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Mini Review

Induction Treatment Prior to Chemo-Radiotherapy in Nasopharyngeal Carcinoma: Triplet or Doublet Chemotherapy?

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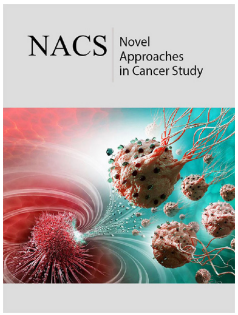
ISSN: 2637-773X



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Submission: August 13, 2019

Published: August 30, 2019

Volume 3 - Issue2

How to cite this article: Maeve A Hennessy, Patrick G Morris. Induction Treatment Prior to Chemo-Radiotherapy in Nasopharyngeal Carcinoma: Triplet or Doublet Chemotherapy?. Nov Appro in Can Study. 3(2). NACS.000557.2019.
DOI: 10.31031/NACS.2019.03.000557

Abstract

Nasopharyngeal carcinoma is a malignancy that is endemic in Asia and North Africa. The current standard of care for loco-regionally advanced disease is platinum-based concurrent chemo-radiotherapy. However, relapse remains a common issue and novel approaches are needed. Phase II trials have shown encouraging results when induction chemotherapy with gemcitabine and cisplatin is added to chemo- radiation. In a major recent advance, a phase III trial has demonstrated significantly improved recurrence-free survival (RFS) and overall survival (OS) for this approach compared to chemo- radiotherapy alone. Results from this trial showed a 4.3% improvement in OS over standard therapy at 3 years, (94.6% vs 90.3%), with an expected increase in acute adverse events. In this article, we put this treatment in context of other proven approaches in nasopharyngeal carcinoma. Of note, there is a lack of comparative data in relation to the optimal induction regimen. It remains to be seen whether or not treatment with the gemcitabine-cisplatin doublet differs significantly from the established induction triplet of docetaxel, cisplatin and fluorouracil (TPF) with regard to efficacy or toxicity. The decision to opt for either a gemcitabine-based doublet or taxane-based triplet induction regimen is likely best made after careful consideration of an individual patient, but it is likely that many more patients would tolerate gemcitabine-cisplatin compared to TPF. The role of immunotherapy is currently under investigation and could prove a promising strategy in combination with induction therapy. It is likely that future treatment strategies in the management of nasopharyngeal carcinoma will adopt a more personalized approach.

Background

Nasopharyngeal carcinoma (NPC) is a malignancy that is most common in Asia and North Africa. Approximately 130,000 patients were affected globally in 2018. The incidence of NPC is two to three times higher in males and peaks in the sixth decade of life [1]. Over 70% of patients present with locally advanced disease and the current standard of care for this cohort is concurrent chemo-radiotherapy with a platinum-based agent [2,3]. Although this approach is highly effective, tumour relapse and toxicities remain substantial issues. It has been suggested that adding additional cycles of chemotherapy to the standard treatment might improve both recurrence-free survival (RFS) and overall survival (OS). However, high rates of toxicity have been documented in patients undergoing adjuvant chemotherapy post chemo-radiotherapy, leading to a low percentage of patients (approximately 50-75%) completing their scheduled adjuvant chemotherapy. An alternative approach is to give systemic therapy as an induction treatment prior to chemo-radiotherapy as it is hoped that this might result in better tolerability and greater dose intensity. Induction chemotherapy might also facilitate the reduction of tumour burden thus allowing for smaller radiation fields [4].

Previous phase III trials have examined induction chemotherapy in unselected head and neck squamous cell carcinoma (SCC). Posner et al. [5] compared induction chemotherapy with the triplet of docetaxel, cisplatin and fluorouracil (TPF) to the cisplatin and fluorouracil (PF) doublet every three weeks for three cycles, followed by chemo-radiotherapy. A significantly improved OS was seen in patients who received TPF versus those who received PF [5]. Following on from these encouraging results, Sun et al. [6] conducted a phase III trial in locally advanced NPC at 10 institutions in China, which examined induction therapy with TPF prior to concurrent chemo-radiotherapy versus concurrent chemo-radiotherapy alone. Treatment doses in this trial were lower compared to the previously described TPF regimen:

docetaxel (60mg/m2 rather than 75mg/m2), cisplatin (60mg/m2 rather than 100mg/m2), and continuous intravenous fluorouracil (600mg/m2/day x 5 days rather than 1000mg/m2/day x 4 days) [6]. This trial showed that TPF induction chemotherapy followed by concurrent chemo-radiotherapy could significantly increase RFS and OS in NPC compared with concurrent chemo-radiotherapy alone [6]. Despite these positive results, widespread adoption of the TPF regimen at either of these dose schedules has been challenging in everyday clinical practice. An alternative approach is the combination of gemcitabine-cisplatin, which has demonstrated activity and a tolerable safety profile in phase II trials [7,8].

Key Results from the Trial

Against this background, Zhang et al. [9] conducted a randomised phase III trial of 480 patients, which was recently published in the New England Journal of Medicine (NEJM). This study aimed to further investigate the safety and efficacy of adding induction gemcitabine-cisplatin to concurrent chemo- radiotherapy in newly diagnosed, locally advanced NPC. In this trial, patients were randomised 1:1 to induction chemotherapy with cisplatin 80mg/m^2 on day 1 with gemcitabine 1g/m^2 on day 1 and 8 every 21 days for three cycles or to no induction chemotherapy. Cisplatin concurrent with radiotherapy was administered at a dose of 100mg/m^2 every 21 days [9]. In this study, induction chemotherapy was associated with an improved 3-year RFS and OS. At a median follow-up of 42.7 months, the 3-year RFS was 85.3% in the induction chemotherapy group and 76.5% in the standard-therapy group (HR 0.51; 95% CI, 0.34 to 0.77; P=0.001). Similarly, OS at 3 years was 94.6% and 90.3% respectively (HR 0.43; 95% CI, 0.24 to 0.77) [9]. The regimen was well tolerated with a total of 96.7% of the patients completing three cycles of induction chemotherapy. The induction doublet group had a higher incidence of Grade III or IV adverse events: (75.7% versus 55.7%). Specifically, there was a higher incidence of neutropaenia, thrombocytopaenia, anaemia, nausea, and vomiting with induction therapy. Grade III or IV neutropaenia occurred in 28.0% versus 10.5% respectively. One person in the induction chemotherapy arm had febrile neutropaenia. Grade III or IV late toxic effects were seen in 9.2% in the induction group and 11.4% in the standard group [9].

Strengths of the Study

This was a well-designed, randomized, multicenter, phase III trial [9]. This facilitated a direct comparison between two treatment strategies in order to establish superiority. The patient characteristics at baseline were well balanced between the two treatment groups. A large clinical benefit was demonstrated in the induction chemotherapy group with patients not only experiencing better 3-year RFS but also improved 3-year OS rates [9]. These impressive results clearly establish the use of induction gemcitabine and cisplatin as a new standard of care in newly diagnosed NPC.

Overall, in this study, 79.9% in the induction arm and 95.8% in the standard therapy arm received at least 200mg/m^2 of concurrent cisplatin. As expected, patients who had induction chemotherapy received less intensive concurrent chemo-radiotherapy: the median dose intensity for concurrent cisplatin was 200mg/m2 in the induction group and 300mg/m2 in the standard group. The median cumulative dose of cisplatin was 440mg/m2 in the induction group, but only 26.4% patients received the full cumulative dose of 540mg/m2.9 Nonetheless, this dose intensity is impressive and the control arm is in line with the current standard of care for concurrent cisplatin (100mg/m^2 day 1, 22, 43) [4]. Although many investigators opt to give weekly cisplatin at a dose of 30-40mg/m^2, the evidence for this approach is relatively weak. A phase III randomised trial conducted by Noronha et al. [10] compared cisplatin 30mg/m2 weekly to cisplatin 100mg/m2 once every three weeks concurrently with radiotherapy in locally advanced head and neck SCC, and found that cisplatin once every three weeks at 100mg/m2 resulted in more toxicity but superior loco-regional control and should remain the standard of care. Critics of this study have suggested that the dose of cisplatin (30mg/m2) in the experimental arm was too low and so ongoing research is examining cisplatin 40mg/m2 weekly. A further option is the use of carboplatin over cisplatin. In a Phase III trial looking at cisplatin versus carboplatin, fewer patients in the cisplatin arm completed concurrent chemo-radiotherapy plus three cycles of adjuvant chemotherapy compared to those in the carboplatin arm. The patients in the cisplatin group had more renal toxicity, nausea, vomiting and anaemia. The more favorable toxicity profile of carboplatin means it could be considered as an alternative in patients with reduced renal function, poorer performance status or older age, albeit at the cost of potentially lower efficacy [11].

Limitations of the Study

It is worth noting that differences in patient demographics might affect the generalizability of the results of the Zhang et al. [9] study outside of Asia. NPC can be classified into different histological subtypes: Type I SCC, Type II keratinising undifferentiated carcinoma and Type III non-keratinising undifferentiated carcinoma. NPC predominantly occurs in Asia where the Type III subtype is the commonest form of NPC [12]. In contrast, NPC is a relatively rare disease in the United States and typically demonstrates squamous differentiation. The squamous type of NPC differs from Type III NPC in its association with the Epstein Barr virus (EBV) and sensitivity to chemotherapy and radiotherapy [12]. Three of the largest randomized trials looking at the treatment of NPC have been conducted in China [9]. It would be interesting to see how these results translate in a broader patient cohort and whether or not the inclusion of various subtypes would influence outcome.

One of the main limitations of this study by Zhang et al. [9] is that induction chemotherapy prior to chemo- radiation was compared to chemo-radiation alone, i.e. there was no comparison to other induction chemotherapy regimens. Hence one of the questions that remains unanswered is whether or not induction with the gemcitabine-cisplatin doublet is superior to induction with the TPF triplet, in terms of improved survival rates with manageable toxicity [5,6,9].

Discussion

Although direct comparisons should be interpreted cautiously, it would seem that the efficacy of the gemcitabine-cisplatin regimen used in Zhang et al. [9] was at least as good as that seen with

the TPF regimen reported by Sun et al. [6](3 year RFS of 85.3% versus 80% and a 3 year OS of 94.6% versus 92% respectively). The RFS and OS with gemcitabine-cisplatin is also superior to TPF as reported by Posner et al. [5] however this was in unselected patients with head and neck cancer (Table1) [5]. All three studies document significant adverse effects, in particular neutropaenia and febrile neutropaenia in the induction therapy groups [5,6,9]. The highest rates of grade III or IV neutropaenia were seen in the trial by Posner et al. [5] with 83% of patients in the TPF group and 56% of patients in the PF group affected. This is in contrast to Sun et al. where 42% of patients in the TPF group experienced grade III or IV neutropaenia [6]. Posner et al. [5] also had the highest rates of febrile neutropaenia, 12% in the induction therapy group as compared to 0.4% and 3% in the Chinese studies. Patients who received gemcitabine-cisplatin in Zhang et al. [9] had the lowest rates of neutropaenia and febrile neutropenia of the three studies (Table 1). Of note, primary prophylaxis with recombinant granulocyte colony-stimulating factor (GCSF) was not undertaken in these studies [5,6,9]. Due to the high rates of febrile neutropaenia occurring with TPF chemotherapy, many Investigators now give primary prophylactic GCSF to this patient cohort.

Table 1: Comparison of induction chemotherapy regimens in head and neck cancer.

	Zhang et al. [9]		Posner et al. [5]		Sun et al. [6]	
Number of Patients	480		501		480	
Patient Population	Loco-regionally advanced NPC		Stage III/IV Head and Neck SCC		Stage III-IVB (except T_3-$_4$N0) NPC	
	Experimental therapy	**Standard therapy**	**Experimental therapy**	**Standard therapy**	**Experimental therapy**	**Standard therapy**
Induction Chemotherapy Regimen	**G** 1g/m^2 D1, D8 **P** 80mg/m^2 D1 Every 21 days x 3 cycles	-	**T** 75mg/m^2 D1 **P** 100mg/m^2 D1 **F** 1,000mg/m^2 D1-D4 Every 21 days x 3 cycles	**P** 100mg/m^2 D1 **F** 1000mg/m^2 D1-D5 Every 21 days x 3 cycles	**T** 60mg/m^2 D1 **P** 60mg/m^2 D1 **F** 600mg/m^2 D1-D5 Every 21 days x 3 cycles	-
Concurrent Chemo-radiation Regimen	**P** 100mg/m^2 Every 21 days x 3 cycles	**P** 100mg/m^2 Every 21 days x 3 cycles	**C** AUC 1.5 Every 7 days x 7 cycles	**C** AUC 1.5 Every 7 days x 7 cycles	**P** 100mg/m^2 Every 21 days x 3 cycles	**P** 100mg/m^2 Every 21 days x 3 cycles
3 Yr RFS (%)	85.3	76.5	49	37	80	72
3 Yr OFS (%)	94.6	90.3	62	48	92	86
Grade III/IV Neutropaenia (%)	28	10.5	83	56	42	17
Febrile Neutropaenia (%)	0.4	0	12	7	3	0
Grade III/IV Anaemia (%)	9.6	0.8	12	9	2	2
Grade III/IV Mucositis (%)	28.9	32.1	21	27	41	35

It is not surprising that there was a higher overall incidence of acute adverse events among the patients treated with induction chemotherapy versus those who received concurrent chemo-radiotherapy alone. Specifically, severe neutropaenia, thrombocytopaenia, anaemia, nausea and vomiting were all more common. Acute grade I and II nephrotoxic effects were also greater with the higher cumulative dose of cisplatin in the induction group [9]. There is a lack of data comparing induction regimens, however the earlier phase III trial that looked at TPS showed a high incidence of grade III or IV acute adverse events, despite dose modifications [6].

Another factor to consider is that induction chemotherapy requires a longer treatment duration and therefore it is a select group of patients with better performance status who would be able to tolerate this more intensive treatment regimen. In the study by Zhang et al. [9], patients were required to have a Karnofsky Performance Status (KPS) of at least 70 to be eligible for inclusion and were excluded if they had severe co-existing illnesses. The median age of patients receiving induction chemotherapy in this trial was 46, 78% of patients had a KPS of 90 and only 2.9% had a KPS of 70.9 Hence even the gemcitabine-cisplatin doublet might not be generalizable to all patients with NPC.

Immunotherapy is another emerging therapeutic strategy, which has proven to be effective in recurrent head and neck cancer. A randomised phase III trial conducted by Ferris et al. [13] assessed the use of Nivolumab, an anti-programmed death 1 (PD-1) monoclonal antibody, in recurrent SCC of the head and neck in patients who had received prior platinum therapy. Patients treated with Nivolumab had a longer OS than those in the standard treatment group (7.5 months versus 5.1 months, HR0.69, 0.53-0.91) and this was regardless of tumour PD-L1 expression or p16 status. In the Nivolumab arm, p16 positive tumours did better than p16 negative tumours with a median overall survival of 9.1 months versus 7.5 months. Hence, p16 is prognostic but not necessarily predictive of response to immunotherapy. Further research in this area might define a role for immunotherapy as part of induction therapy.

Allowing for the challenges in making these comparisons, it appears that the gemcitabine-cisplatin doublet is likely at least as active as the TPF triplet, but with a superior toxicity profile in NPC. Whether gemcitabine-cisplatin is an appropriate induction therapy in head and neck malignancies outside of the nasopharynx is unknown. The data supporting the broader use of gemcitabine-cisplatin are limited by the highly selected patient population studied (in terms of geography, age, performance status and primary tumour site) and lack of direct comparison with a triplet chemotherapy such as TPF. Nonetheless, induction chemotherapy with gemcitabine-cisplatin is now a standard of care.

Conclusion

The study by Zhang et al. [9] has clearly shown that the addition of induction chemotherapy with gemcitabine-cisplatin to concurrent chemo-radiotherapy significantly improved RFS and OS among patients with loco-regionally advanced NPC. Treatment was well-tolerated with high compliance rates; therefore, this can be considered as a first-line treatment option in patients with node-positive or T3/4 disease. Although direct comparisons are challenging, the magnitude of the improvements in RFS at 3 years with gemcitabine-cisplatin are at least as good as with TPF in an earlier phase III trial. It remains unclear whether there is a significant difference in the efficacy or toxicity of these two regimens. There is a lack of comparative data and therefore the decision to opt for either a gemcitabine-based doublet or taxane-based triplet induction regimen is likely best made on an individualized case-by-case basis. Survivors of NPC can live for several decades following treatment; therefore, we need long-term follow up data of efficacy and late toxicity before we definitively replace chemo-radiotherapy as the standard of care. Finally, the role of novel therapies in this disease are under investigation and it remains to be seen whether the addition of immunotherapy to induction therapy for NPC could represent a promising combination strategy in the future [14].

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