TECHNICAL REPORT

Intra-arterial cetuximab for the treatment of recurrent unresectable head and neck squamous cell carcinoma†

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Importance: Management of recurrent head and neck squamous cell carcinoma is a common and challenging clinical problem in head and neck oncology.

Objective: Here we present the first reported case of super-selective intra-arterial (SSIA) microcatheter based local delivery of cetuximab for head and neck cancer. This technical report describes the techniques used to deliver the SSIA dose of cetuximab, as well as the patient outcome.

Design: This technical report is part of an ongoing Phase I Clinical Trial

Setting: The New York Head and Neck Institute (NYHNI) is a full-service otolaryngology and neurosurgery department at Lenox Hill Hospital, part of the Northwell Health System. The NYHNI serves a diverse patient population with a wide range of head and neck diseases in a tertiary hospital setting.

Intervention: SSIA Cetuximab

Participant: A patient presents to our clinic with recurrent unresectable squamous cell carcinoma of the nasopharynx. He is recruited into the first cohort of a phase I clinical trial to assess the safety of SSIA cetuximab, dose starting at 100mg/m². Adjuvant chemoradiation therapy is also given.

Main Outcome(s) and Measures: Safety, as measured by toxicity of SSIA cetuximab.

Results: SSIA Cetuximab has been demonstrated to be a safe and feasible procedure in this technical report.

Conclusions and Relevance: This case illustrates technical feasibility and a very preliminary assessment of the safety of a novel delivery of a biologic agent for squamous cell carcinoma of the head and neck, which is part of an ongoing phase I clinical trial.

Trial Registration: NCT02438995

Keywords: Intra-arterial, head and neck cancer, nasopharyngeal cancer, squamous cell carcinoma, cetuximab, recurrent squamous cell carcinoma, Phase I clinical trial
INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) represents roughly 3% of all new cancers diagnosed in the United States, with squamous cell carcinoma accounting for approximately 95% of all head and neck carcinomas. (1) Various molecular and genetic alternations are known to play a significant role in the pathogenesis of HNSCC. (2) Notably, patients with high epidermal growth factor receptor (EGFR) levels are known to have shorter overall and progression free survival with EGFR expression being detectable in 95% of HNSCC. (3,4)

The monoclonal antibody cetuximab targets EGFR, and has been used in the treatment of many different kinds of cancer including HNSCC, as well as colorectal cancer, and glioblastoma multiforme. (5-13) Cetuximab has been established as a first line treatment along with radiation therapy in loco-regionally advanced HNSCC as well as front line in the treatment of recurrent or metastatic HNSCC when used in combination with platinum based chemotherapeutics. (7,9,14)

For the many patients with unresectable and/or recurrent tumors, the disease is uniformly fatal, and the typical median survival is 6 months. (15) Chemotherapy plays only a role in palliative management, but does not provide good long-term outcomes. (16)

One method, which has shown promising outcomes in various other neoplasms, is the use of intra-arterial (IA) chemotherapy in order to deliver selective and locally concentrated doses and minimize systemic toxicity. Most previous IA studies have used platinum-based chemotherapeutics, which have a known significant toxic profile.(17,18)

Here, we present a technical report of a patient with unresectable recurrent squamous cell carcinoma who received IA delivery of cetuximab (Erbitux, Eli Lilly & Co, Indianapolis, IN, USA) as part of an approved phase I clinical trial (NCT02438995) to determine drug safety and tolerability. This clinical trial was ethically approved by the Institutional Review Board (IRB) of the Feinstein Institute of Medical Research.

SETTING

The New York Head and Neck Institute (NYHNI) is a full-service otolaryngology and neurosurgery department at Lenox Hill Hospital, part of the Northwell Health System. The NYHNI serves a diverse patient population with a wide range of head and neck diseases in a tertiary hospital setting.

HISTORY AND PRESENTATION

A 38-year old Asian male presented to our clinic with recurrent nasopharyngeal carcinoma (NPC). He had a known history of Epstein Barr Virus (EBV) positive undifferentiated non-keratinizing nasopharyngeal cancer (NPC) that was originally diagnosed in December 2013 after the patient experienced epistaxis and nasal congestion.

The patient’s initial tumor was Stage IV-A, T4N2M0. The extent as delineated by PET/CT was centered mainly in nasopharynx along the left fossa of Rosenmuller. There was also extensive skull base involvement, intracranial extension, bilateral retropharyngeal and level II cervical lymphadenopathy. The patient’s past medical history was non-contributory except for tuberculosis which resolved more than 10 years prior to this presentation.

The patient subsequently completed radiation therapy (RT) 1-year prior and chemotherapy 9 months prior to presenting at our clinic. Radiotherapy consisted of RapidArc RT to the bilateral neck, 57Gy given in 30 fractions at 1.9Gy/fraction; RapidArc RT to the supraclavicular regions at 50Gy given in 25 fractions at 2Gy/fraction with a 6Gy boost bilaterally; Gross disease in nasopharynx received an additional dose of 15.4Gy in 7 fractions at 2.2Gy/fraction. Concurrent chemotherapy was given in 26 cycles, each cycle consisting of 7 days. Cisplatin was given on day 1 of each cycle at 40mg/m².

The patient had a complete response to this initial treatment, as measured by CT scan. However, routine follow-up PET imaging done 6 months after this initial treatment showed recurrence demonstrated by significant FDG uptake in the left skull base, left post-rotalateral nasopharynx and right retropharynx. (Figure 1D). MRI performed soon after confirmed a pathologic right lateral retropharyngeal lymph node and soft tissue fullness in the left lateral retropharyngeal region compatible with either parapharyngeal recurrence of the primary tumor, or retropharyngeal nodal disease (Figure 1A-C). The patient had been experiencing left hearing loss and his exam was significant for left middle ear serous effusion.

Biopsy performed in April 2015 confirmed the recurrence, a non-keratinizing NPC, differentiated type (WHO 2A). The location and extent of the patient’s recurrent disease was deemed unresectable. After a thorough discussion of his treatment options, the patient and his family elected to enroll in the IA cetuximab clinical trial.

OPERATIVE COURSE

The patient received two treatments of IA cetuximab three weeks apart.
The patient was part of a dose cohort with a pre-assigned IA cetuximab dose of 100mg/m², which would be infused at a rate of no more than 3-4mL/minute. Premedication with an H1 antagonist (Benadryl 50mg) was given intravenously 30-60 minutes prior to administration of cetuximab. 100mg of oral Doxycycline was also given as prophylaxis to prevent integumentary associated drug toxicities, (19) a well-recognized complication of cetuximab.

**Figure 1.** Pre-IA cetuximab. Axial pre-contrast (A) and post-contrast (B) T1-weighted MRI images demonstrate a heterogenously enhancing right lateral retropharyngeal lymph node (solid white arrow) as well as non-enhancing left lateral retropharyngeal fullness (dashed white arrow). Axial STIR image (C) demonstrates heterogenous high signal in the right lateral retropharyngeal node, while the left sided process is isointense. Both areas demonstrate FDG avidity on the PET image (D).

**IA cetuximab first cycle**

The MRI was reviewed and it was decided that the primary supply to the tumor was from the left internal maxillary artery as well as bilateral ascending pharyngeal arteries. Digital Subtraction Angiography (DSA) examination in the AP and lateral projections of the right ascending pharyngeal artery demonstrated a large ascending pharyngeal branch...
Figure 2. Selected angiographic images represent the approach of the super selective intra-arterial (SSIA) cetuximab infusion. (A) DSA examination in anterior-posterior (AP) view of the left internal maxillary artery at the site of SSIA cetuximab injection. There is no evidence of tumor blush. (B) DSA examination (lateral view) of the left internal maxillary artery at the site of the SSIA cetuximab. There is no evidence of tumor blush. (C) DSA examination (AP view) of the left ascending pharyngeal artery at site of SSIA of cetuximab. There is no evidence of tumor blush. (D) DSA examination (lateral view) of the left ascending pharyngeal artery at the site of SSIA of cetuximab. There is no evidence of tumor blush. (E) DSA examination (AP view) of the right ascending pharyngeal artery at the site of SSIA of cetuximab. There is evidence of hypervascularity and early venous drainage consistent with tumor blush. (F) DSA examination (lateral view) of the right ascending pharyngeal artery at the site of SSIA of cetuximab. There is evidence of hypervascularity and early venous drainage consistent with tumor blush.
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with prominent venous drainage. The left Internal Maxillary Artery (IMAX) received 66ml of cetuximab (Figure 2 A, B), left ascending pharyngeal received 8ml (Figure 2 C, D), the right ascending pharyngeal received 8ml (Figure 2 E, F). After all injections, the post cetuximab DSA examinations demonstrated no changes when compared to the previous angiograms.

Figure 3. Post-IA cetuximab. Axial pre (A) and post (B) contrast T1-weighted images and axial STIR image (C) demonstrate no change in size or imaging features of right lateral retropharyngeal lymph node (solid white arrow) with slight decrease in volume of left lateral retropharyngeal soft tissue (dashed white arrow). PET image (D) shows resolution of FDG uptake in left lateral retropharyngeal region (dashed white arrow), with persistent uptake in right lateral retropharyngeal lymph node (solid white arrow).

IA cetuximab second cycle

The second cycle of cetuximab used the same approach as the first. During the second cycle, 65ml of cetuximab was infused into the left IMAX over 8 minutes. Following that, 9ml of cetuximab was then injected into the left ascending pharyngeal over 3 minutes followed by a 9ml injection into the right ascending
pharyngeal over 4 minutes. Post infusion DSA examination of all 3 arteries after the injection of cetuximab was stable when compared to the previous angiogram.

PATIENT OUTCOME

The patient experienced no drug related toxicities from this treatment, nor were there any endovascular complications. Imaging was performed one month after both sessions of IA cetuximab. MRI findings were stable (Figure 3A-C). PET/CT scan showed persistent activity in the region of the right lateral retropharyngeal node. However, there was diminished FDG uptake in the left lateral retropharyngeal region (Figure 3D) when compared to the previous PET scan (Figure 1D).

The patient’s case was discussed during a multidisciplinary tumor board, and it was decided that the best further management of this patient would be for another course of re-irradiation and chemotherapy. Two months after re-irradiation and chemotherapy, imaging showed continued resolution of right lateral retropharyngeal lymph node with persistent though diminished fullness left lateral retropharyngeal soft tissues. PET image (D) demonstrates complete resolution of FDG uptake.

Figure 4. Post-RT and chemo. Axial pre (A) and post (B) contrast T1-weighted images and axial STIR image (C) demonstrate resolution of right lateral retropharyngeal lymph node with persistent though diminished fullness left lateral retropharyngeal soft tissues. PET image (D) demonstrates complete resolution of FDG uptake.
after the patient’s dose of IA cetuximab, he was started on concurrent chemoradiotherapy. Radiotherapy (RT) was delivered via intensity-modulated radiation therapy (IMRT) protocol to the nasopharynx and bilateral retropharyngeal lymph nodes, with 60 Gy given in 30 fractions at 2 Gy/fraction. Chemotherapy was given in 6 cycles, each cycle consisting of 7 days. Carboplatin was given on day 1 of each cycle at 2 AUC; Paclitaxel was given on day 1 of each cycle at 30 mg/m².

After the patient completed the IMRT and carboplatin-paclitaxel regimen, he was started on an additional regimen of carboplatin-capecitabine chemotherapy. This consisted of 3 cycles of 28 days each. Carboplatin was given on day 1 of each cycle at 6 AUC; Capecitabine was given on day 1 to day 14 of each cycle at 850 mg/m².

After the patient completed 2 of the 3 planned cycles of adjuvant chemotherapy, he went for his scheduled follow up MRI and PET/CT scans. MRI demonstrated resolution of the previously identified pathological right retropharyngeal lymph node with persistent but diminished fullness in the left lateral retropharyngeal region (Figure 4A - C). Concurrent PET/CT showed no significant areas of FDG uptake, with resolution of activity in the right lateral retropharyngeal node (Figure 4D). On comparison with the prior PET images (Figures 1D, 3D), complete resolution of FDG uptake was felt compatible with complete response.

At the time of publication, the patient is currently well without having experienced any treatment related toxicities from any of his treatments. He is currently being monitored with follow up MRI and PET scans done in 6 and 12 month intervals respectively.

**DISCUSSION**

Roughly two thirds of patients with HNSCC show locoregionally-advanced disease at presentation and despite aggressive management, up to 60% of patients will develop local disease failure. (20) Surgery plus radiotherapy has been the mainstay of treatment of HNSCC. However, the incorporation of systemic agents, especially those that have selective targets, has led to improved outcomes showing significant benefit in loco-regional control and recurrent disease. (21-23)

In locoregionally advanced primary disease, outcomes show that cetuximab plus radiotherapy is superior to radiotherapy alone at 5-year outcomes. (24) That being said, palliative therapy with both platinum-based cytotoxic agents and cetuximab results in a median survival of 10 months. (21) In the TREMPLIN study, the efficacy of chemotherapy versus biotherapy was compared in patients undergoing treatment of HNSCC for laryngeal preservation. There was no superiority shown between treatment groups. However, treatment compliance was higher in the cetuximab arm. (25)

Importantly, unresectable disease still remains a challenge in the treatment of HNSCC. In the case of loco-regionally-advanced and unresectable disease numerous meta-analyses have shown that chemo radiation therapy is superior to radiation therapy alone. (22,26,27)

Phase II studies using intra-arterial cisplatin for locally advanced head and neck cancer have had promising results. (17,28,29) However, a follow up phase III trial showed no benefit to using IA Cisplatin over IV chemoradiation with the overall toxicity in the two arms begin comparable. (18) The results of this trial have been controversial; since the intra-arterial infusions were divided between both carotid arteries, there was the possibility of suboptimal infusion of chemotherapy in the IA patients, which could have accounted for the negative result. (30) Furthermore, the HPV status of their patients was not established which could have further confounded the results.

This is the first reported attempt at intra-arterial biotherapy in the treatment of HNSCC. The use of intra-arterial cetuximab has previously been used as salvage therapy for hepatocellular carcinoma in combination with 5-fluorouracil and cisplatin, and the toxicity profile was found to be acceptable with no grade 4 toxicities noted in any of the 12 patients. (31) Considering the toxicity of systemic molecularly targeted therapy the use of intra-arterial drug administration may benefit patients by potentially reducing systemic toxicity.

**CONCLUSION**

This is the first reported use of intra-arterial delivery of cetuximab for the management of head and neck cancer. This treatment methodology allows for selective high dose biotherapy, which leads to increased local dosage plus the potential for lower systemic side effects. In this technical report, safety of IA cetuximab has been demonstrated in one patient. Anti-tumor activity with complete resolution was also demonstrated in combination with adjuvant chemoradiotherapy. Completion of the phase I clinical trial is needed to ascertain the safety of IA cetuximab for patients with recurrent unresectable HNSCC.

**REFERENCES**


