Chemotherapy in nasopharyngeal carcinoma: Review of results at University Hospital, Kuala Lumpur.

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Summary

Nasopharyngeal carcinoma (NPC) is one of the commonest presentation of head and neck cancers in Malaysia, especially in the Chinese. The standard treatment is radical radiotherapy to the post-nasal space and the neck. Chemotherapy is given to patients with primary advanced disease and to patients with recurrence. The study reviews results of chemotherapy given to 33 patients at the University Hospital, Kuala Lumpur, over the last four years.

Key words: Nasopharyngeal carcinoma (NPC), Chemotherapy review.

Introduction

NPC is one of the commonest head and neck cancers in Malaysia, especially in the Chinese.[1] Recent advances in diagnosis, namely raised serology levels towards Epstein Barr Virus (EBV) and improved computerised axial tomography (CT) scanning of suspected patients, have led towards early diagnosis and treatment.[1] Unfortunately, cases are still seen in late stages of the disease. The standard treatment of NPC is radical radiotherapy. The usual dose is 65–70 Grays fractionated daily over 6½ to 7½ week period. Chemotherapy is given to patients with advanced primary disease and to patients with recurrence or metastasis of tumour. Over the past four year period at the University Hospital, Kuala Lumpur, patients have received chemotherapy for various indications. The regime employed was a combination of cyclophosphamide, vincristine, methotrexate and adriamycin. These drugs were given intravenously in six cycles at three weekly-intervals. The results of this chemotherapy regime are reviewed here.

Materials and Method

Over the last four year period between 1982 to 1986 at the University Hospital, Kuala Lumpur, all patients seen and suspected of having NPC have a standard work-up protocol. This includes a complete ear, nose and throat (ENT) and general examination, determination of antibody titres to Epstein-Barr virus antigens, liver function test; complete blood picture including haemoglobin and eythrocyte sedimentation rate, CT scan of the nasopharynx (PNS), bone and liver scans are done on all patients. A biopsy from the post nasal space is done to confirm the diagnosis and

treatment is then instituted. Patients who present with an advanced stage of disease (either with metastasis to bone or liver/lung, or with evidence of intracranial involvement) and those who have tumour recurrence on follow-up are given chemotherapy; the dosage is calculated to the body surface area.

A total of 33 NPC patients were treated with cyclophosphamide (600 mg/m^2), vincristine (1.2 mg/m^2), methotrexate (40 mg/m^2) and adriamycin (40 mg/m^2). Cyclophosphamide was given through a Dextrose-saline infusion, the rest as bolus intravenously. The patient's general status and haematological profile were monitored before the next dose in 3 weeks. Six cycles were given at three weekly intervals, at the end of which the response to chemotherapy was evaluated by clinical and radiological examination including CT scan, liver and bone scan. The results of these studies were analysed.

Results

Of the 33 patients studied over the last four years, the main indication for chemotherapy was a positive bone scan in 19 patients (Table 1).

Table 1
Indications for chemotherapy

Indication for Chemotherapy	No. of patients*
Scans:	
Bone scan positive	19
Liver scan positive	6
CT scan of post-nasal space positive	5
Advanced stage of tumour at time of diagnosis (T_{3c} OR N_3 OR M_1)	6
Clinical Recurrence:	
Lymph nodes – upper deep cervical	3
– submental	2
Intracranial (multiple cranial nerve palsy)	1

* Some patients had > 1 indications for chemotherapy.

Bone scan was done routinely as a work-up protocol for all patients and repeat bone scans done on patients who had progressive bone pain, raising serology levels or clinical deterioration on follow-up.

The main areas of bone involvement in our series were vertebral (14 patients) especially the lower lumbar vertebrae, the last four ribs (nine patients), iliac bone and sacraum (five patients), and other bones (five patients). A liver scan done simultaneously on these patients revealed five patients who had both positive liver and bone scan.

Multiple cranial nerve palsies coming on after radiotherapy can be caused by post-radiation fibrosis or recurrence at the base of skull. These patients were investigated by repeating antibody

titres levels against EBV, CT scan of the post-nasal space and base of skull and a biopsy of the post-nasal space. There was one such patient with cranial nerve palsy due to clinical recurrence of tumour who received chemotherapy. However, five other patients were diagnosed by CT scan to have tumour recurrence and given chemotherapy.

Six patients had advanced stage of disease at time of presentation and diagnosis. These patients had in addition to tumour in the post-nasal space and neck nodes, intra-cranial extension or bone/liver scan positive. These six patients received chemotherapy in addition to radiotherapy.

There were five patients with lymph node recurrence proven on excision biopsy. Two had recurrence in the submental area and three had recurrence in the upper deep cervical nodes.

There were seven patients who received chemotherapy within six months of their diagnosis (Table 2). Six were those with advanced carcinoma at time of presentation, the other developed bone pain during radiotherapy and a repeat bone scan after six weeks showed bony metastasis at that time. The majority (12) of patients presented for chemotherapy between 1–2 years after completion of treatment with radiotherapy. Nine other patients on follow-up period of 2–5 years were found to require chemotherapy. It appears that recurrence of diseases or clinical deterioration due to metastasis presents in the majority between six months to two years. There were two cases who required chemotherapy even after five years follow-up, one developing bony metastasis, and the other developing recurrence at the submental, pre- and post-auricular lymph node.

Table 2
Interval between initial diagnosis of NPC and initiation of chemotherapy

Interval between initial diagnosis and commencement of chemotherapy		No of patients
6/12		7
6/12	– 1 year	3
1 year	– 2 years	12
2 years	– 5 years	9
	> 5 years	2

Of the 33 patients (Table 3), five patients were transferred out, two to General Hospital, Kuala Lumpur, because of poor health. These patients had advanced primary disease, thus transferring them reduced their misery encountered during the daily travel to the Institute of Radiotherapy. The other three patients were sent back to their respective state hospitals for chemotherapy. Three patients did not return from leave. Attempts to contact them were unsuccessful and review of their records showed that they were in poor clinical health during their chemotherapy.

Three patients had stable disease on follow-up. Out of these three, two had no change in their lymph node size, the other showed no change in the repeat bone scan.

The majority of patients (18) had progressive disease on follow-up after the completion of chemotherapy. The bone pains became progressively worse and new bony metastasis were detected on repeat bone scan.

Table 3
Response of patients to chemotherapy

Response to chemotherapy	No. of patients
Stable disease	3
Progressive Disease	19*
Partial remission	2
Complete response	1
Did not complete course	8

* one died after first dose of chemotherapy

Some developed cranial nerve palsies due to skull base infiltration. One patient with very advanced tumour stage died after the first dose of chemotherapy. There was only one patient who showed complete after chemotherapy. This patient was stage II (Ho's classification) when diagnosed in May 1983. He completed a full course of chemotherapy. On follow-up in July 1984, a bone scan showed metastatic deposits in L_3, L_5, and left fifth rib. He received six doses of chemotherapy and localised radiotherapy to his lumbar spine. He improved clinically and repeat bone scan in July 1987 showed improvement. He remains well when last seen on follow-up in August 1988.

Toxicity was noted to be minimal in most cases. The symptoms included nausea (80%), vomitting (40%) and alopecia (50%). Blood counts in the patients revealed no significant change in hemoglobin levels; leucopenia in 45% of the patients. Platelet levels were unaffected. There was no substantial alteration in the renal status.

Discussion

Nasopharyngeal carcinoma is one of the commonest head and neck cancers in Malaysia, especially among the Chinese.[1] The introduction of high-resolution computerised axial tomography (CT scan) and antibody levels of IgA against the viral capsid antigen (VCA) of the Epstein Barr virus (EBV) have led to detection of early cases of nasopharyngeal carcinoma.[1] The main factor affecting survival is the initial staging.[2] The standard treatment for nasopharyngeal carcinoma is radical radiotherapy.[2] Advances in techniques to yield better loco-regional control and survival in NPC have included accurate simulation planning, and the use of wide radiation field including the elective radiation of the whole neck.[3,4] Despite the improved results in head and neck cancers, the prognosis for patients with nasopharyngeal tumours remain grave, with overall five years survival rates ranging from 30–45%.

In view of the high failure and mortality rate resulting from treatment with radiotherapy alone, various centres have used chemotherapy to improve the survival rates. Chemotherapy of head and neck cancer has been a palliative effort in advanced forms or as a part of combined therapeutic approach with surgery and/or irradiation. Regime vary in these centres but are usually combined drug approach repeated over a three weekly interval for six cycles. Our experience has been with cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2, adriamycin 40 mg/m^2 and vincristine 1.2 mg/m^2 (up to a maximum of 2.0 mg), repeated at 3 weekly interval for 6 cycles. These anti tumour drugs have activity against epidemoid carcinoma and are conventionally used in many centres.

Unfortunately, the results have not been encouraging in our study. There has been only one complete remission (4%) following chemotherapy, the others have progressive disease (85%) and have progressively worsened. This is in contrast to other studies[6,7,8] This is possibly due to the fact that the patients receiving chemotherapy are those in the late stages and with distant metastasis, who were already in poor performance status.

Recently, reports of cis-platinum containing regimes have given encouraging results. At doses ranging between 60–120 mg/m^2 intravenous, every three weeks, this drug used in combination with 5-flourouracil and bleomycin has been shown to produce objective response in 30 to 60% of cases.

There is a move towards using chemotherapy in the initial stage of the disease as an adjuvant rather than palliation. It is hoped that further studies on these new aspects will result in improved survival rates for these patients.

Conclusion

The standard treatment for NPC is radical radiotherapy. Chemotherapy is reserved for patients who developed recurrence, either in lymph nodes, base of skull infiltration and for patients with bone and liver metastasis. The regime of cyclophosphamide, adriamycin, methotrexate and vincristine has proven to yield poor results to such patients. A new regime consisting of cis-platinum, bleomycin, 5-flourouracil has recently been started and the results are under review at the University Hospital, Kuala Lumpur.

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