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Research Article

Exploring Induction Chemotherapy Regimen in Locally Advanced Nasopharyngeal Carcinoma (NPC): A Retrospective Comparative Analysis

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Abstract

Introduction: The nasopharyngeal carcinoma (NPC) is indeed strongly associated with Epstein-Barr virus (EBV) infection, and exhibits a specific geographical distribution with a higher incidence in certain regions of the world, particularly in Southeast Asia. Radiotherapy is generally considered the main treatment method, but it offers relatively limited disease control for nasopharyngeal carcinoma at the locoregional level, A recent meta-analysis concluded that induction chemotherapy had the potential to improve both progression-free survival and overall survival. This study focuses on the role of induction chemotherapy in the treatment of nasopharyngeal carcinoma and examined the efficacy and toxicity of two treatment regimens, aiming to identify the optimal chemotherapy regimen.

Results: The median follow-up time was 27 months , Kaplan-Meier analyzes revealed no significant differences between the two groups in terms of 2-year failure-free survival (FFS, P = 0.235), 2- year overall survival (OS, P = 0.292), survival without locoregional failure at 2 years (LFFS, P =0,49) and survival without distant failure at 2 years (DFFS , p=0,24) . The overall response rate after treatment was 89% in the Doxorubicin cisplatin group and 81% in the cisplatin gemcitabine combination group.

Conclusion: There were no significant differences in response rates and PFS and OS between the two treatment regimens, but a significantly higher response rate was observed in the cisplatin + Doxorubicin group. However, this study was retrospective, and limited data on toxicity were available; hence, the results should be interpreted with caution.

Keywords: Local advanced nasopharyngeal cancer, Induction therapy, Comparison of regimens

Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer characterized by an imbalanced global geographic distribution, with the highest incidence in the regions of southern China, Southeast Asia, and North Africa [1] NPC exhibits a notable gender disparity, with higher risk in males [2]. Furthermore, almost 70% of patients are diagnosed with locally advanced stage II-IVB disease [3]. The most common histological type of NPC in Maghreb countries is undifferentiated nasopharyngeal carcinoma (UCNT) [4]. Morocco is an endemic area for UCNT, with an incidence considered intermediate by the world health organization WHO [5], with a rate of 3.7 cases per 100,000 according to the Casablanca Cancer Reg-

istry [5]. Given the anatomically challenging location for surgical intervention and the radiosensitivity of NPC, radiotherapy constitutes the primary treatment approach. However, its effectiveness in controlling locally advanced NPC is somewhat limited. As a result, previous studies have established CCRT as the standard of care for locally advanced NPC, specifically in stages III and IVA [6].

There is growing body evidence of supporting the use of platinum-based IC followed by CCRT for treatment of locally advanced NPC. Several trials have shown a survival advantage compared to CCRT alone [7]. Nevertheless, the ideal regimen for IC remains uncertain.

In our local practice, IC has consistently been the standard of care for stage III and IVA NPC with a preference for a regimen consisting of 5FU- cisplatin (PF) or Doxorubicin and cisplatin (DP) administered every 3 weeks for 3 cycles. However, following the publication of the phase III randomized controlled trial in 2019 that showed a survival benefit for gemcitabine-cisplatin (GC) IC followed by CCRT, and the subsequent update of the international guidelines recommending GC as the preferred option for patients with EBV-related NPC, our practice has changed. We have transitioned to using the GC regimen as IC regimen.

The present study aims to retrospectively compare two IC regimens (GC versus DP) for patients with locally advanced NPC.

Materials and Methods

Study Design and Participants

This is a retrospective study involving 105 cases of locally advanced NPC patients collected between January 2016 and October 2022 at the Oncology Hospital " CHU Hassan II" in Fez, Morocco. inclusion criteria consisted of newly diagnosed, biopsy-proven non-metastatic NPC, age over 18, Karnofsky performance score (KPS) > 70%, first-line IC for at least 2 cycles followed by CCRT, and adequate renal function. Patients in the GC group received induction chemotherapy comprising gemcitabine (1000 mg per square meter, days 1 and 8, intravenous infusion) and cisplatin (80 mg per square meter of body surface area, day 1, intravenous infusion). Patients in the DP group received chemotherapy consisting of doxorubicin (60 mg per square meter, day 1, intravenous infusion) plus cisplatin (80 mg per square meter, day 1, intravenous infusion) every 3 weeks for 3 cycles. The concurrent chemotherapy regimen consisted of cisplatin (100 mg per square meter, intravenous infusion) every 3 weeks for 2-3 cycles during radiotherapy. A CT scan of the head and neck was performed before treatment and at the end of the IC, or in the event of clinical disease progression. The radiological assessment has been centrally reviewed by the same radiologist for all study participants and categorized using RECIST criteria. Toxicity has been assessed before each cycle including haematological tests.

Statistical Analysis

Statistical analyses were performed using SPSS softwarev26 Progression-free survival (PFS) and overall survival (OS) analyses were conducted using the Kaplan-Meier method with log-rank tests to assess differences between groups.

Results

A total of 104 cases were included. Table 1 provides an overview of the general clinical characteristics of the two groups. Across the entire cohort, the incidence rates of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 3% (n = 3), 51% (n = 54), 31% (n = 33), and 15% (n = 15), respectively. The overall response rate (ORR) was 54% (n = 57). The median follow-up time was 27 months , Kaplan-Meier analyzes revealed no significant differences between the two groups in terms of 2-year failure-free survival (FFS, P = 0.235), 2- year overall survival (OS, P = 0.292), survival without locoregional failure at 2 years (LFFS, P =0,49) and survival without distant failure at 2 years (DFFS , p=0,24) . The overall response rate after treatment was 89% in the Doxorubicin cisplatin group and 81% in the cisplatin gemcitabine combination group.

Patients in the DP group exhibited less grade 3-4 thrombocytopenia (p>0,05) but more grade 3-4 leukopenia and neutropenia compared to those in the GP group (p>0,05) (Table 1) (Figure 1).

Table 1: Patient characteristics.

Characteristic	DP group (N=62)	GP group (N=43)
Median age years (19-79)	51 (20-77)	47 (19-79)
Sex - no. (%)		
Male	35	30
Female	28	12
Karnofsky performance - status score		
100	13	10
90	45	20
80	4	10
70	0	3
Tumor category - no. (%)		
T1	2	4
T2	11	10
T3	21	10
T4	26	17

Node category - no. (%)		
N1	18	12
N2	25	20
N3A	9	3
N3B	4	2
Disease stage - no. (%)		
III	31	30
IVA	21	13

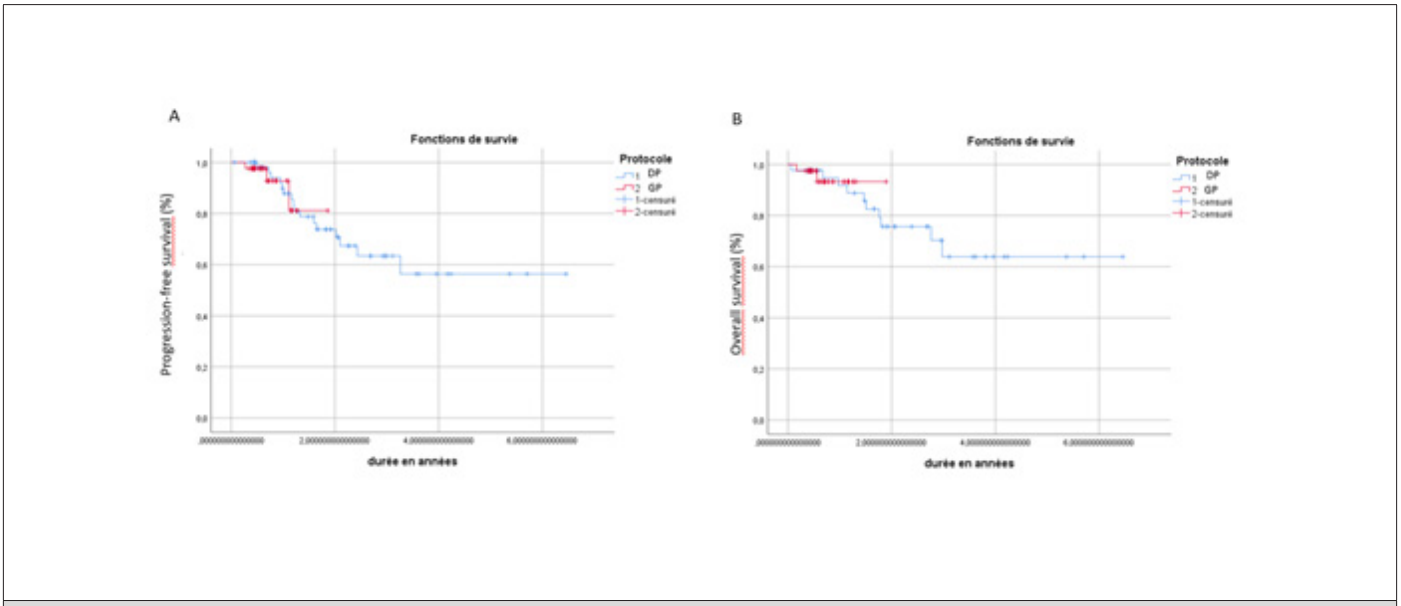

Figure 1: Kaplan–Meier curves of progression-free survival (A) and overall survival (B) for patients with locally advanced NPC receiving DP or GP induction regimens.

Discussion

Concurrent platinum-based chemoradiotherapy constitutes the standard of care for patients with advanced nasopharyngeal carcinoma [8-10]. However, nearly 30% of these patients may experience local recurrence or distant metastases and treatment failure [8,9].

As a result, many trials have evaluated the role of induction chemotherapy followed by CCRT. A meta-analysis that performed an individual patient data analysis of 1193 patients included in 4 randomized trials, with a median follow up of 5 years, has concluded that the addition of IC to CCRT significantly prolonged both progression-free survival (PFS) (HR = 0.70, 95% confidence interval, 0.56-0.86 p =0.0009) and overall survival (OS) (HR = 0.75, 95% CI 0.57-0.99, p =0.04). This led to a 5-year absolute benefit of 9.3%% and 5.5%, respectively. IC+CCRT also reduced rates of distant failure (HR = 0.68, 95% CI 0.51-0.90, p = 0.008) and had a tendency to improve local control (HR = 0.70, 95% CI 0.48 to 1.01, p=0.06). [7] Interestingly, No differences in survival were observed among different IC regimens, including TPF, GCP (gemcitabine-carboplatin-paclitaxel), TP (docetaxel-cisplatin), PF (cisplatin- 5FU) were detected. However, it's worth noting that no trial with anthracycline based regimen has been included in this meta-analysis, nor did it include GP regimen [11].

GP regimen has been widely used and studied in recurrent or metastatic NPC and may extend PFS with acceptable adverse events [12]. Recent studies have shown that GP therapy administered in the induction phase achieves favourable clinical outcomes without severe toxicities [13]. In a Chinese phase III trial published in the New England Journal of Medicine, *Zhang, et al*. [13] reported that 94.6% of patients (226 out of 239) responded after GP induction chemotherapy prior to starting chemoradiotherapy in newly diagnosed stage III to IVB patients; 24 patients (10.0%) achieved complete response, and 202 (84.5%) achieved partial response with GP. This yielded an absolute survival benefit of 8.8% and 4.3% at 3-years for PFS and OS respectively. This benefit persists at 5 years with an absolute benefit of 9.1% in OS (87.9% vs 78.8%, HR=0.51 (95% CI 0.34-0.78); p=0.001) without increasing late toxicities. This regimen is currently the preferred IC regimen by the NCCN guidelines with a category 1 for EBV-associated disease and 2A for non-EBV-associated NPC (ref).

The combination of anthracycline and cisplatin has lower level of evidence. The combination of epirubicin and cisplatin (EP) as IC was studied in a phase III trial by the Asian-Oceanian Clinical Oncology Association in patients with locally advanced undifferentiated or poorly differentiated NPC .The analysis showed no benefit from adding EP neoadjuvant chemotherapy to CCRT for patients

with locally advanced NPC, although the overall incidence of recurrence was reduced with the addition of EP to CCRT.

In Morocco, historically, the IC regimens for the treatment of locally advanced NPC mainly consisted of PF or DP. Currently, the recommended regimen is GP based on the Asiatic phase III trial conducted by *Zhang Y, et al*.

Given the absence of a confirmatory trial conducted in Morocco, we decided to evaluate the efficacy and safety data of patient cohort treated with the newly adopted GP regimen and compare it to a historical cohort of patient treated with DP.

In our study, the overall response rate to IC chemotherapy was lower than that reported in the literature, and particularly compared to the findings by *Zhang Y, et al*. with the GP induction regimen (54% vs 94.5% respectively). The lower response rates observed in our study should be confirmed by a larger prospective trial, which could include tumour biomarkers, and investigate pharmacogenetic factors to explore the reasons behind this possible reduced chemosensitivity.

However, we notably found that patients receiving DP-based induction achieved a significantly higher response rate than those receiving the GP regimen with 60 % achieving PR compared to 39.5% in the GP regimen.

Furthermore, we observed lower PFS and OS rates at 2 years, which could be attributed to either more biologically aggressive disease or reduced chemosensitivity.

This study has a lot of limitations, including its retrospective nature, the small number of patients, and a comparison to a historical cohort. However, the significance of these finding should not be overlooked. When considering the final report of *Zhang Y, et al*. in which they demonstrated a significant positive correlation between the depth of tumour response to IC (CR vs PR vs SD/PD) and survival (5-year OS of 100% vs 88.4% vs 61.5% p=0.005), and despite the absence of statistically significant differences in PFS or OS between DP and GP, these finding raise questions about adopting GP for our patients.

We believe that a confirmatory randomized trial is warranted to investigate the optimal IC in locally advanced NPC in Moroccan population.

Conclusion

In summary, our study concluded that a DP induction regimen was superior to GP regimens for locally advanced high-risk NPC in term of response rate with acceptable toxicities. Further studies are needed to validate our results and to inform the local guidelines.

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