Editorial

Nedaplatin: a new paradigm in nasopharyngeal cancer

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Comment on: Tang LQ, Chen DP, Guo L, *et al*. Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 2018;19:461-73.

Received: 17 May 2018; Accepted: 22 June 2018; Published: 30 June 2018.

doi: 10.21037/anpc.2018.06.01

View this article at: http://dx.doi.org/10.21037/anpc.2018.06.01

Radiotherapy concurrent with cisplatin either weekly or every 3 weeks' regimen has been accepted as the standard of care for locoregional advanced stage of nasopharyngeal cancer for decades (1-5). Although it has shown a statistically significant benefit in terms of locoregional control and survival rate when compared with radiotherapy alone, but severe acute and late toxicities might affect the quality of life (QoL), mainly nausea, vomiting, impaired renal function, and hearing toxicity (6-9).

Acute toxicities mainly in hematologic and renal toxicity of chemotherapy also had the effect on the compliance of treatment. The intergroup 0099 study reported the compliance of concurrent chemoradiotherapy (CCRT) in only 63% (1). The Thai study using the same regimen of CCRT as in the intergroup 0099 also demonstrated the similar result of compliance rate of CCRT at 59% (10).

Several new chemotherapy regimens in combination with radiotherapy were studied to find the best way to improve both in efficacy and toxicities. For example, a more convenient carboplatin—based chemoradiotherapy had been tested and showed better tolerability with a lower rate of severe gastrointestinal toxicities and nephrotoxicities than of standard cisplatin-based regimen (10). However, the efficacy of carboplatin-based chemoradiotherapy had not been consistently confirmed to improve outcome by others investigators.

Nedaplatin is a recent promising alternative drug for cisplatin which had shown a good potential for radiosensitizer activity in early studies with less nephrotoxicity and gastrointestinal toxicity compared to the incidence reported from cisplatin-based regimen (11-13). Tang *et al*. have successfully performed an open labeled randomized trial comparing nedaplatin to cisplatin both given at 100 mg/m^2 every 3 weeks concurrent with intensity-modulated radiotherapy in stage II–IVB, nasopharyngeal carcinoma in 2 hospitals in China. The investigators reported the 2-year progression-free survival as primary end point in the nedaplatin group is non-inferior to cisplatin group, with the difference of 1.9% and 1.0% in the intention-to-treat and per protocol population analysis respectively. Nedaplatin also had an advantage of more convenient administration without the requirement for intravenous fluid hydration and diuretics for renal protection. Analysis of safety showed that nedaplatin group had significant less acute grade 3 or 4 toxicity of nausea (2% *vs*. 9%), vomiting (6% *vs*. 18%) and anorexia (13% *vs*. 27%) than cisplatin group. Patient in nedaplatin group had higher frequency of severe grade 3 or 4 thrombocytopenia than in cisplatin group (6% *vs*. 2%). The late toxicity of grade 3 or 4 auditory or hearing was less frequent in nedaplatin group than cisplatin group (2% *vs*. 6%). The investigators however found that treatment compliance of patient in nedaplatin group who could receive 3 cycles of concurrent treatment was lower than in cisplatin group (57% *vs*. 65%) and could be a confounder when determining the difference in treatment associated toxicity between two groups. About 17% of patients in nedaplatin group had thrombocytopenia and require treatment delay exceeded the timeframe of third cycle of nedaplatin administration. In post-hoc analysis in subset of patients who could receive all 3 cycles of nedaplatin or cisplatin, the

investigators reported no different in either occurrence of locoregional relapse, distant relapse or survival between two groups.

An update of the MAC-NPC meta-analysis (12) demonstrated a survival benefit at 5 years by 6.3% and had a benefit in all endpoints (progression-free survival, locoregional control, distant control, and cancer mortality) in locoregionally advanced disease treated by CCRT with or without adjuvant chemotherapy. The scheme of treatment in this study using CCRT with nedaplatin without adjuvant chemotherapy which is the common practice for the treatment of nasopharyngeal cancer in many Asian countries. This study prescribed the dose to the skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, and lymph node level IB to level V lower (54–56 Gy) than other guidelines (56–60 Gy). Nevertheless, the locoregional relapse rate at 2 years was acceptable and similar to the historical data. This study appropriately controlled the quality of radiotherapy treatment protocol which is the utmost imperative treatment component and an important factor of treatment achievement for NPC patients.

Focus to the financial difficulties domain in EORTC QLQ-C30 in this study, as we know that socioeconomic status was the most substantial flexible that correlated with the QoL. Lam *et al.* (13) studied the household income of Chinese adults and demonstrated that low-income households had poorer QoL and also was the threshold for weakening of both physical and mental QoL. Besides, the distribution of socioeconomic status of the patients in both groups was not described in this study.

This study is clearly stated primary and secondary endpoints. This is a properly reported statistical methodology, logical and rational concept of the study and the use of appropriate study design (randomized controlled trial). Non-inferiority trial enables a direct comparison of the effectiveness of new concurrent chemotherapy regimen; nedaplatin and a standard-of-care regimen. The study provides an accurate description of target population, explanation of the sample size calculation, randomization, allocation and blocking in enough details relevant data for multicenter clinical trial. They did valid description and sufficient explanation of statistical tests. However, they did not plan to undertake any interim analyses. It is also shows the high proportion of eligible patients who were randomized, the small number not getting their randomized treatment (but still included in intention to treat analysis), and the small numbers removed from analysis or lost to follow-up.

This was a randomized phase 3 trial with a large number of patients with good quality control of radiotherapy. The results of this study appeared promising. However, it is crucial to wait for the long term outcome of efficacy of overall survival and toxicity of these regimens and data of cost-effective analysis before we could firmly conclude that nedaplatin based concurrent chemotherapy could be an alternative treatment option to the long standing standard cisplatin-based regimen during radiotherapy in patients with nasopharyngeal cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Nasopharynx Cancer*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/anpc.2018.06.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/anpc.2018.06.01
Cite this article as: Chitapanarux I, Charoentum C, Traisathit P. Nedaplatin: a new paradigm in nasopharyngeal cancer. Ann Nasopharynx Cancer 2018;2:10.

