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Original Research

Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: Long-term results of a phase 3 multicentre randomised controlled trial

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KEYWORDS
Nasopharyngeal carcinoma;
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Long-term results

Abstract ***Aim of the study:*** Previous results from our trial showed that adjuvant cisplatin and fluorouracil chemotherapy did not significantly improve survival after concurrent chemoradiotherapy (CCRT) in locoregionally advanced nasopharyngeal carcinoma (NPC) at 2 years. Here, we present the data of long-term survival and late toxicities to further assess the ultimate therapeutic index of adjuvant chemotherapy (AC).
Methods: Patients with stage III–IVB (except T3-4N0) NPC were randomly assigned to receive CCRT plus AC or CCRT only at seven institutions in China. Patients in both groups received cisplatin 40 mg/m^2 weekly up to 7 weeks concurrently with radiotherapy. The CCRT plus AC group subsequently received adjuvant cisplatin 80 mg/m^2 and fluorouracil 800 mg/m^2/d for 120 h every 4 weeks for three cycles. The primary end-point was failure-free survival.
Results: Two hundred and fifty-one patients were randomised to the CCRT plus AC group and 257 to the CCRT only group. After a median follow-up of 68.4 months, estimated 5-year failure-free survival rate was 75% in the CCRT plus AC group and 71% in the CCRT only group (hazard ratio 0.88, 95% confidence interval 0.64–1.22; p = 0.45). 66 (27%) of 249 patients in the CCRT plus AC group and 53 (21%) of 254 patients in the CCRT only group developed one or more late grade 3–4 toxicities (p = 0.14).
Conclusion: Adjuvant cisplatin and fluorouracil chemotherapy still failed to demonstrate significant survival benefit after CCRT in locoregionally advanced NPC based on the long-term follow-up data, and addition of adjuvant cisplatin and fluorouracil did not significantly increase late toxicities.
Registration number: NCT00677118.

1. Introduction

Radiotherapy is the primary treatment modality for non-disseminated nasopharyngeal carcinoma (NPC). The landmark Intergroup-0099 Study was the first randomised trial to achieve a 31% improvement in the 3-year overall survival rate in the latter group by adding concurrent chemotherapy and adjuvant chemotherapy (AC) to radiotherapy, and, since 1998, this regimen has been deemed the standard of care for advanced NPC [1]. However, the Intergroup-0099 Study and subsequent three similar trials were unable to tease out the contribution of AC, as the control arm was radiotherapy alone [1–4]. In addition, there were three pure phase 3 'AC trials' for NPC, in which AC was used alone, and all these trials failed to demonstrate a positive impact on survival [5–7]. Based on the results of above trials, the role of the addition of AC to concurrent chemoradiotherapy (CCRT) is questionable.

We therefore performed a phase 3 trial to compare CCRT plus AC with CCRT alone, to appraise the contribution of AC in locoregionally advanced NPC. After a median follow-up period of 37.8 months, the 2-year results had been published and demonstrated that adjuvant cisplatin and fluorouracil chemotherapy did not significantly improve failure-free survival after CCRT in locoregionally advanced NPC [8]. However, it should be noted that the follow-up period is relatively short, especially for overall survival, and there were no data on detailed late toxicities at that time. Thereafter, meta-analyses which involved our trial and focused on AC in advanced NPC, unanimously failed to demonstrate a significant advantage from using AC to treat advanced NPC [9–11]. Hence, the purpose of this progress report is to verify the long-term survival and late toxicities and to further assess the ultimate therapeutic index of AC in patients with locoregionally advanced NPC.

2. Patients and methods

2.1. Participants

Between 1st June 2006 and 5th March 2010, we did an open-label phase 3 multicentre randomised controlled trial at seven institutions in China. Eligible patients were aged 18–70 years with non-metastatic, histologically proven non-keratinising stage III or IV NPC, except T3-4N0 (6th American Joint Commission on Cancer staging system) [8]. All participants provided written informed consent. Our protocol was approved by the ethics committee or institutional review board at each centre.

2.2. Randomisation and masking

Random assignment was done (via sealed envelopes) by the Clinical Trials Centre, Sun Yat-sen University Cancer Centre, with a computer-generated random number code. Participants were stratified according to treatment centre and randomly assigned in blocks of four based on a one-to-one treatment allocation (the