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EDITORIAL

How to treat recurrent/metastatic head and neck cancer: the economic issue in real-world practice

Head and neck cancer (HNC) is the sixth most common type of cancer globally[1]. Early stage (stage I–II) can be treated by surgery or radiotherapy only. Locally advanced stage (stage III–IVa) can be treated by surgery and radiotherapy with/without chemotherapy, or radiotherapy with/without chemotherapy with salvage surgery in reserve for residual or recurrent disease. In stage IVb inoperable disease, surgery is impossible and radiotherapy with or without chemotherapy should be considered[1]. However, more than 50% of locally advanced HNC patients relapse locoregionally or at a distant site after primary therapy[2]. Patients with distant metastatic and/or locoregionally recurrent diseases that are deemed to be incurable by surgery or radiotherapy are identified as recurrent/metastatic (R/M) HNC. For this group of patients, platinum-based chemotherapies are the first choice of treatment[3].

In 2008, Vermorken *et al.* published that the addition of anti-epithelial growth factor receptor (EGFR) monoclonal antibody to platinum-based chemotherapy was an effective regimen to prolong overall survival (OS) up to 10.1 months for R/M HNC[4]. The major problem in real-world practice is the economic issue. Hannouf *et al.* developed a model to assess the cost-effectiveness of adding cetuximab to platinum-based chemotherapy for first-line RM/HNC, and an incremental cost-effectiveness ratio (ICER) exceeded $100,000 US dollars per QALY (quality adjusted life year) gained[5]. Even in Taiwan with public health insurance famous around the world, most patients pay by themselves with an average of US$4800 dollars per month. This economic issue should be more concerning since newly developed drugs can improve the outcomes for R/M HNC but the costs are even higher. Just in 2016, the FDA approved two anti-PD1 immune checkpoint inhibitors, pembrolizumab and nivolumab, for R/M HNC progressing after platinum-based chemotherapy[6,7]. Both anti-PD1 antibodies can prolong survival for R/M HNC patients who have been refractory to first-line therapy but the average cost would be more than US$10,000 per month. The condition is similar in most developing countries and this is difficult for HNC patients because most of them have lower socioeconomic status[5,8,9].

Several alternative regimens have been tried to improve clinical outcome for R/M HNC without using novel target drugs. For example, some trials have been performed to examine a docetaxel, cisplatin and 5-fluorouracil (TPF) regimen in R/M HNC, since recent studies have shown that this triple combination therapy is a successful regimen with better outcomes than traditional cisplatin and 5-fluorouracil in an induction setting for locally advanced HNC[10,11]. However, the toxicities for R/M HNC should be of more concern in the palliative setting because docetaxel is commonly associated with myelosuppression and the continuous 96 hour infusion of 5-FU is inconvenient. Modification with dosage reduction may be a safer way to use TPF in R/M HNC but the effectiveness should be carefully evaluated.

In a phase II study, which enrolled 19 locally advanced or R/M HNC patients, it showed that, under the triple regimen, the objective response rate (ORR) could reach up to 44%[12]. In the Lin *et al.* study, which enrolled 55 Taiwanese R/M HNC patients treated with a dosage reduced docetaxel/cisplatin/5-FU (mTPF) regimen, the ORR and OS of this regimen were 56% and 10 months, respectively[13]. Yossi *et al.* also showed that dosage reduced TPF was a useful regimen for Western countries in R/M HNC treatment, with ORR 39%[14]. In the current study, Demirci *et al.* article enrolled 80 R/M HNC patients and showed that dosage reduced TPF (docetaxel 60 mg/m^2 on day 1; cisplatin 60 mg/m^2 on day 1; 5-FU 600 mg/m^2 day 1 to 5; a cycle every 3 weeks for a total of 2–6 cycles) improved ORR and OS up to 46.3% and 11.5 months, respectively[15]. Although the dosage reduction of TPF varied in different studies, all of these studies showed that dosage reduced TPF was an effective regimen as first-line R/M HNC treatment[13,14]. In addition, although the most common grade 3–4 adverse events were neutropenia (22–55%), and anemia (10–13%), these adverse events seems to be manageable, even though granulocyte-colony stimulating factor (G-CSF) support is still suggested for patients who have ever suffered from grade 3–4 myelosuppression.

Because most HNC patients have lower socioeconomic status[8,9], how to maximize the cost-effectiveness of currently available therapeutic agents is a major issue for clinics. A dosage reduced TPF regimen has been considered as an alternative first-line regimen for R/M HNC in some real-world practice. More evidence to show the effectiveness and safety profile for TPF in palliative R/M HNC therapy will provide more help in a certain group of patients.

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