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Nasopharyngeal carcinoma outcome with induction chemotherapy followed by concurrent chemoradiotherapy

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ABSTRACT

Treatment of Nasopharyngeal Carcinoma (NPC) has been based on the Intergroup 0999 trial with chemoradiation (CRT) and consolidation chemotherapy (CT). While effective, toxicities are significant. As a result, many oncologists use induction chemotherapy (IC) followed by CRT, citing better tolerance with anecdotally no worse outcome. We reviewed 95 NPC patients treated between 2005 and 2015 at MDACC with IC followed by CRT. Median age was 49 years. Fifty-seven were T3/T4 and 62 were N2-3. The most common IC regimen was a platinum-taxane doublet (N = 72). 83 patients completed IC. Grade 3–4 toxicities with IC occurred in 10 patients. There were 15 primary site complete responses (CR), 68 partial responses (PR),6 stable disease (SD), and 2 progressed. There were 10 nodal CR, 73 PR, 4 SD, and 3 progressed. 92 patients received RT, 74 with CRT. At completion of treatment, there were 81 CR and 8 PR patients.

Post radiation toxicities included mucositis and skin rash (37), oto- toxicity (25), PEG placement (12), and osteonecrosis (2). Three-year progression free survival (PFS) and distant metastasis free survival (DMFS) were 77.3% and 78%. CRT for advanced NPC is standard, but IC remains controversial. Early trials failed to show a benefit but used older chemotherapy and pre-intensity modulated radiation therapy (IMRT) methods. Modern trials with platinum-taxane regimens and IMRT have shown reasonable PFS and OS results with acceptable toxicity. This retrospective review of IC followed by CRT showed acceptable toxicity and good response and survival outcomes. This approach has, for many oncologists, become a standard.

Introduction

Nasopharyngeal Carcinoma (NPC) is an epithelial carcinoma of the nasopharynx, invariably associated with the Epstein Barr Virus (EBV) [1]. Worldwide, there are approximately 86,000 incident cases annually [2]. It is an uncommon cancer in the United States with an incidence of 0.5–2 per 100,000 compared with 25 per 100,000 in southern China [3]. In the United States, the most common histology, seen in approximately two-thirds of patients, is undifferentiated, non-keratinizing (World Health Organization Type III); in China, this type accounts for 95% of all nasopharyngeal cancers [4]. The type III tumors tend to have a more favorable prognosis. Less common is the differentiated, non-keratinizing (WHO Type II), and well differentiated, keratinizing (WHO Type I) is the least common.

Surgery has little role in the management of NPC, except in rare T1N0 tumors or as a salvage attempt in refractory/recurrent disease. Single modality radiation therapy is usually used for early stage tumors, T1-2, N0; while combined modality with chemotherapy and radiation is standard for higher T stage or positive nodal involvement [5].

The typical standard chemoradiation approach has been based on the Intergroup 0099 trial [6]. This large cooperative group randomized study demonstrated an improvement in survival with concurrent chemoradiation with high dose cisplatin followed by adjuvant chemotherapy compared to radiation alone and remains the preferred standard treatment by the National Comprehensive Cancer Network (NCCN) [7].

There are few trials comparing induction chemotherapy followed by chemoradiation vs the guideline recommended standard of concurrent chemoradiation followed by adjuvant chemotherapy. As such, the comparison of these two approaches have utilized meta-analyses, with their inherent limitations [5,8]. The Intergroup trial was conducted in the pre-Intensity Modulated Radiation Therapy (IMRT) era, which is now a standard radiotherapy approach due to better locoregional control compared to pre-IMRT studies [9]. As a result, many patients are now offered induction therapy, usually with a platinum-taxane doublet such as cisplatin and docetaxel, followed by IMRT radiation

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therapy with concurrent cisplatin or carboplatin, often given as a weekly low dose vs the every 21-day high dose protocol.

Study methods

Patient selection

With permission from the Institutional Review Board (IRB-MDACC; protocol PA16-1137), we conducted a retrospective review of patients with nasopharyngeal carcinoma treated between 2005 and 2015 at MD Anderson Cancer Center with induction chemotherapy followed by concurrent chemoradiation. Patients were over the age of 18 years and only patients who received treatment at MDACC with induction chemotherapy followed by radiation with or without concurrent chemotherapy were included. All patients who received radiation were treated with IMRT. Patients with a diagnosis other than squamous cell carcinoma (SCC), undifferentiated/differentiated carcinoma, or the older terminology "lympho-epithelial carcinoma" were excluded from the analysis. A total of 95 patients met criteria for analysis.

Study design

We evaluated TNM stage, type of induction regimen given, response in both the primary and regional nodes, toxicities with the induction regimen, radiation and type of concurrent chemotherapy given, overall response upon completion of chemoradiation, and progression free survival (PFS) and distant metastases free survival (DMFS). Responses were defined using the revised Response Evaluation Criteria in Solid Tumors (RECIST), [10]. Complete Response (CR) was disappearance of all target lesions; Partial Response (PR) was ≥30% decrease in the sum of the longest diameters of target lesions; Progressive Disease (PD) was ≥20% increase in the sum of the longest diameters of target lesions or appearance of new lesions; and Stable Disease was neither PR nor PD.

Statistical methods

PFS and DMFS were calculated from the end of radiation treatment using the Kaplan-Meier algorithm based on a first event analysis for all endpoints. PFS was defined as an alive patient and without local, regional, or distant recurrence, and toxicities were defined using the Common Terminology Criteria for Adverse Events (CTCAE) version 4, [11]. Staging was defined using the American Joint Committee on Cancer (AJCC) staging manual, seventh edition, [12].

Results

Patient characteristics

Patient characteristics are shown in Table 1. There were 74 men and 21 women. Median age was 49 years, range 18–83. 88 patients were white/Hispanic, six Asian, and one African-American. All patients were advanced stage—combined TNM stage III or IV disease, (T1-2 N2, T3N0-2, T4N0-2, or any TN3). T3/T4 tumors accounted for 57 (60%) of the patients, (T3 = 19, T4 = 38). Sixty-two (65%) patients were N1-2 nodal stage. WHO class II/III was evident in 53 evaluable patients, (class III = 39, class II/III = 14). In 51 patients with evaluable viral analysis of their tumor tissue, 33 (65%) were EBV-positive, 12 (22%) were EBV-negative, and six (12%) were HPV-positive. Induction chemotherapies are shown in Table 2. The most common induction regimen was a platinum (carboplatin or cisplatin) plus a taxane (docetaxel or paclitaxel) doublet; with 72 (76%) patients receiving this combination.

Treatment efficacy

Response to induction chemotherapy is shown in Table 3. Primary site response included compete response (CR) in 15 (16%) patients, partial response (PR) in 68 (72%) patients, stable or unchanged (SD) in six (6%) patients, and progression in two (2%) patients. Nodal response included CR in ten (11%) patients, PR in 73 (77%) patients, SD in four (4%) patients, and progression in three (3%) patients.

Table 1
Patient characteristics.

Total patients	N = 95 (M74/F21)
Median age	49 (18–83)
T stage[*]	
Tx	12
T1	10
T2	16
T3	19
T4	38
N stage	
N0	10
N1	59
N2	26
WHO class II/III	14
WHO class III	39
EBV tested	45 (33 pos/12 neg)

* American Joint Committee on Cancer (AJCC) Staging System, 7th Ed

Table 2
Induction chemotherapy regimens.

Regimen	Number of patients
Triplet regimen	23
Paclitaxel, Ifosfamide, platinum (TIC)	4
Paclitaxel, carboplatin, cetuximab (PCC)	9
Docetaxel, Platinum, 5FU (TPF)	10
Doublet regimen	72
Paclitaxel, cisplatin	6
Paclitaxel, carboplatin	20
Docetaxel, cisplatin	38
Docetaxel, carboplatin	10

Table 3
Response to induction therapy.

Response	Primary site	Nodal site
Complete (CR)	15	10
Partial (PR)	68	73
Stable (SD)		6
Progression	2	3
Combined response[*]	Number of patients	Induction regimen[**]
CR (p) + CR (n)	5	2-Cisplatin, docetaxel 2-TPF 1-PCC
CR (p) + PR (n)	10	6-Cisplatin, docetaxel 3-TPF 1-Carboplatin, docetaxel
PR (p) + PR (n)	69	21-TPF 19-Cisplatin, docetaxel 9-Carboplatin, docetaxel 8-PCC 6-TIC 6-Carboplatin, paclitaxel

* p = primary, n = nodal.

** TPF = paclitaxel, platinum, 5FU; PCC = paclitaxel, carboplatin, cetuximab; TIC = paclitaxel, ifosfamide, platinum.

Toxicity

Eighty-three (87%) of patients were able to complete the full course