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Review Article

Efficacy and safety of cetuximab sarotalocan in recurrent/locally advanced head-and-neck cancer: A comprehensive review

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ABSTRACT

Head-and-neck cancers (HNCs) are the sixth most common cancer in the world and account for 30% of all cancers in India. The emergence of monoclonal antibodies has significantly improved the outcomes of advanced HNC. Sometimes, these antibodies lack the required potency against cancer cells and added measures are needed. RM 1929 (cetuximab sarotalocan), a near-infrared photoimmunotherapy, is one of the upcoming treatment modalities that is being widely studied in recurrent HNC. It is currently approved for treatment in Japan. In this review article, we have studied various clinical trials and case reports to assess the efficacy and safety of cetuximab sarotalocan. All clinical trials examined in this article demonstrated positive clinical outcomes. Pain at the post-operative site was the most common complication; however, there was no impact on the quality of life of these patients. At present, a global phase III trial is ongoing where ASP 1929 (cetuximab sarotalocan) is being compared with the physician's choice of treatment and is expected to conclude in the second half of 2024. This article is a brief review of this new therapy with currently available efficacy data.

Keywords: Cetuximab saratolocan, RM 1929, Photoimmunotherapy, Head-and-neck cancer

INTRODUCTION

As per the Global Cancer Statistics 2020 (GLOBOCON), HNC is the sixth most common cancer in the world, with 870,000 new cases and 440,000 deaths in 2020.[1] In our country, HNC accounts for around 30% of all cancers.[2] HNC is the most common cancer diagnosed in males in India. Squamous cell carcinoma is the most common histology. Tobacco consumption is the major etiological factor in HNC. The incidence of human papillomavirus-associated HNC is increasing in the Western world, and it is anticipated that within the next two decades, cases of oropharyngeal cancer will surpass those of oral cavity cancer.[3]

In India, more than 60% of HNC patients present in the locally advanced stage.[4] Poor outcomes in these patients can be ascribed to late-stage presentation, early recurrence, lack of cancer care facilities, poor adherence to advice, and less effective salvage therapy after recurrence. This results in a dismal 5 years overall survival (OS) rate of as low as 35% among the locally advanced HNCs.[5]

BEYOND CHEMOTHERAPY IN MANAGEMENT OF HNCS

The advent of monoclonal antibodies (anti-epidermal growth factor receptor [EGFR], programmed death 1 [PD-1], and PD ligand 1 [PD-L1] inhibitors) has shown promising results in locally advanced and recurrent HNC.

Nivolumab is an anti-PD-1 monoclonal antibody. Around 20–40% of peripheral blood T-cells express PD-1 receptor, and 70–75% of these receptors are required to be occupied for its activation. The conventional dose of nivolumab is 3 mg/kg; however, it was observed that nivolumab, at a dose of 0.3 mg/kg (single dose), can achieve 70% receptor occupancy. Hence, this drug is now being investigated in lower doses across multiple cancer sites.[6] One such phase III study was conducted by Patil *et al*. HNC patients, both newly diagnosed and recurrent, who were being planned for therapy with palliative intent were randomized into two groups.[7] One arm consisted of triple metronomic chemotherapy (TMC), which included celecoxib, methotrexate, and erlotinib; the experimental arm consisted of TMC plus 20 mg intravenous nivolumab (TMC-I arm). The median follow-up was 10.9 months. Median OS in TMC and TMC-I arms was 6.7 and 10.1 months, respectively. The 1-year OS was 16.3% and 43.4% in TMC and TMC-I arms, respectively ($P = 0.0052$).[7] Based on these results, low-dose nivolumab can be considered an alternate standard of care for locally advanced/recurrent HNC patients.

Pembrolizumab is associated with improved response in patients of head-and-neck squamous cell carcinoma with PD-L1 expression. KEYNOTE 048 trial compared pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy in untreated locally incurable recurrent or metastatic HNC. In patients with PDL1 combined positive score (CPS) score >20, pembrolizumab alone improved OS versus cetuximab with chemotherapy (median 14·9 months vs. 10·7 months, $P = 0·0007$). Median OS benefit was also seen in patients with PD-L1 CPS >1. Pembrolizumab with chemotherapy also improved OS in the total population when compared to cetuximab with chemotherapy (13·0 months vs. 10·7 months, $P = 0·0034$). Neither pembrolizumab alone nor with chemotherapy improved progression-free survival (PFS) in the second interim analysis.[8]

Vascular endothelial growth factor inhibitors, including tyrosine kinase inhibitors, demonstrate immunomodulatory properties. A single-arm phase II trial studied the effect of cabozantinib combined with pembrolizumab in recurrent/metastatic HNC patients. Seventeen out of 33 patients (52%) had a partial response (PR), and 39% had stable disease, an overall response rate of 91%. Median OS was 22.3 months, and 1-year survival was 68.4%. Median and 1-year PFS were 14.6 months and 54%, respectively. Overall, the combination was well tolerated.[9]

Cetuximab is a chimeric mouse-human monoclonal antibody against the extracellular domain of EGFR that can inhibit the functions of EGFR and induce cancer cell death through antibody-dependent NK cell-mediated cytotoxicity. Cetuximab monotherapy in patients with relapsed/refractory HNC has a response rate of 13%. When combined with cisplatin, the response rate increased (10% vs. 26%) but not survival compared with cisplatin alone. The EXTREME study, which combined cetuximab with platinum (cisplatin or carboplatin) and fluorouracil, resulted in improved median PFS (5.6 months vs. 3.3 months), OS (10.1 months vs. 7.4 months), and response rates (36% vs. 20%) compared with chemotherapy alone.[10]

Frequently, these antibodies alone lack the necessary potency against cancer cells, thereby necessitating additional measures. This is where antibody-drug conjugates step in, enhancing the therapeutic potential by widening the treatment's effectiveness. In addition to this, near-infrared photoimmunotherapy (NIR-PIT) is also an emerging treatment modality in HNC patients and is being studied widely.

PHARMACOLOGY OF CETUXIMAB SARATOLOCAN

RM 1929 (cetuximab saratolocan), a NIR-PIT, which consists of an anti-EGFR chimeric monoclonal antibody, cetuximab, conjugated with IRDye 700DX, a near-infrared photosensitizing dye. Non-thermal red light (690 nm) is used to activate the dye, which results in damage to cell membrane integrity. RM 1929 is injected in the body, following which illumination of the tumor is done with non-thermal red light 24 ± 4 h after the antibody conjugate infusion. This delay is required for drug distribution within the tumor. Illumination of deep tumors (>1 cm from surface) is done by cylindrical diffusers placed in needle catheters, whereas superficial tumors (<1 cm from surface) are illuminated using frontal diffusers. Cylindrical diffusers are placed in the tumor under radiographic guidance; each catheter is placed 1.8 ± 0.2 cm apart. The illumination time for both frontal and cylindrical diffusers is 5 min for each treated area. The specific binding of the drug to EGFR of cancer cells leads to selective destruction of these cells. Moreover, light activation of RM1929 further causes rapid tumor destruction.

CLINICAL TRIALS AND APPROVALS

Cognetti *et al*. conducted a phase 1/2 trial in two parts.[11] The first part of the study was done to determine the maximum tolerated dose or maximum feasible dose of RM 1929 along with fixed light dose. The dose was escalated from 160 mg/m^2

to 320 and 640 mg/m^2 with 50 J/cm^2 for superficial lesions or 100 J/cm^2 for interstitial lesions. In part 2 of the study, a drug dose of 640 mg/m^2 with light doses the same as the ones used in part 1 was used. A dose of 640 mg/m^2 was recommended based on results from the first part of the study, which demonstrated that this dose of RM 1929 achieved adequate EGFR saturation. Thirty patients with recurrent locoregional HNC, not amenable to surgery, radiotherapy, or chemotherapy were enrolled in this study. The median age of the participants was 68.5 years with the majority male patients (80%). All 30 patients in part 2 of the trial had undergone previous surgery and radiotherapy. Seventy percent of patients received chemotherapy, and ten out of 30 patients received anti-PD-1 therapy (pembrolizumab and nivolumab). The most common site of recurrence was neck nodes (43%), followed by oral cavity (30%) and oropharynx (23%).

The unconfirmed objective response rate (ORR) was 43.3% (95% confidence interval [CI]; 25.46–62.57%). Four (13.3%) patients achieved a complete response (CR), and 9 (30.0%) patients achieved a PR. The confirmed ORR was 26.7% (95% CI; 12.28–45.89%). The median OS was 9.30 months. The most common treatment-emergent adverse effects (TEAE) were fatigue, dysphagia, constipation, erythema, and peripheral edema. Higher grade TEAE was seen in 19 (63.3%) patients, which included anemia, dysphagia, oral pain, pneumonia, application site pain, localized edema, hyponatremia, tumor hemorrhage, and tumor pain. Three deaths were reported, which were caused by tumor hemorrhage, arterial hemorrhage, and pneumonia. As per investigators, these deaths were not attributable to the treatment and were considered to occur as a result of tumor response to treatment or tumors encroaching the major blood vessels.[11]

Tahara *et al*., in a phase I single-center and open-label study, enrolled three female Japanese patients with recurrent HNC who had failed 3 or more lines of therapy.[12] The primary objective of the study was to evaluate the safety of a single cycle of RM 1929 in patients of recurrent HNC who could not be treated with surgery, radiotherapy, or chemotherapy. The same drug and light doses were used as in the study by Cognetti *et al*.[11] Two patients achieved PR, and one patient progressed on treatment. Low-grade TEAE was seen in all three patients. One patient complained of grade 3 pain at the application site, which was transiently resolved within 24 hours.[12]

Nishikawa *et al*. reported a case series of ten patients with recurrent HNC treated with photoimmunotherapy (RM 1929).[13] Seventy percent of these patients had PR, and CR was recorded in 30% of the patients. All these patients had at least one low-grade adverse event, pain and edema being the most common complications. Out of the ten patients, long-term follow-up data was available for only two patients. Both these patients had good responses without any grade 3/4 adverse effects.[13]

Okamoto *et al*. assessed the quality of life (QOL) in patients with unresectable locally advanced or recurrent HNC treated with photoimmunotherapy.[14] Nine patients were included in the study and were given QOL evaluation forms before and 4 weeks after starting treatment. The primary endpoint was the QOL assessment. This was done using the European Organization for Research and Treatment of Cancer QOL Questionnaire Core 30 Module and the QOL Questionnaire HNC Module. The secondary endpoints were ORR, OS, PFS, and adverse events. All ten patients had undergone surgery and radiotherapy, whereas only two patients had received chemotherapy. None of the patients progressed at the end of 4 weeks; however, on longer follow-up over several months, four patients progressed. There was no significant difference in QOL among these patients before and after treatment.[14]

All the studies that were conducted suggested that pain was one of the most severe TEAEs in patients receiving photoimmunotherapy. All TEAEs noted in the studies could be attributed to IR700 dye since the majority of patients experienced application site pain and edema and not generalized rashes seen with cetuximab. Shibutani *et al*. conducted a retrospective case series study to assess the pattern and severity among these patients.[15] It was observed that pain level was higher among patients who received tumor illumination through cylindrical diffusers when compared to frontal diffusers. Similarly, the need for fentanyl injections was also greater in patients where cylindrical diffusers were used. Maximum and most severe pain was experienced immediately or 1 h after tumor illumination.[15]

The other evolving treatment modality for advanced HNC is electrochemotherapy, where a chemotherapeutic agent (cisplatin or bleomycin) is instilled directly into the tumor. Short-intensity high-voltage electric pulses are then applied, which increases the cell membrane permeability, allowing better chemotherapy penetration into the tumor cells. However, this method is most suitable for superficial tumors. The other drawbacks include the risk of tumor spillage and post-treatment tissue swelling.[16]

FUTURE DIRECTIONS

There is an ongoing global phase III trial (ClinicalTrials.gov ID NCT03769506) of ASP 1929 photoimmunotherapy versus physician's choice of treatment in recurrent HNC. ASP 1929 is a drug device combination treatment, same as RM 1929. Patients who have previously received at least two lines of chemotherapy are being recruited in this trial. Physician's choice of treatment includes cetuximab, methotrexate, or docetaxel. Primary endpoints are PFS and OS; the key

secondary endpoint is ORR. Patients will receive a maximum of 8 cycles within a span of 12 months, each cycle not <4 weeks apart. This trial is being conducted in the USA, EU, and Asia and is expected to conclude by September 2024. In India (CTRI/2023/05/052728), recruitment is ongoing at cancer centers in Gujarat and Tamil Nadu.

CONCLUSION

RM 1929 showed significant efficacy in patients with recurrent/unresectable HNCs with tolerable side effects. Further phase III trials will provide a more detailed understanding of its therapeutic benefits.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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