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Efficacy and safety of molecular-targeted therapies in nasopharyngeal carcinoma: A network meta-analysis

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ADMINISTRATIVE INFORMATION

Support - International Medical University.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 August 2023 and was last updated on 05 August 2023.

INTRODUCTION

Review question / Objective What is the efficacy of molecular-targeted therapies in nasopharyngeal carcinoma? What are the potential harms of molecular-targeted therapies in nasopharyngeal carcinoma?

Rationale Molecular targeted therapies can be focused into two pathways: vascular endothelial endothelial growth factor receptor (VEGFR)and the epidermal growth factor receptor (EGFR) pathways. There was evidence of high expression of VEGF in NPC and its association with unsatisfactory prognosis. It is believed that VEGF cascade plays an important role in tumour growth, angiogenesis, and metastasis in NPC. The similar findings applied to EGFR, where its binding could participate in controlling proliferation, apoptosis and differentiation of NPC cells, which is a common finding in many epithelial tumours. (1) Among the molecular-targeted therapies, sorafenib, sunitinib, axitinib, famitinib, and pazopanib are undergoing clinical trials. (1, 6, 7). In addition, endostatin, an endogenous anti-angiogenic inhibitor, is approved for non-small cell lung cancer in 2005 and currently it is under trial for NPC patients. EGFR inhibitors such as cetuximab, getinib, nimotuzumab and erlotinib have been undergoing clinical trials for their effectiveness in NPC.

There were a total of 17 published network meta-analysis and all of them focused on conventional chemotherapy. All published network meta-analysis reviewed on conventional chemotherapies. In conclusion, NPC is a complex disease where there are roles of EBV infection, ethnic, geographical location, genetics, immune, environmental factors as well as probably gender. Although there was a gradual decline in NPC globally, its incidence is still high in SEA, especially in Malaysia. There was a meta-analysis on efficacy and tolerability of immunotherapy in advanced NPC, but the analysis targeted mainly on programmed-death 1(PD-1) inhibitors. The effectiveness of molecular-targeted therapies in NPC has not been analysed and its role in the management of NPC should be explored further.

To our knowledge, this is still a gap for a more detailed understanding. Our objective is to study the efficacy and safety of molecular targeted therapies in NPC in conventional treatment regimens for observation of more effective treatments with less toxicity.

Condition being studied Nasopharyngeal carcinoma (NPC) is a type of carcinoma with an apparent geographical and racial distribution, and it is mostly prevalent in East and Southeast Asia. Worldwide incidence of NPC is not common but 70% of NPC cases are from the East and Southeast Asia. It is the fifth most common cancer among male residents in Malaysia, fifth most common cancer between 2012-2016 and forth most common cancer in Malaysian Chinese males. Even among SEA regions, there is geographical distribution pattern. For instance, NPC incidence rate is significantly high in the Southern China for the People Republic of China and similarly, the higher incidence rate is reported among Chinese and the natives from Sabah and Sarawak in Malaysia. The prevalence is exceptionally high in men in Malaysia.
NPC arises from the epithelial lining of the nasopharynx, is frequently observed in the pharyngeal recess. Multiple factors contribute to the development of NPC includes viral factors (e.g., Epstein-Barr virus infection) and non-viral factors (e.g., genetic susceptibility, family history, ethnicity, exposure to occupational solvents, tobacco smoking, and consumption of salted fish etc.).
Primary treatment of NPC is radiotherapy, and the other options are chemotherapy and surgery. Intensity modulated radiotherapy is preferred. Newly developed cancer therapies such as immunotherapy and targeted therapies are also reported to have improved outcomes in NPC patients.
Current immunotherapies can be categorized into three: immune check point inhibition, adoptive immunotherapy, and active immunotherapy. (1,3) Since the expression of PD-1 (programmed cell death protein 1) has been noticed in most NPC tumours and it is related to high risk of recurrence and metastasis after conventional chemotherapies, targeting PD-1/PD-L1 may be a new promising new therapy for NPC patients.

METHODS

Participant or population People with nasopharyngeal carcinoma regardless of the stage of the staging of cancer.

Intervention Any intervention which includes i) Molecular targeted therapies (e.g., anti-VEGFR (Vascular EndothelialGrowth Factor)or anti-EGFR (Epidermal growth factor receptor)) with or without conventional chemotherapy/chemoradiotherapy/ radiotherapy.

Comparator Conventional chemotherapy/ chemoradiotherapy/radiotherapy with or without molecular targeted therapy.

Study designs to be included Randomized controlled trial.

Eligibility criteria Studies published in English language only will be included. Studies must report at least one outcome related to overall survival rate, median survival rate, progression free survival rate and/or adverse effects.

Information sources We will follow the PRISMA-checklist 2020. A stepwise approach of will be carried out as described elsewhere in the literature. An extensive electronic search of the multiple databases will be done to identify relevant studies available from inception to August 2023.
Ovid MEDLINE
EBSCOhost
Cochrane Central Register of Controlled Trials (CENTRAL)
PubMed
We will also search the following clinical trials registries such as ClinicalTrials.gov (http://www.clinicaltrials.gov/). A manual search will be performed in the reference lists of the relevant studies. To do so, appropriate MeSH terms with suitable Boolean operators will be used. We will contact to the study authors or trialists if more information is needed.

Main outcome(s) Overall survival rate; Median survival rate; Progression free survival rate; Any reported serious or non-serious adverse events.

Quality assessment / Risk of bias analysis The methodological quality of the studies will be assessed using the Cochrane risk of bias tool, for randomized controlled trials. Methodological quality assessment will be carried out by the two independent investigators and any discrepancy will be solved by a discussion with the third investigator.

Strategy of data synthesis The efficacy of different therapeutic regiments will be compared by pairwise meta- analysis. Risk ratio and 95%confidence level will be measured for dichotomous outcomes and mean difference, or

standard mean difference will be measure for continuous outcomes. Year-specific survival rate (e.g. 5-year survival rate) will be dichotomous outcome and median survival rate will be categorised as continuous outcomes. Data extraction and analysis will be carried out independently by the two investigators. Adverse events will be reported based on the severity (serious or non-serious), based on organ system (e.g., cardiovascular, or respiratory) or grading (grade 1 – mild, asymptomatic, or mild symptoms) or grade 5 (death related to adverse events).

Subgroup analysis Subgroup analysis will be done according to the age, gender, disease severity, staging and/or comorbidities if data permits.

Sensitivity analysis Heterogeneity will be assessed using the χ^2 test and the I^2 statistic. The I2 value of 25% will consider as low heterogeneity, 50% as the moderate heterogeneity, and more than 75% as a high heterogeneity. A two-tailed P value of less than 0.05 will be considered statistically significant. A funnel plot will be done to detect the publication bias.

Country(ies) involved Malaysia.

Keywords Nasopharyngeal carcinoma ,network meta-analysis, targeted therapies, randomized clinical trial, systamatic review and meta-analysis.

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