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Review Article

The dogma of Cetuximab and Radiotherapy in head and neck cancer – A dawn to dusk journey

Sapna Krishnamurthy [a,*], Imtiaz Ahmed [a], Rohan Bhise [b], Bidhu K Mohanti [c], Atul Sharma [d], Thorsten Rieckmann [e], Claire Paterson [f], Pierluigi Bonomo [g]

[a] Department of Radiation Oncology, KLES Belgaum Cancer Hospital & KLES Dr Prabhakar Kore Hospital and MRC, Belgaum, Karnataka, India
[b] Professor of Medical Oncology, JN Medical College, KLES Belgaum Cancer Hospital & KLES Dr Prabhakar Kore Hospital and MRC, Belgaum, Karnataka, India
[c] Professor of Radiation Oncology and Director, KIMS Cancer Centre, Kalinga Institute of Medical Sciences, Bhubaneshwar, Orissa, India
[d] Professor of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India
[e] Department of Otorhinolaryngology and Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg-Eppendorf, Germany
[f] Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow G12 0YN, UK
[g] Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

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ABSTRACT

Since the introduction of Cetuximab as a biological molecule against Epidermal Growth Factor Receptor (EGFR), its use in the cancers of head and neck region is widely explored. With the recognition that EGFR expression is associated with radioresistance and poor prognosis, incorporation of an anti-EGFR agent along with Radiotherapy (RT) is a logical and attractive option. Cetuximab in combination with RT as Bio-Radiotherapy (BRT) is considered one of the standard treatment modalities in Locally Advanced Head and Neck Squamous Cell Cancers (LA-HNSCC). Many important phase-III clinical trials were undertaken simultaneously, where the use of Cetuximab BRT was tested in various clinical scenarios with different hypothesis. With the studies still ongoing and the results awaited, its use was continued in clinical practice. Today the results are out and definitely not encouraging. After the initial success, Cetuximab has miserably failed to win over cisplatin based chemoradiation which is the current standard of care in LA-HNSCC. Hence, it is the need of the hour to re-evaluate and define the present role of Cetuximab in the definitive management of LA-HNSCC in the light of the latest clinical evidence..

1. Introduction

Treating Locally Advanced Head and Neck Squamous Cell Cancer (LA-HNSCC) is a challenge, requiring multimodality approaches. Traditionally, surgery followed by post-operative radiotherapy has been the standard [1]. With the concept of organ preservation; growing knowledge of interaction between radiotherapy (RT) and chemotherapy; newer insight into tumor biology - like association of epidermal growth factor receptor (EGFR) over-expression, there has been re-emergence of curative RT. RT in the form of altered fractionation [2] or in combination with chemotherapy as concurrent chemo-radiation (CCRT) [3] or in combination with targeted therapy as bio-radiotherapy (BRT) [4] are the current standard of care in non-oral cavity LA-HNSCC in many countries. As of today, with the robust evidence supporting CCRT [3] the role of BRT with anti-EGFR monoclonal antibodies (mAbs) must be revisited.

Since the results of Bonner study (IMCL 9815) [4], the use of Cetuximab (a mouse–human chimeric mAb) with RT has become one of the standard treatment regimens. Though initially its use was mostly limited to patients who would not tolerate high dose chemotherapy, over time its use has been explored in varied indications and combinations – as a de-escalation strategy in human papilloma virus (HPV) positive disease [5,6], as treatment intensification with standard CCRT [7,8] or direct comparison with standard CCRT [9,10]. While awaiting these results, Cetuximab-RT has been used as an alternate to CCRT. Today results of these trials are out and none of them support the routine use of Cetuximab in the curative setting. But there seems to be no loud noise in announcing the failure unlike the jazz which was played when the trials were started. Hence, it is highly pertinent to discuss the rise and fall of Cetuximab in the management of LA-HNSCC.

In this article we attempt to review and critically analyze the use of Cetuximab and RT in the definitive treatment of LA-HNSCC.

* Corresponding author.
E-mail address: sapna.imtiaz@gmail.com (S. Krishnamurthy).

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2. Overview of Cetuximab in head and neck cancer

2.1. EGFR in head and neck cancers

Epidermal Growth Factor Receptor – EGFR is a transmembrane protein belonging to Erb B family of receptor tyrosine kinases. It modulates the growth signals from growth factors like Epidermal Growth Factor and Transforming growth factor alpha triggering a cascade of intracellular events that lead to cellular proliferation, survival, differentiation and migration. Cancer cells escape this highly regulated mechanism by over-expression or receptor mutations leading to constitutive receptor activation in part without the need for ligand binding [11].

Over-expression of EGFR is seen in many epithelial cancers including cancers of the head and neck region [12]. It is associated with not only aggressive behavior and poorer outcomes [13] but also resistance to RT [14,15]. It is also seen that RT itself can induce increased expression of EGFR leading to acquired resistance [16]. Treatment with Cetuximab enhanced the radio-response in preclinical studies [17,18]. Hence, combining Cetuximab and RT is logical and proven.

2.2. Cetuximab

Cetuximab is a recombinant chimeric IgG1 monoclonal antibody against the ligand binding domain of EGFR. It binds with 10-fold higher affinity to EGFR than the normal ligands preventing both homo and hetero-dimerization of EGFR leading to inhibition of auto-phosphorylation and inhibition of EGFR signaling. It is administered intravenously starting with a loading dose of 400 mg/m^2 one week before RT and then weekly at 250 mg/m^2 concurrent with RT. Mild to moderate infusion reactions, skin rashes on face and upper body are some of the common adverse effects [19].

2.3. Radiobiological rationale of CCRT and BRT

The strategy of combining chemotherapeutic agents with RT is one of the major breakthroughs in the modern day oncology practice backed by strong biologic rationale. Steel and Peckham [20] classified this strategy into four groups – 1.spatial cooperation, 2.independent toxicity, 3. enhancement of tumour response and 4.protection of normal tissues (e.g. amifostine). Concurrent addition of cisplatin to RT uses the 3rd principle - chemotherapy enhancing the tumour response of RT as they interact at the molecular, cellular or patho-physiologic level resulting in an augmented anti-tumour effect. This effect is beyond the mere additive effect of each of the modalities leading to supra-additive or synergistic effect [21]. Enhancing tumour response by counteracting determinants associated with radio-resistance like EGFR over-expression is also a major rationale which is used in BRT, which probably fits into spatial cooperation.

A randomly selected agent cannot be incorporated for use along with RT but rather has to undergo vigorous testing in in-vitro and in-vivo preclinical studies before they can have a meaningful clinical use. At the same time it is obvious that when two treatments are delivered simultaneously associated toxicities are likely accentuated. Thus, the combination that gives a good therapeutic ratio should be the treatment of choice.

In this regard cisplatin is the most commonly used chemotherapeutic agent in the CCRT of LA-HNSCC. It has been extensively investigated in preclinical studies as a potent radio-sensitizer [22] that has demonstrated a meaningful benefit in the clinical setting too [3].

Anti-EGFR mAbs are the biological response modifiers used concurrently with RT as BRT in LA-HNSCC and Cetuximab is the most commonly used mAb.

Each of these combinations has their unique way of interaction with RT with different therapeutic and toxicity profile.

2.4. Cetuximab and radiation interaction

Preclinical studies by Huang [17] and Milas [18] have demonstrated that Cetuximab binds to EGFR inhibiting it and thereby enhances the radiation response by - inhibition of DNA repair [23], amplification of radiation induced apoptosis and necrosis, inhibition of tumour angiogenesis, immune mediated cell death as evidenced by tumour infiltration with granulocytes, recruitment of antigen dependent cellular cytotoxicity (ADCC) and complement mediated cellular lysis. These effects were observed in both single and fractionated RT interpreted as counteracting radioresistance induced by over expression of EGFR.

3. Evolution of the clinical use of BRT

Results with RT alone in LA-HNSCC were not encouraging. There was constant research to better this in the late 1990 s and early 21st century. With the identification of EGFR and its implications on the tumour biology and treatment of head and neck cancers, the concept of targeted therapy was gaining momentum. Growing concerns regarding accentuated toxicities associated with CCRT and possible better safety profile of anti-EGFR mAbs, paved way to combine Cetuximab and RT, marking the beginning of the BRT era. Since then, the use of Cetuximab and RT has been studied in varied combinations with varied hypothesis in the definitive management of LA-HNSCC. Some of the important trials are discussed here.

3.1. Bio-radiotherapy

The IMCL 9815 trial published by Bonner et al. [4], was a phase 3 trial demonstrating clear benefit of Cetuximab in the definitive management of LA-HNSCC. Here, Cetuximab-RT was compared with RT alone. The study arm showed a better median loco-regional control (LRC) of 24 months ($p = 0.005$) compared to RT alone (14.9 months) and a better overall survival (OS) of 49 months vs 29 months (32% and 26% risk reduction in disease progression and death respectively). Long term data showed an absolute 5 year OS benefit of 9.2% [24], which is similar to the benefit observed upon addition of cisplatin [2,3], without substantially increasing the adverse effects. Thus Cetuximab-RT became one of the standards of care in the management of LA-HNSCC.

In 2016 a sub-analysis of this trial compared the outcome in 182 patients with oropharyngeal tumors and available p16 status as a surrogate for HPV-induced carcinogenesis [25]. While it was concluded that the addition of Cetuximab to RT increased LRC, OS, and progression free survival (PFS) in both cohorts, the benefit was far more pronounced for those with p16 positive tumors (3 year OS: HR 0.38 vs. 0.93).

3.2. Dose intensification

As anti EGFR mAbs sensitized tumours to cisplatin [26] and radiation [17,18] treatment intensification with addition of Cetuximab to CCRT was tested in Radiotherapy Oncology Group (RTOG) 0522 trial [7]. CCRT was accelerated fractionation and cisplatin − 2 cycles (100 mg/m^2). Cetuximab + Cisplatin + RT arm showed more frequent treatment interruptions (29% v/s 10%, $p = 0.001$) and more grade 3–4 toxicities than cisplatin-RT regimen without any statistically significant OS or LRC benefit (3Y OS 72.9% v/s 75.8%, $P = 0.32$). Hence, RTOG 0522 strongly recommended against the use of Cetuximab-Cisplatin-RT regimen. Of mention is that 70% of the oropharyngeal primaries had HPV positive tumours.

GORTEC 2007-01 [8] evaluated whether the addition of Carboplatin and 5- Fluoro Uracil (5FU) chemotherapy to Cetuximab-RT was of any benefit compared to Cetuximab-RT alone. This trial was restricted to patients with N0-N2a and non-clinically palpable N2b disease. 3 year PFS was 53% v/s 40% ($p = 0.017$) in the CT + Cetuximab + RT arm but no OS benefit was demonstrated. Acute grade 3 toxicities, feeding tube dependence and frequent hospitalization (42% v/s 22%, $p = 0.001$)

were high in CT + Cetuximab + RT arm including 10 treatment related deaths. It also has to be noted that this study had late accrual, high event rate, and the hazard ratio (HR) for PFS was more than the targeted HR. Authors concluded that considering the current standard of care, the trial could have a limited clinical impact. But, for patients not eligible for high-dose Cisplatin (impaired renal or hearing functions) and considered for Carboplatin plus FU, addition of Cetuximab-RT can still be used keeping in mind the increased probability of toxicities. However, it needs to be considered that since Cetuximab was included in both arms; increased efficacy through Cetuximab cannot be directly concluded.

3.3. De-Escalation strategy in HPV positive patients

The subset of oropharyngeal cancer patients who have HPV positive tumours, form a separate cohort having favourable outcomes. They are young and have higher survival with standard high dose CCRT. For the fear of long term toxicities and to better the quality of life (QOL), many de-escalation strategies are being studied. One among them is to replace cisplatin with Cetuximab whereby reducing the toxicities without altering the outcomes. The relative risks and benefits of this protocol were studied almost simultaneously in US and Europe in RTOG 1016 [5] and De-ESCALaTE HPV [6] studies respectively and also in Trans-Tasman Region [27].

RTOG-1016 was a non-inferiority trial comparing Cetuximab-RT with Cisplatin-RT exclusively in HPV positive oropharyngeal cancers. RT was delivered in accelerated fractionation (70 Gy in 35 fractions at 6 fraction/week) and chemotherapy consisted of 2 cycles of high dose cisplatin (100 mg/m^2). Cetuximab-RT arm showed inferior OS, PFS (5Y PFS – 67% v/s 78%, P = 0.0002) and higher loco-regional failure (LRF) rates (5Y 17% v/s 9.9%, P = 0.0005). Though toxicity profile were different, grade 3 or more acute toxicity rates did not differ (81.7% v/s 77.4%, p = 0.16).

De-ESCALaTE HPV aimed to compare mainly the treatment toxicities of Cetuximab-RT and Cisplatin-RT affecting long term QOL and to show that Cetuximab could be a less toxic alternative. All were low-risk HPV positive (non-smokers or lifetime smokers with a smoking history of <10 pack-years) oropharyngeal cancer patients. RT was delivered in conventional fractionation (70 Gy in 35 fractions) and chemotherapy consisted of 3 cycles of 3 weekly Cisplatin (100 mg/m^2). Here again 2Y OS (89% v/s 97.55, P = 0.0012) was lower and recurrence rates were higher (18% v/s 6%, P = 0.0007). Grade 3–5 toxicities were similar in both the groups - the mean number of events per patient was 4.8 (p = 0.98) though toxicity profiles were different. In post hoc analysis, stage III patients as per AJCC 8th edition had a larger 2 year OS detriment with Cetuximab (67% v/s 93%, p = 0.03).

The study from Australia-New Zealand by the Trans-Tasman Radiation Oncology Group (TROG) 12.01 [27] also looked into symptom severity in low-risk HPV positive oropharyngeal cancer, comparing Cetuximab and RT with weekly cisplatin (40 mg/m^2). There was no difference in the primary endpoint of symptom severity between the two arms (p = 0.66) with the T-score (mean number of > grade 3 acute adverse events) of 4.3 in the cisplatin arm and 3.8 in the Cetuximab arm, (p = 0.10). The 3 -year failure-free survival (FFS) was 80% v/s 93% in the Cetuximab v/s weekly cisplatin arm (p = 0.015); and concluded that Cetuximab had inferior FFS without improvement in symptom burden or toxicity compared to weekly Cisplatin-RT.

All of these studies demonstrated that Cetuximab use was detrimental compared to cisplatin based chemotherapy in HPV positive oropharyngeal tumours.

3.4. Comparison with Chemoradiation

Once the updated results of MACH-NC *meta*-analysis were published in 2009 [28], many studies were undertaken to directly compare Cetuximab-RT with CCRT. One such phase III study was ARTSCAN III [9], comparing Cetuximab-RT with CCRT with weekly cisplatin (40 mg/m^2). Even before the planned analysis, the study was prematurely closed as results of contemporary retrospective study [29] was published that showed inferiority of Cetuximab-RT regimen. The comparative arm in this study used 40 mg/m^2 dose of weekly Cisplatin with standard Dose RT. Here again, 85% of the cases constituted oropharyngeal primary and 90% of these were HPV positive. 3 year LRF was 23% v/s 9% (p = 0.003), hence concluded that Cetuximab-RT is inferior to even weekly Cisplatin-RT.

3.5. Cetuximab in induction and adjuvant chemotherapy

GORTEC 2007-02 [10] tested whether induction chemotherapy followed by BRT was superior to Chemoradiation. Induction chemotherapy consisted of 3 cycles of TPF regimen (Docetaxel, Cisplatin and 5FU) followed by Cetuximab-RT versus CCRT with Carboplatin-5FU. This trial was restricted to heavy nodal disease – N2b (clinically palpable nodes), N2c and N3. There was no difference in the 2 year LRC or PFS or OS between the two arms. Acute toxicities were more in the study arm with 12 fatalities. Almost 20% of patients receiving TPF did not receive RT; hence, the authors concluded that this particular regimen did not improve outcome.

Delos-II [30] was a randomized phase 2 study conducted to prove the hypothesis that Cetuximab when added to induction chemotherapy and RT improves Laryngectomy-free survival in patients with advanced larynx or Hypopharyngeal cancer. Sixteen weeks of Cetuximab was given with TPF induction regimen and RT compared with Induction chemotherapy followed by RT alone. Addition of Cetuximab did not show superior Laryngectomy-free survival (2Y 46% v/s 47%) but had high rates of adverse event (even 4 deaths) compelling the investigators to omit the 5-Fluoro-uracil component from the TPF regimen.

Another phase II study [31] evaluated the role of 12 week maintenance Cetuximab with the hypothesis that maintenance Cetuximab could play a role in hampering the viability of a possible residual disease after a curative intent treatment with RT and Cetuximab in patients with locally advanced oropharynx cancers. Though 1 year LRC in the maintenance arm were slightly higher – 59% v/s 47% (p = 0.25) it could not be maintained in the second and third year were the LRC were 44% v/s 44% and 37% v/s 38% respectively. The authors concluded that maintenance Cetuximab may reduce the aggressiveness of the minimal residual disease but is not enough to eliminate it, and it will finally reappear.

Time and again, most of the hypotheses to fit Cetuximab in all of the 3 domains – Concurrent, Induction and Adjuvant setting in the definitive management of LA-HNSCC have been proven to be futile.

Salient features of these studies are depicted in Table 1 for comparison.

3.6. Other anti-EGFR mAbs

Many similar Anti-EGFR mAbs other than Cetuximab have been clinically studied in the management of LA-HNSCC as BRT.

Concert 1 and 2 [32,33] trials were amongst the first non-Cetuximab BRT trials. Both are phase 2 trials evaluating Panitumumab which is a fully human anti-EGFR mAb. Concert 1 [32] tested treatment intensification with panitumumab (9 mg/kg X 3 cycles) added to cisplatin (75 mg/m^2 X 3 cycles) and RT with standard high Dose (100 mg/m^2) and RT. 2 year LRC was 61% in panitumumab arm v/s 68% in the cisplatin arm (p = NS). Toxicities were high with almost 40% patients could not complete the treatment in Panitumumab arm. Hence, no benefit only toxicities were documented. Concert 2 [33] compared panitumumab and accelerated RT with high dose cisplatin (100 mg/m^2 X 2 cycles) and accelerated RT. 2 year LRC was 51% in panitumumab arm v/s 61% in the cisplatin arm (p = 0.06). The authors concluded that panitumumab cannot replace Cisplatin.

Canadian HN.6 study [34] was a phase 3 study which compared panitumumab and accelerated RT with standard high dose cisplatin

Table 1
Cetuximab – Bio-Radiotherapy Phase III Trials.

Trials	Study years	Study arms	Chemo therapy	HPV positive [a]	Median F/U (years)	Progression free survival	Overall survival	Comment
IMCL 9815	1999–02	RT + CET RT	–	41%	4.5	–	55% v/s 45%[b,e]	Cetuximab is better
RTOG 0522	2005–09	RT + CIS + CET RT + CIS	3 weekly Cisplatin	70%	3.8	59% v/s 61%[c,e]	76% v/s 72%[c,e]	No benefit More toxicity
GORTEC 2007–01	2008–14	RT + CT + CET RT + CET	Carboplatin +5 FU	21%	4.4	53% v/s 40%[b,e]	61% v/s 55%[c,e]	No OS benefit CT - different
GORTEC 2007–02	2009–13	TPF → RT + CET RT + CT	Carboplatin +5 FU	21%	2.8	32% v/s 32%[c,e]	38% v/s 42%[c,e]	No benefit More toxicity
RTOG 1016	2011–14	RT + CET RT + CIS	3 weekly Cisplatin	100%	4.5	67% v/s 79%[b,f]	78% v/s 85%[b,f]	Cetuximab is Detrimental
DE-ESCALATE	2012–16	RT + CET RT + CIS	3 weekly Cisplatin	100%	2.1	–	89% v/s 97%[b,d]	Cetuximab is Detrimental
ARTSCAN III	2013–18	RT + CET RT + CIS	Weekly Cisplatin (40 mg/m^2)	90%	3.1	67% v/s 88%[b,e]	78% v/s 88%[c,e]	No benefit of Cetuximab
TROG 12.01	2013–18	RT + CET RT + CIS	Weekly Cisplatin (40 mg/m^2)	100%	4.1	80% v/s 93% [b,e]	–	Cetuximab is Detrimental

CET – Cetuximab; CIS – Cisplatin; CT – Chemotherapy; TPF – Docetaxel, Cisplatin and 5-Fluoro Uracil.
a = among oropharyngeal primary; b = p value significant; c = p value not significant; d = 2Y; e = 3Y, f = 5Y.

CCRT. There was no significant difference in 2 year PFS and OS (79% v/s 75% and 85% v/s 88%). Toxicity rates were similar but with different toxicity profiles. Here again non-inferiority or superiority of Panitumumab-RT was not demonstrated.

While most of the BRT studies come from US or European regions, Indian study [35] is the only study from south-east Asian Region where tobacco related and HPV negative tumours are more common. Addition of humanized anti-EGFR mAb - Nimotuzumab to weekly cisplatin CCRT was compared with weekly Cisplatin-RT regimen. 2 year LRC and PFS favoured nimotuzumab arm (LRC-67% v/s 57%, p = 0.006; PFS-62% v/s 50%, P = 0.003), though there was no OS benefit. Toxicities were slightly more in the study arm but not statistically significant. Only 10% of the Oropharyngeal tumours showed HPV positive status. Subset analysis in HPV negative Oropharyngeal tumours [36] showed a higher magnitude of benefit with respect to LRC, PFS and OS (2 year PFS 57.2% v/s 31%, p = 0.001). The authors concluded that addition of nimotuzumab to weekly cisplatin CCRT is beneficial more so in HPV negative tumours and proposed this as an alternative regimen to high dose Cisplatin CCRT.

Danish Head and Neck Cancer group (DAHANCA) – 19 [37] evaluated anti- EGFR-1 mAb – Zalutumumab (8 mg/kg) given weekly with accelerated RT and concomitant daily hypoxic Radio-sensitization with Nimorazole (Stage III-IV carcinomas received weekly cisplatin 40 mg/m^2 during RT); in comparison with RT + Nimorozole (+CT). The 3-year LRC was 78% in the Zalutumumab-arm vs 79% in the control-arm (p = NS) and did not show any PFS or OS benefit.

Salient features of these studies are depicted in Table 2 for comparison.

3.7. *Small molecule tyrosine Kinase Inhibitors (TKIs)*

TKIs inhibit EGFRs by targeting the receptor tyrosine kinases [38] and thereby interrupting intracellular signal transduction. Drugs like Gefitinib [39], Erlotinib [40] and Lapatinib [41] combined with RT were tested in Phase 2/3 studies in LA-HNSCC. Again none of these agents could demonstrate superiority over Cisplatin.

Outcome results of these studies are depicted in Table 3.

4. Discussion

Defining the optimal management of LA-HNSCC is an arduous task owing to – 1.Heterogeneity in the location of the primary tumour and its natural history (oral cavity tumours v/s pharyngeal tumours v/s laryngeal tumours); 2. Different tumour biology (HPV positive v/s HPV negative oropharyngeal primaries, role of EGFR and treatment resistance); 3.Preferred Treatment modality (Surgery v/s Radiotherapy v/s Chemoradiation); 4.Evolution of newer treatment modalities (targeted therapy, immunotherapy, evolving RT techniques); 5.Treatment related

Table 2
Bio-Radiotherapy Trials using other anti-EGFR mAbs.

Trials	Study years	Study arms	Chemo therapy	HPV positive [a]	Median follow UP (years)	Progression free survival	Overall survival	Comment
CONCERT 1[b]	2007–2009	RT + CIS + PAN RT + CIS	3 weekly Cisplatin	–	2.3	61% v/s 68% [c,d]	–	No benefit of Panitumumab
CONCERT 2[b]	2007–2009	RT + PAN RT + CIS	3 weekly Cisplatin	24%	2.3	41% v/s 62%[d,f]	63% v/s 71%[d,g]	Panitumumab cannot replace Cisplatin
CANADIAN STUDY	2008–11	RT + PAN RT + CIS	3 weekly Cisplatin	71%	3.9	79% v/s 75%[d,g]	85% v/s 88%[d,g]	No benefit of Panitumumab
INDIAN STUDY	2012–18	RT + CIS + NIM RT + CIS	Weekly Cisplatin (30 mg/m^2)	10%	3.1	62% v/s 50%[d,f]	64% v/s 58%[d,g]	Only PFS benefit Cisplatin dose is very low
DAHANCA 19	2007–2012	RT + CIS + NIMZOLE + ZAL RT + CIS + NIMZOLE	Weekly Cisplatin (40 mg/m^2)	75%	3.0	HR – 1 [e]	HR – 0.9 [e]	No benefit of Zalutumumab

CET – Cetuximab; CIS – Cisplatin; PAN – Panitumumab; NIM – Nimotuzumab; NIMZOLE – Nimorozole; ZAL – Zalutumumab; HR – Hazard Ratio.
a = among oropharyngeal primary; b = Phase2 study; c = Loco-regional Control; d = 2Y; e = 3Y, f = p value significant; g = p value not significant.

Table 3
Trials of Small Molecule Tyrosine Kinase Inhibitors and RT.

Trials	Study years	Study arms	Chemo therapy	TKI dose	Median follow UP (years)	Primary endpoint	Result	Comment
GREGOIRE [a,b]	2006–2009	CT + RT + GEF CT + RT + PL	3 weekly Cisplatin	250 mg/day 500 mg/day	2	LCR	32.7% v/s 33.6% (p = NS)	No benefit
MARTINS [a]	2006–2011	CT + RT + ER CT + RT	3 weekly Cisplatin	150 mg/day	2	CRR	52% v/s 40% (p-NS)	No benefit
HARRINGTON [b,c]	2006–2013	CT + RT + LAP CT + RT + PL	3 weekly Cisplatin	1500 mg/day	3	DFS	56.9% v/s 57.7% (p-NS)	No benefit More toxicity

GEF – Gefitinib, PL – Placebo, ER – Erlotinib, LAP – Lapatinib, LCR – Local Control Rate, CRR – Complete Response Rate, DFS – Disease Free Survival.
a – phase 2 study; b – used maintenance therapy also; c - post op adjuvant high risk patients receiving CCRT.

acute and long term toxicities; 6.Treatment outcomes are not always weighed with survival (concept of functional organ preservation and quality of life); 7.Treatment planned should meet the established economics.

Any novel approach, even Cetuximab has to compete with the existing standard of care in an evidence-based manner and has to overcome all these challenges, only then it can be accepted and applied in clinical practice.

4.1. Rise and fall of Cetuximab

a. Re-exploring the Bonner study:

It has been sixteen years since the Bonner Study, which established the use of Cetuximab in the definitive management of LA-HNC. In these 16 long years Cetuximab use has been explored in a diverse milieu of LA-HNSCC management as discussed earlier. But has it really made as big an impact as conceived or is it just preemption? If we re-look into this important study, it can be noted that the study was published in 2006, when CCRT was not considered standard yet [42] and it was a genuine attempt to answer what else can be done beyond RT alone. In the study, median age was 56 years, 90% had Karnofsky performance scale (KPS) of 80 and more, KPS 60–70 constituted only 10% and inclusion criteria clearly mentions to have normal renal and liver function tests (RFT and LFT). But this data seems to have been misinterpreted to fit Cetuximab into our practice in patients with old age, low KPS, deranged RFT or LFT and displace cisplatin. Also, in the five year update, the OS data stratified by pre-treatment characteristics clearly showed no benefit in patients with age > 65 years and KPS of 60–80; only use of altered fractionation with concomitant boost RT and oropharyngeal primaries showed benefit [24].

b. Cisplatin as a primary competitor

Whenever the efficacy of Cetuximab has to be evaluated, it should be seen in the backdrop of cisplatin, as this is the current standard.

Cisplatin and radiation interaction has been studied since 1970 s. The very concept of combining chemotherapy concurrent with radiation is that, even if they are less effective on their own, the combination renders them more effective owing to synergistic effects. Various mechanisms of interaction have been hypothesized and proven in pre-clinical studies as well [21]. Cisplatin being highly electron affinic, the platinum moiety enhances the free radical mediated damage induced by radiation by increasing the free radical generated by radiation and capturing the electrons released from irradiated DNA [43]. Addition of Cisplatin causes excessive oxidative loading in cytoplasm [44] and induces DNA cross linking thereby increasing radiation induced SSBs and DSBs (single and double strand breaks) [45]. By causing G2 phase cell cycle arrest, G2-M phase radio-sensitivity is enhanced. It also acts by inhibiting sub-lethal damage repair and acts as Hypoxic cell sensitizer as well [46]. Hence the combination of Cisplatin and RT has overlapping and complementing actions at every level - DNA or Cytosolic, which cannot be matched by Cetuximab and RT combination where the targets for each of these are located at different sites and hence less overlapping and less complementary.

For reasons unknown, Cetuximab has not been able to perform well as expected in the clinical setting. Could this non-overlapping and non-complementary mechanistic interaction with RT be a possible explanation?

There is no phase III study comparing Cetuximab and RT with the current standard of high dose Cisplatin in unselected patient group. Neither did it show any benefit in comparison with weekly single agent Cisplatin [9,27] nor with Carboplatin [47]. More over Cisplatin is a cheaper drug than Cetuximab and when Cetuximab is not showing much of benefit, the cost-benefit aspect also has to be addressed especially in low and middle income countries.

c. Cetuximab in HPV positive patients:

These patients have very good prognosis with a 5 year survival of 75–85% [5,7]. Because of concerns about toxicity and diminished quality of life with high dose Cisplatin and RT, Cetuximab substitution in place of Cisplatin as de-escalation strategy is very attractive. Due to the oncogenic properties of E6 and E7 onco-proteins, HPV positive tumours are less dependent on altered signaling pathways and have less driver mutations [48]. Even before this could be known and without any previous HPV-related preclinical evidence Cetuximab was hurriedly introduced in this cohort, the very results of which are showing unfavourable outcomes. In line with the clinical data, *in vitro* studies demonstrated failure of Cetuximab to induce radiosensitivity in HPV positive HNSCC cell lines [49]. In De-ESCALaTE HPV [6], use of Cetuximab instead of cisplatin equaled one extra death at 2 years for every twelve patients treated. It was recognized that the good survival outcomes of patients with HPV positive low risk oropharyngeal carcinomas was also due to the type of treatment received and not merely a reflection of favourable tumour biology and CCRT with cisplatin therefore currently remains standard of care.

Overall, nearly 3000 patients have received Cetuximab treatment in clinical trials alone without any benefit but rather a detrimental effect.

4.2. Other anti- EGFR use in BRT

While Concert 1,2 [32,33] and Canadian HN.6 [34] study could not demonstrate the benefit of Panitumumab as against high dose cisplatin CCRT, the Indian study of treatment intensification with Nimotuzumab [35] and weekly Cisplatin showed good LRC and PFS benefit in Indian population where the HPV positive oropharyngeal cancers are less (7–10%). Nimotuzumab is an indigenously produced anti EGFR, which is molecularly and biologically different from Cetuximab. It inhibits both ligand-dependent and independent signaling of EGFR and has a better toxicity profile over Cetuximab due to bivalent binding [50]. But this is a single institution study and the comparison arm was weekly Cisplatin at 30 mg/m^2 dose, whose very efficacy is debatable. In fact the same team of researchers has proved that weekly Cisplatin with 30 mg/m^2 dose is less efficacious than high dose 100 mg/m^2 three-weekly cisplatin in the treatment of head and neck cancers [51]. Zalutumumab [37] also could not etch itself with Chemoradiation or with hypoxic sensitizers. While the big brother (anti-EGFR mAbs) could not hold the fort, the small molecule TKIs too followed him.

4.3. Present role of Cetuximab

Cetuximab is the biological molecule which has peeked into all possible windows in the definitive treatment of LA-HNSSC and has miserably failed in the real world setting [5, 6, 7, 8, 9 and 10]. It has simply bowed down to standard high dose cisplatin, despite the similar benefit observed in the Bonner trial. It has been unsuccessful even against weekly cisplatin or even single agent carboplatin which are the modifications in patients who do not tolerate high dose cisplatin. De-escalation strategy has not yielded fruitful results in HPV positive disease despite the rather cautious approach with maintenance of full dose RT (70 Gy). Hence, only patients who fail to qualify into any of these approaches, but are still candidates for radical treatment may probably be the only indication left, which was traditionally mistaken as all patients with renal or hepatic dysfunction or all elderly frail patients.

As per the clinical recommendations for defining platinum unsuitable – platinum ineligible in head and neck cancer patients planned for Chemoradiation [52] two set of criteria are defined-.

1. Criteria for absolute contraindication for Cisplatin - ECOG (Eastern Cooperative Oncology Group) performance status score of grade 3 or higher, hearing loss or neuropathy of grade 2 or higher based on the NCI CTC (National Cancer Institute Common Toxicity Criteria) version 4.0.

2. Criteria for high risk cases - Treating the patients falling under this criterion with Cisplatin, require extra caution.

The panel recommended that cisplatin dose of less than 100 mg/m^2 or carboplatin or taxanes or low dose gemcitabine or cetuximab can be considered as alternative in these high risk cases. Even treatment with altered fractionation alone is an option.

A Surveillance Epidemiology and End Results (SEER) data assessing care value for older patients receiving radiotherapy alone or with cisplatin or with Cetuximab for LA-HNSCC [53] observed no survival difference but a higher rate of emergency admissions and higher spending in patients receiving Cetuximab-RT.

So not all Platinum ineligible patients are eligible to be treated with Cetuximab, these patients also have to be carefully selected in the wake of the present evidence.

Is there any predictive bio-marker that would possibly help in patient selection for Cetuximab therapy? To date there are no such markers and EGFR expression itself is known to be of no predictive value [54].

4.4. Future direction

Has the last nail in the coffin been hammered for Cetuximab in LA-HNSCC? Mostly yes, but researchers won't agree. With the future looking into immunotherapy (immune checkpoint inhibitor drugs targeting PD-1or PD-L1), a novel concept of combining immunotherapy with anti-EGFR agent and RT is hypothesized as anti-EGFR agents also act by immune modulation. The REACH study by the GORTEC group - Randomized Trial of Avelumab-Cetuximab-Radiotherapy Versus standard of care (CCRT) in LA-HNC, whose interim data was recently presented as an abstract [55], showed that the combination of anti PD-L1 – Avelumab plus Cetuximab and RT did not improve PFS (1 year PFS 64% v/s 73%; HR-1.27) and was found to be futile when compared to standard of care, especially in the cohort which used Cisplatin based CCRT.

This demonstrates that even the future seems to be bleak for Cetuximab in the definitive setting, though its use is continued to be explored in recurrent and metastatic setting along with immunotherapy [56].

In the battle of superiority between chemotherapy, targeted therapy and immunotherapy, whose role is that of an adjunct in CCRT, radiotherapy is a mute spectator.

5. Conclusion

With nearly two decades into Cetuximab-Bio-Radiotherapy, based on the positive IMCL 9815 results and while awaiting further data from additional randomized trials, thousands of patients have been treated with Cetuximab in the clinical practice. Now that the results are out and are evidently against the use of Cetuximab as an alternative to standard chemoradiation, it is time to accept and witness the dawn to dusk journey of Cetuximab in the definitive management of LA-HNSCC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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