia and febrile neutropenia was reported in several studies. The study also reported that the incidence of grade 4 neutropenia can be lowered with lower doses of both cisplatin and docetaxel. No incidence of neutropenic fever was seen in their study with lower dose. Nevertheless, lower dose does not seem to lower the activity against metastatic nasopharyngeal carcinoma. [15]

b) Cisplatin and paclitaxel

The efficacy of this regimen on NPC is confirmed. However, this regimen is associated with grade 3/4 neuropathy and bone marrow suppression. [16] Recently, a phase I/II dose-finding study carried out by Yan Hua et al has found that there was no intolerable aggravation of neuropathy in patient with metastatic NPC treating with nanoparticle albumin-bound paclitaxel (nab®-Paclitaxel) plus Cisplatin. Nab-paclitaxel plus cisplatin is thus consider as highly active regimen with moderate toxicity which warrants further investigation in a phase III study. [17]

c) Carboplastin + paclitaxel

Combination of carboplastin with paclitaxel has gained popularity due to high response rate. Its convenience of oral administration provides an extra advantage. Studies showed that most patients can tolerate with this regimen. [18,19] Dose limiting neurotoxicity has been reported in both studies and trial carried out by Yeo et al. and Tan et al. respectively. Mild to moderate myalgia and paresthesias of the extremities in particular the upper limbs were seen, but they generally do not cause bothersome to the patients. [18,20] Severe grade neutropenia with neutropenic fever has been observed in the study done by Yeo et al. [20] One toxic death had occurred in the trial by Tan et al. (1999).

3. Gemcitabine-based regimen

a) Cisplatin/gemcitabine

Synergistic cytotoxic effects between gemcitabine and cisplatin (GC) have been observed both in vivo and in vitro. This combination is ease of administration and can be given as an ambulatory outpatient schedule. A study carried out by R. K. C. Ngan et al. which involved patient with Chinese ethnicity with mostly undifferentiated or non-keratinizing histology have confirmed the efficacy of GC combination on this group of subject. Moderate myelotoxic and negligible neuropenic sepsis have been observed. Majority of the patient actually felt better in term of general well-being or symptom control. [21] However, a phase II trial carried out by Jason Chia-Hsun Hsieh et al. reported that one patient died of aspiration pneumonia, concomitantly with Grade III anemia, Grade IV leucopenia and Grade IV thrombocytopenia. [22]

b) Gemcitabine/vinorelbine

The use of vinorelbine with gemcitabine has been studied by several researchers and has shown to be effective in the treatment for the metastatic NPC patients resistant to platinum-based chemotherapy. Cui Chen et al. reported that tolerated hematogic side effect like leucopenia, neutropenia, anemia and thrombocytopenia were seen in the patient. No treatment-related deaths occurred. However, further clinical study is warranted. [23]

B) Second-line chemotherapy: Monochemotherapy

Platinum-based (cisplatin and carboplatin) chemotherapy is the mainstay in the management of metastatic NPC. [24] 5-fluorouracil (including capecitabine), taxanes (paclitaxel and docetaxel), irinotecan, vinorelbin and gemcitabine are the common cytotoxic agents employed as second-line for the patients progressing after first line platinum combination therapy. Yet, the response rates are usually lower as compared to first-line therapy. [25]

1. Cisplatin

Cisplatin's mechanism of action is correlated with its potential to form cross linkage with the purine bases of the DNA. By interfering with DNA repairing mechanisms, it causes DNA damage and eventually promoting apoptosis in cancer cells. However, due to drug resistance and undesirable side effects, for instance nephrotoxicity, ototoxicity, nausea and vomiting, other platinum-containing drugs have also been employed. [25]

2. Carboplatin

Carboplatin is one of the cisplatin analogues that have been developed to minimize the side effects of cisplatin, particularly the elimination of nephrotoxic effect, while preserving its antitumor activity. Thus carboplatin is an option in patients with renal impairment or intolerance to cisplatin or in elderly patients. [26] However, the major drawback of carboplatin is its myelosuppressive effect. [25]

3. 5-flurouracil

5-fluorouracil (5-FU) is a pyrimidine analogue that inhibits thymidylate synthase required for the synthesis of thymidine. This inhibition eventually leads to diminished DNA synthesis and DNA repair. 5-FU is relatively toxic as it causes myelosuppression and gastrointestinal disorders such as nausea and vomiting as well as diarrhea. In order to overcome these limitations, prodrugs of 5-FU has been developed. [27,28]

4. Capecitabine

Capecitabine is an oral fluoropyramidine carbamate. It is a prodrug of 5-FU that is selectively tumor-activated. The drug achieves its action through exploitation of the remarkably higher thymidine phosphorylase activity in malignant cells than in normal cells, allowing the preferred transformation of capecitabine to 5-FU in malignant cells. Capecitabine's selective tumor activation property permits continuous tumor exposure to 5-FU. This reduces the side effects by decreasing the incidence of normal tissues in contact with capecitabine. [29]

A study by Chua et.al in 2008 revealed high incidence of hand-food syndrome (HFS) in most of the patients in spite of the use of prophylactic topical emollient creams. However, the condition

was reversible and ameliorated following dose alteration, Hematological toxicity was mild and no treatment-related deaths were reported. The study suggested that the use of single agent capecitabine should be considered in metastatic patients after prior treatment with other chemotherapeutic regimens. [29]

5. Paclitaxel

Paclitaxel is a choice for the management of platinum-resistant patients with metastatic NPC. [30] Paclitaxel promotes microtubules assembly and stabilizes the tubules against depolymerization. This results in buildup of microtubule bundles within the cells, subsequently inducing cell death through interruption of typical microtubule dynamics necessary for cell division.

A phase 2 trial conducted by Au et al. using paclitaxel for 24 metastatic NPC patients reflected that neutropenia was the primary hematological toxicity. However, this did not persist beyond seven days in any patient. The study suggested that paclitaxel monotherapy in metastatic NPC is unlikely to produce a significant outcome improvement. Hence, the incorporation of paclitaxel into combination chemotherapy is a way to increase its effectiveness due to a higher response rate obtained. [31]

6. Docetaxel

Docetaxel is a semi-synthetic taxane that has also demonstrated activity in platinum-resistant patient with metastatic NPC. To the best of our knowledge, the study by J. Ngeow et al. in 2008 is the first and the only study that was carried out to confirm the activity of docetaxel in platinum-resistance patient with metastatic NPC. Their findings suggest that docetaxel is an active agent in platinum-resistance patients with metastatic NPC. [32] Weekly dosing is preferred as it is associated with less myelosuppression when compared to the administration every 3 weeks. Generally, docetaxel is well tolerated, but can cause a significant decline in quality of life throughout the treatment. [32,33]

7. Irinotecan

Irinotecan is a camptothecin analog that binds to the topoisomerase I-DNA complex during DNA replication and inhibiting the resealing of single-strand breakage. [34] A phase II study performed by Vanderbilt-Ingram Cancer Centre to evaluate the efficacy and tolerability of irinotecan in patients with recurrent or metastatic head and neck carcinoma (RMHNC). The results of cohort 1 which involved 22 patients treated with 125 mg/m^2 irinotecan by infusion revealed that grade 3 toxicities of nausea and vomiting, diarrhea as well as neutropenia was observed in the patients. While other 16 patients in cohort 2 treated with reduced dose of 75 mg/m^2 showed a better tolerance with absence of grade 3 neutropenia. However, preliminary data demonstrated that lower doses of irinotecan are of lower effectiveness. Hence, combining irinotecan with other agents appear to be a logical step to enhance its effectiveness while avoiding the toxicities associated with high dose regimens. [35]

8. Vinorelbine

Vinorelbine is a semi-synthetic vinca alkaloid which arrests mitosis by the inhibition mitotic microtubular assembly during metaphase. A phase II study by Degardin M et al. demonstrated that vinorelbine is an active agent in treating RMHNC. The major toxicity observed was grade 3/4 severe short lasting neutropenia that has occurred in about half of the patients. [36]

9. Gemcitabine

Gemcitabine is another option for platinum-resistant patient. It is a pyrimidine analogue, a ribonucleotide reductase inhibitor that exert its effect by competing with deoxycytidine triphosphate (dCTP) for incorporation into DNA and competitively inhibit DNA chain elongation. This subsequently leads to DNA fragmentation and cell death. [37] Gemcitabine has been reported by several researchers to be an effective single agent in the management of previously treated NPC patients in numerous studies. [37,38] However, treatment with gemcitabine can lead to myelosuppression.

A phase II trials involved chemonaïve and previously treated patients by Foo et al. reported that neutropenia which is uncommon in chemonaïve patient had seen in previously treated patients. No treatment -related deaths were reported. [39] Another phase II clinical study involved previously treated platinum-based chemotherapy by Li Zhang et al. revealed well tolerated neutropenia and no neutropenic fever were observed. [37,38]

Combining gemcitabine with other chemotherapy drugs would serve as a reasonable way to enhance its chemotherapeutic effectiveness against NPC. [37]

Polychemotherapy

Polychemotherapy is the use of aggressive combination chemotherapy (more than doublet

combination chemotherapy) which is not routinely recommended because it does not show to be superior to doublet combination chemotherapy. [10] Although the response rates were clearly improved, it is however also associated with elevated toxicity and extraordinarily high treatment-related mortality with no improvement in overall survival (OS) as reported in several trials like CAPABLE trial which incorporating cisplatin, methotrexate, bleomycin, cyclophosphamide and adriamycin, Phase II Trial by Abdelkrim Taamma et al. which incorporating 5-Fluorouracil, Bleomycin, Epirubicin, and Cisplatin etc. [10,19,39,40]

Management of chemotherapy-induced side effect

Chemotherapy-induced side effects

1. Mucositis secondary to cancer therapy

Mucositis is a side effect that occurs in 20% to 40% of patients undergoing chemotherapy. Oral mucositis manifests as erythema and/or ulceration of the oral mucosa, while gastrointestinal mucositis appears as pain, nausea/vomiting and diarrhea. [41] Hence, proper measures should be taken for prophylaxis of mucositis.

a) Oral mucositis

Proper oral care is vital because it reduces the effect of oral microbial flora, alleviates pain and bleeding associated with pain and bleeding, prevents soft tissue infections and minimises the risk of dental complications. [42] Thus, oral care hygiene should be practiced by all patients. Besides that, regular self-assessment of oral pain is recommended. Topical anesthetics can be considered to eliminate oral discomfort. Dental examinations and treatment should be done prior to chemotherapy, and continued throughout the course of treatment and follow up. [43]

To prevent oral mucositis among patients receiving standard-dose chemotherapy, Cochrane review concluded that cryotherapy can reduce mucositis of all severities in adults, specifically those receiving 5-fluorouracil. [44] A recent phase 2 clinical trial discovered that cryotherapy made with chamomile infusion was superior to cryotherapy with water, with lower occurrence of mucositis, less mouth pain and no ulcerations. [45]

b) Gastrointestinal mucositis

To prevent gastrointestinal mucositis in patients undergoing standard-dose chemotherapy involving methotrexate and 5-fluorouracil, ranitidine or omeprazole can be recommended. [42] Omeprazole and ranitidine demonstrated favourable outcome of reduced upper gastrointestinal symptoms and ulceration, but omeprazole emerged as the more superior agent as it can prevent global endoscopic worsening by chemotherapy. [46]

2. Chemotherapy-induced nausea and vomiting (CINV)

CINV is a distressing side effect of chemotherapy, so much so that it drove 1 in 5 patients to delay or decline potentially curative treatments. [47] Therefore, the aim of antiemetic therapy is to administer prophylactic treatment. With the advancement in medicine, successful antiemetic therapy can prevent CINV in 80% of the patients. [48]

Table 1: Emesis risk of chemotherapeutic agents recommended for treatment of metastatic NPC [48,49]

Emesis risk	Chemotherapeutic agents
High (>90% without antiemetics)	Cisplatin
Moderate (30-90% without antiemetics)	Carboplatin
Low (10-30% without antiemetics)	Capecitabine Docetaxel, Fluorouracil, Gemcitabine Paclitaxel

For patients receiving chemotherapeutic agents with high emesis risk, a three -drug regimen is recommended, which includes a neurokinin$_1$ (NK_1) receptor antagonist, a serotonin$_3$ (5-HT_3) receptor antagonist plus dexamethasone. [49,50] For patients undergoing chemotherapeutic agents with moderate emesis risk, a two-drug regimen is recommended, with palonosetron as the choice of 5-HT_3 receptor antagonist plus dexamethasone administered. [49,50]

In the most recent update by American Society of Clinical Oncology (ASCO), it was recommended that oral combination of netupitant and palonosetron (NEPA) plus dexamethasone

should be made available as an alternative option to the existing regime due to its efficacy in preventing CINV in chemotherapy with high and moderate emesis risk. [51]

For patients receiving chemotherapeutic agents of low emesis risk, dexamethasone is usually the choice of prophylactic treatment. [48-50] However, other single antiemetic agent such as a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, for example metoclopramide, can be considered. [49]

It is important to note that prophylactic treatment should be provided according to the chemotherapeutic agent with the highest emetic risk should a combination of agents be administered during chemotherapy. [50]

3. Chemotherapy-induced diarrhea (CID)

CID is a prevalent side effect, especially when bolus fluorouracil is involved, with the incidence being reported to be as high as 83%. [52,53] CID can result in severe complications associated with fluid and electrolyte losses, malnutrition and deterioration of quality of life. [54] Therefore, it is essential to manage CID effectively to ensure a smooth chemotherapy.

It has been established that loperamide is suggested as the first-line treatment, with the initial oral dose of 4mg followed by 2mg every 2-4 hours or after each loose stool, with the maximum dose of 16mg/day. [53] This regime is usually effective for grade 1 and 2 diarrhea, but reassessment is required 12-24 hours after initiating treatment to ensure complete resolution of CID. [53,54]

Table 2: Summary of recommendation for antiemetic therapy [49-51]

Emesis risk	Regime on day of chemotherapy	Regime on subsequent days
High	Neurokinin$_1$ (NK_1) receptor antagonist (aprepitant or fosaprepitant) + serotonin$_3$ (5-HT_3) receptor antagonist + dexamethasone **OR** NEPA + dexamethasone	Dexamethasone for 2 days + aprepitant for 3 days (Fosaprepitant is only administered on day 1)
Moderate	5-HT_3 receptor antagonist (preferably palonosetron) + dexamethasone **OR** NEPA + dexamethasone	Dexamethasone for 3 days
Low	Dexamethasone **OR** 5-HT_3 receptor antagonist **OR** Metoclopramide	None

Table 3: Criteria for severity of CID (in patients without ostomy)

Toxicity grade	Criteria
1	Increase of <4 stools per day over baseline
2	Increase of 4 - 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline Incontinence Hospitalization indicated Limiting self-care
4	Life-threatening consequences Urgent intervention indicated
5	Death

Note: Adapted from National Cancer Institute [55]

For uncontrollable grade 1 or 2 diarrhea, or *de novo* grade 3 or 4 diarrhea, octreotide should be administered subcutaneously, with the recommended dose of 100 μg three times daily, and can be increased up to 500 μg/day if there is no improvement after 24 hours of persistent diarrhea. [53] In a prospective study to investigate the effectiveness of 100 μg against 500μg octreotide in patients with ≥grade 3 CID who are refractory towards loperamide, it was found that 500μg was significantly more effective, with 90% of resolution in the 500μg group, as compared to 61% in the 100μg group. [56] Hospitalisation is advised so that intravenous fluids and antibiotics can be administered as required. [54]

Complication

Complications of Treatment for Nasopharyngeal Carcinoma (NPC)

Radiation therapy and chemotherapy are highly used in NPC patients since nasopharyngeal carcinoma is considered radia-sensitive and with

high efficacy proven. With more advanced disease, options may be limited to external beam radiation techniques with integration of chemotherapy. However, NPC patients who undergo radiation therapy or chemotherapy are present with common manifestations such as brain injuries, trismus, hearing loss or xerostomia (**Table 4**). Analysis of 695 NPC patients by Wang et al. revealed there are 14 patients (1.5%) present with brain injuries, 127 patients (13.6%) present with trismus, 290 patients (31.1%) present with hearing loss and 361 patients (38.7%) present with xerostomia after received IMRT. Radiation-related cranial nerve palsy can also be observed in NPC patients after receiving IMRT. [57] Sometimes, neck fibrosis may be one of the important risk factors of development of cranial nerves palsies, including the optic nerve, the trigeminal nerve, the abducens nerve, the vagus nerve and the hypoglossal nerve. Yeoh et al. demonstrated that the hypoglossal nerve palsy with the highest prevalence of 89.5%, followed with the two-nerve palsies complications with a prevalence of 68.4% in patients after receiving IMRT. In addition, radiation-induced temporal lobe changes may also present in NPC patients after radiation therapy. [58] Vincent et al. stated that there are temporal lobe changes in 47 patients (2.5%) and bilateral lesions in 12 patients (35%) observed with CT imaging, and with MRI imaging, unilateral abnormalities and bilateral temporal lobe changes are abstracted with a prevalence of 24% and 58%, respectively. [59] In certain cases, severe bleeding of nasopharyngeal related to nasopharynx necrosis were observed after radiotherapy with high dose or regimen on soft tissue and internal carotid artery. [60]

Salvage therapy

a) Radio therapy and bradytherapy

Salvage therapy is performed when a tumour relapse after complete remission of NPC with treatments including radiation therapy or chemotherapy. The common salvage therapies in treating recurrent NP are radiotherapy, brachytherapy or surgical resection, either alone or in combination. Similar as compared to the primary treatments, toxicities may present after these salvage regimens. The acute complications of reirradiation demostrated in Xiang L et al. study stated that 14 (28.6%) out of 49 patients with recurrent NPC present with skin, mucosa and xerostamia. [61] Furthermore, serious neurological complications such as temporal lobe necrosis, cranial nerve palsy, trismus, brain stem damage as well as deafness may be observed in patients treated with secondary radiotherapy. [62] A study of 28 patients with locally recurrent NPC treated with salvage IMRT reirradiation by Hua and colleagues revealed that the prevalence of about 50% (n=14) patients developed mucosal necrosis with severe headaches. [63] Li has also indicated that prevalence of 37.9% (n=133) of bloody nasal discharge and 31.1% (n=109) with headache in a study of 351 patients with recurrent NPC. [62] Another study of 60 patients previously irradiated diagnosed with locally recurrent T1 and T2 NPC were observed with headache, mucosal necrosis, cranial neuropathy and temporal lobe necrosis after being treated with reirradiation with IMRT, in prevalence of 31.6%, 30.0%, 25.0% and 21.6%, respectively. In this study, 3 patients were found with MRI-detected radiation encephalopathy, 2 with cranial nerve palsy (1 with facial numbness and another 1 with swallowing difficulty) and 2 with mucosal necrosis after 1st course of radiotherapy. 3 patients (5%) developed grade 3 acute necrosis, 15 patients (25%) grade 2 acute mucositis and 9 (15%) grade 2 skin injury. In addition, 8 patients with mucosal necrosis further developed carotid blowout syndrome during follow up. Furthermore, there is a prevalence of 15.2% patients diagnosed with carotid blowout syndrome after being treated with stereotactic radiosurgery (SRS) for recurrent NPC. [64] To be highlighted that replanning with IMRT reirradiation is carried out in patients with metastatic NPC treatment, especially when the NPC has spread to spinal cord, brainstem or related important organs. Study has abstracted that patient who undergo IMRT replanning had low incidence of 8.5% temporal lobe necrosis compared to those with no IMRT replanning with higher incidence of 14.3%. [60] Apart from that, cranial nerve palsy, which is considered as a rare complication may be experienced in patients with recurrent NPC following a secondary radiotherapy. [62] Mc Donald and colleagues have abstracted 41 (2.6%) out of 1554 patients who received a reirradiation developed Carotid blowout syndrome. [65]. The (**Table 4**) below shows the summary of evidence of complications of radiation therapy in recurrent NPC.

b) Surgical resection

Apart from radiotherapy, surgical resection is feasible salvage options for patients diagnosed with recurrent locoregional NPC, particularly for the early-stage recurrences. However, late toxicities such as cerebrospinal fluid leak, meningitis and encephalocele may be seen in patients after surgical resection. A case report regarding a 59-year-old male patient with recurrent NPC complaint of grade 2 chronic xerostomia after radiotherapy and a facial nerve paralysis due to surgical intervention in June 2013. [66] Headache and palatal fistula may be observed in patients undergo brachytherapy. In addition, SRS represents another option for salvage for providing highly conformal radiation with sharp falloff of dose to surrounding normal tissues. There is a prevalence of 15.2% patients diagnosed with carotid blowout syndrome after being treated with stereotactic radiosurgery (SRS) for recurrent NPC. [63] In year 2016, FDA has approved the treatment of recurrent or metastatic head and neck cancer with pembrolizumab, associated with common adverse reaction of fatigue, decreased appetite, and dyspnoea. [67]

The study on complications of secondary treatment after recurrent NPC is vital for healthcare team to make decision on appropriate treatment in particular cases. The benefits of the chosen treatment should outweigh the complications or toxicities to maintain the quality of life in patients with recurrent NPC.

Prevention

Nasopharyngeal carcinoma is often diagnosed at advanced stages with only <50% of disease-free survival. Even though, a few studies have been conducted on the etiology of NPC, but a definite interaction of the causes have not been achieved. [72] Hence, secondary prevention such as early detection or screening and early treatment in NPC are developed. Early detection and vaccination would eventually prevent nasopharyngeal cancer and its complication despite vaccination might be not the best choice for people that already carry the Epstein-Barr virus (EBV). Epstein-Barr virus (EBV), is one of the causative factor that is often associated with NPC. Screening tests such as EBV serology test and nasopharyngoscopy are sensitive methods which showed that regular screening with these methods results in early detection of cancer. Besides, the survival rate is also much higher and exceeds 90% for those cancers that are detected in the screening program. [72,73]

Epstein-Barr virus (EBV) serology test uses EBV antibody indicators such as VCA/IgA and EA/IgA to be examined by the immune-enzymatic methods. Further, EBV-associated antibodies have a higher sensitivity and specificity in NPC, hence they can be used for NPC diagnosis and as screening predictors. For instance, IgA antibodies against the EBV capsid antigen (VCA/IgA) provide a specificity and sensitivity up to 90% in the diagnosis of NPC. In addition, the examination of EBV related antibodies is reasonable and simple. [72]

Vaccination can overcome the systemic immunosuppression that exist in nasopharyngeal cancer to boost the relevant T-cell response and immunity against EBV. This eventually increases the number of T-cells in the patient and sustain for a long time of period. There are two EBV proteins, EBNA1 and LMP1 that are consistently expressed in nasopharyngeal cancer. [74] EBNA1 is important to the virus since it maintains the viral DNA in dividing cells. EBNA 1 contains large glycine/alanine repeated domain which interferes with the protein's presence of HLA-class I antigen processing pathway and this reduces EBNA1's visibility to CD8+ T-cells. The other protein is known as LMP2 which is essential for the outgrowth of epithelial cells and functions by negatively regulating B-cell receptor signaling. [74,75] Recently, a clinical trial was done on the use of MVA-EBNA1/LMP2 vaccine, which consist oil-based substance called Montanide ISA-51. The substance tends to increase the immune response towards the LMP-2 peptide. Also, it has been concluded that the vaccine is safe despite having side effects such as tiredness, swelling at the site of injection and flu like symptoms which are not lethal. [76]

Novel therapies

Platinum-based chemotherapy regimens are usually regarded as the standard chemotherapy for metastatic nasopharyngeal carcinoma. The combination of first generation platinum anticancer drug cisplatin and docetaxel, a semi-synthetic taxane, is known to show high response rate in metastatic NPC. [73] However, severe adverse effect, including emesis, neurotoxicity, haematotoxicity, and renal toxicity has limited its clinical applications. [74] With that in mind, a new chemotherapy regimen with

improved efficacy and a favorable toxicity profile is needed. [74]

Lobaplatin, a third-generation platinum anticancer shows improved anticancer effects with reduced kidney toxicity and adverse gastrointestinal effects compared to cisplatin. [75] Lobaplatin is approved for the treatment of chronic myelogenous leukemia, inoperable metastatic breast cancer and small cell lung cancer. [76] However, two clinical studies have been performed to investigate the efficacy of lobaplatin in nasopharyngeal carcinoma, which were administered in a combination with docetaxel.

The 21-day chemotherapy regimen of docetaxel (75 mg/m^2, day 1) plus lobaplatin (30 mg/m^2, day 1) was administered by Zhang S. et al. in an open-label, single-arm phase II clinical study on 37 Chinese nasopharyngeal cancer patients with pulmonary and hepatic metastasis. [75] Long GX. et al. also utilised a similar treatment plan for a single-arm, multi-centre phase II study on 39 patients with recurrent and metastatic nasopharyngeal carcinoma, but separated the day of administration of decetaxel (75 mg/m^2, day 1) and lobaplatin (75 mg/m^2, day 2). [74]

RECIST 1.1 was utilised to assess treatment response, [77] and the total efficacy rate as well as disease control rate were calculated per the following formula:

$$\text{Total efficiency} = \left(\frac{\text{Complete Response (CR)+Partial Response (PR)}}{\text{Total number of case}} \times 100\%\right)$$

$$\text{Disease control rate} = \left(\frac{\text{Complete Response (CR)+Partial Response (PR)+Stable Disease (SD)}}{\text{Total number of case}} \times 100\%\right)$$

Both studies produced similar results with Zhang S. et al. reporting a total efficiency of 67.6% and disease control rate of 81.8%, while Long GX. et al. reported 61.5% and 84.6% respectively. Adverse effects of the regimen were mostly tolerable with grade I and II haematologic toxicity such as neutropenia, anaemia, and thrombocytopenia. Nausea and vomiting, fatigue, fever, hypotension, liver or kidney dysfunction were mild. [74,75] This shows that lobaplatin combined with docetaxel is an effective treatment for recurrent and metastatic nasopharyngeal carcinoma with manageable adverse effects.

Although favourable responses were noted, there were several limitations in the clinical studies such as insufficient number of patients, high cost of chemotherapy drug, the fact that these were not randomised-controlled trials, and no maintenance chemotherapy was given for patients sensitised to chemotherapy. [75] Therefore, further studies on the clinical efficacy and safety profile of lobaplatin are required to fully establish lobaplatin as an alternative to cisplatin in recurrent and metastatic nasopharyngeal carcinoma.

CONCLUSION

NPC affects the upper part of the throat, especially the area behind the nose and close to the base of the skull. Patient with NPC usually do not experience any symptoms until they reach advanced stage, which manifests as painless neck lump. NPC can be diagnosed with imaging tests, which includes CT scan, PET scan, MRI, and FNA biopsy. As metastatic NPC is responsive to chemotherapy, the first-line treatment would include doublet chemotherapy, with platinum doublets, which involves the pairing of cisplatin or carboplatin with fluorouracil, gemcitabine and paclitaxel. Alternatively, monochemotherapy can be initiated, with cisplatin or carboplatin being the preferred chemotherapy agent. However, the conventional treatment that includes platinum-based regime is associated with severe side effects. Therefore, efforts have been invested into novel therapeutics for NPC, which involves the replacement of cisplatin with lobaplatin. NPC can be prevented through early detection and vaccination. Although vaccination helps to boost immunity against Epstein-Barr virus (EBV), it may not be effective for people already carrying the virus. There are certain limitations in this study as we mainly focus on the chemotherapy regimen, even salvage treatments such as surgery resection and radiotherapy are available for treating metastatic NPC. Further studies are required to compare the effectiveness between chemotherapy and surgery resection or radiotherapy in treating metastatic NPC.

Table 4: Summary of evidence of complications of radiation therapy in recurrent NPC

COMPLICATIONS OF RADIATION THERAPY IN RECURRENT NPC: SUMMARY OF EVIDENCE

References	Topic	Subjects	Findings Complication/ no. of patients (%)
Kong et al. (2016) [68]	Salvage IMRT for Locally Recurrent NPC after Definitive IMRT: A Novel Scenario of the Modern Era	77 patients with locally or locoregionally recurrent NPC who failed initial IMRT with a curative intent were treated with salvage IMRT	Median OS time: 37.0 months Median PFS time: 20.5 months Mucosal necrosis 31 (40.3%) Temporal lobe necrosis: 7patients (9.1%) Cranial neuropathy: 20 patients (26.0%) Trismus: 18 patients (23.4%) Hearing loss: 4 patients (5.2%)
Chan O et al. (2016) [69]	Reirradiation with intensity-modulated radiotherapy for locally recurrent T3 to T4 nasopharyngeal carcinoma.	38 patients with consecutive rT3 to rT4 NPC treated with IMRT	Hearing loss: 17 patients (44.7%) Temporal lobe necrosis: 4 patients (10.5%) Soft tissue necrosis: 8 patients (21.1%) Dysphagia: 10 patients (26.3%) Massive nasal bleeding: 6 patients (15.8%) Trismus: 3 patients (7.9%)
Yun-Ming Tian et al. (2015) [64]	Long-term survival and late complications in IMRT of locally recurrent T1 and T2 NPC	60 patients with locally recurrent T1 & T2 NPC; reirradiation with IMRT	Severe complication: 39 patients (65.0%) developed at least one severe complications Headache: 19 patients (31.6%) Mucosal necrosis: 18 patients (30.0%) Cranial neuropathy: 16 patients (25.0%) Temporal lobe necrosis: 13 patients (21.6%) Trismus: 11 patients (18.3%) Neck fibrosis: 10 patients (16.7%) Hearing loss: 9 patients (15.0%) Osteonecrosis: I patient (1.7%) Grade III acute mucositis: 25 patients (25%) Grade II skin injury: 9 patients (15%) Carotid blowout syndrome (developed from mucosal necrosis): 8 patients (13.3%)
Xiao W. et al. (2015) [70]	Prognostic Significance of Tumor Volume in Locally Recurrent NPC Treated with Salvage IMRT	291 consecutive patients with locally recurrent, non-metastatic NPC underwent salvage IMRT	Mucosa necrosis: 98 patients (33.7%) Trismus: 88 patients (30.2%) Temporal lobe necrosis:78 patients (30%) Massive haemorrhage: 50 patients(17.2%) Hearing deficit: 70 patients (24%) Severe headache: 56 patients (19.2%) Difficulty in feeding: 16 patients (5.5%) Difficulty in speaking: 15 patients (5.1%) Vision deficit: 13 patients (4.5%)

Xiang L et al. (2004) [71]	Initial experience of using IMRT for recurrent NPC	49 patients with locoregional recurrent carcinoma in the nasopharynx were treated with IMRT between January 2001 and February 2002	**Acute toxicity** Skin, mucosa, and xerostomia: 14 patients (28.6%)
COMPLICATIONS OF RADIATION THERAPY IN NPC: SUMMARY OF EVIDENCE			
References	**Topic**	**Subjects**	**Findings** **Complication/ no. of patients (%)**
Weidong Wang et al. (2014) [57]	Clinical Outcomes and Prognostic Factors of 695 NPC Patients Treated with IMRT	21 patients received radiotherapy only at dose of 66-76 Gy for GTVnx, 60-70Gy for GTVinR/L, 60-66 Gy for CTV1, 55-60 Gy for CTV2, and 50-55 Gy for CTVln,each divided into 30-33 deliveries 459 patients received IMRT+ chemotherapy • 52 patients received induction chemotherapy (100mg/m2 of cisplatin on day 1 and 1000mg/m2 of 5-FU on days 1 through 5 for 1-2 cycles every 3 weeks) with concurrent chemotherapy consisting of 80-100 mg/m^2 of cisplatin every 3 weeks for 2-3 cycles • 181 received concurrent-adjuvant chemotherapy consisting of 80-100mg/m2 of cisplatin every 3 weeks for 2 to 3 cycles followed by adjuvant chemotherapy 80mg/m2 of cisplatin on day 1 and 1,000 mg/m2 of 5-FU on days 1 through 4 for 3 cycles every 4 weeks • 190 patients received concurrent chemotherapy only	**5 year-incidence rate** Brain injuries: 14 patients (1.5%) Trismus: 127 patients (13.6%) Hearing loss: 290 patients (31.1%) Xerostomia: 361 patients (38.7%) **Acute toxicity** Grade I xerostomia: 285 patients (41.0%) Grade II xerostomia: 368 patients (52.9%) Grade III xerostomia: 42 patients (6.1%) Grade I mucositis: 149 patients (21.4%) Grade II mucositis: 303 patients (43.6%) Grade III mucositis: 243 patients (35.0%) Grade I skin reaction: 502 patients (72.3%) Grade II skin reaction: 167 patients (24.0%) Grade III skin reaction: 26 patients (3.7%) Grade I dysphagia: 284 patients (40.9%) Grade II dysphagia: 338 patients (48.6%) Grade III dysphagia: 73 patients (10.5%) **Late toxicity** Grade I xerostomia: 417 patients (60.0%) Grade II xerostomia: 161 patients (23.2%) Grade III xerostomia: 19 patients (2.7%) Grade I hearing loss: 20 patients (2.9%) Grade II hearing loss: 2 patients (0.28%) Grade I hypopsia: 5 patients (0.7%) Grade II hypopsia: 2 patients (0.28%) Grade I brain injury: 2 patients (0.28%) Grade II brain injury: 2 patients (0.28%) Grade III brain injury: 1 patients (0.14%) Grade III severe skin atrophy: 2 patients (0.28%) Grade III trismus: 5 patients (0.70%)

Yeoh et al. (2002) [58]	Radiation-related cranial nerve palsy in patients with NPC	19 NPC patients (15 male and 4 females) were treated with RT at total dose of 7000-13,000 cGy	Single nerve palsy: 4 patients (21.1%) 2 with hypoglossal palsy; 2 with recurrent laryngeal palsy Three-nerve palsies: 2 patients (10.5%) Two-nerve palsies: 13 patients (68.4%) Vagus and hypoglossal palsy: 11 patients (57.9%) Hypoglossal nerve palsy: 17 patients (89.5%) 7 bilateral, 8 left-sided and 2 right-sided Recurrent laryngeal nerve palsy : 6 patients (31.6%) 5 bilateral Accessory nerve palsies: (all bilateral) 50% patients with multiple nerve involvement had palsies that were metachronous Marked neck fibrosis : 12 patients (63.2%) Severe respiratory difficulty : 2 patients with bilateral vocal cord palsy (10.5%)
Vincent et al (2001) [59]	Radiation-induced temporal lobe changes: CT and MR Imaging Characteristics	1916 patients with NPC for 5 years' periods	**CT Imaging** Temporal lobe changes: 47 patients (2.5 %) Bilateral lesions: 12 patients (35%) **MRI Imaging** Unilateral abnormalities: 11 patients (42%) Bilateral temporal lobe changes: 15 patients (58%) 7 patients had chronic hematoma
Kwang et al. (1996) [68]	Sensorineural hearing loss in patients treated for NPC: a prospective study of the effect of radiation and cisplatin treatment. *Int J Radiat Oncol Biol Phys. 1996*	132 patients were treated with NPC	Persistent sensorineural hearing loss: 29 patients (22%)
Lee AWM et al. (1992) [69]	Retrospective analysis of NPC treated during 1976-1985: late complications following megavoltage irradiation *Br. J Radiol. 1992*	4527 patients with NPC were treated with dose of fraction 2.5Gy or 4.2 Gy per fraction	Cranial nerve palsy: 226 patients (5 %) Radiation- induced cranial/ cervical symptomatic nerve palsy: 241 patients (5.3%)
Qin et al. (1988) [70]	Analysis of 1379 patients with NPC treated by radiation. *Cancer. 1988.*	1379 patients received RT	Radiation encephalomyelopathy: 254 patients (18.4%)
Huang et al (1981) [71]	Nasopharyngeal cancer: study II. *Int J Radiat Oncol Biol Phys*	1032 patients	Cranial nerve palsy: 10 patients (1 %)

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