

NEWER DRUGS IN HEAD AND NECK CANCER

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Included

- Oral cavity
- Nasal cavity
- Pharynx
- Larynx
- Lymph node in upper part of neck

Excluded

- Brain
- Eye
- Cancer arising from scalp, skin, muscles & bones of head-neck region



Background

Locally advanced and metastatic disease show poor outcome

Multimodality treatment approach recommended

Radiotherapy and/or surgery not very helpful in many situation

Cisplatin and 5-FU results not encouraging in CRT / CT-RT setting

Site of occurrence or recurrence is important



Limitations

Recent advances in

- Diagnosis

- Treatment

Radiotherapy – IMRT, IGRT, Brachytherapy

Surgery techniques

Chemotherapeutic agents

all have limitations in translating into significant survival benefit



Goal

Added survival benefit

Improved quality of life

Low therapy related toxicity

Affordable therapy



Search for

Higher activity chemotherapy agents

Targeted therapy

Gene therapy



Newer drugs showing better efficacy
(singly or in combination)

- Paclitaxel
- Docetaxel
- Gemcitabine
- Vinorelbine



Targeted therapy

MABs

Cetuximab

Nimotuzumab

Bevacizumab

TKIs

Geftinib

Erlotinib

Lapatinib



All these drugs are being evaluated for

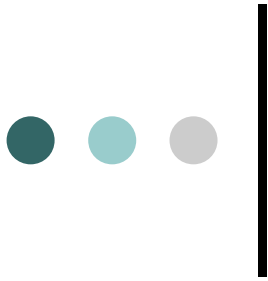
- Chemoprevention
- Recurrent and metastatic disease
- In combination with RT &/or CT

Initial trials have found that combination of the newer agents with the conventional modality of therapy have 30% lower risk of mortality as compared to the conventional one



DOCETAXEL

FDA approval obtained after multicenter, randomised trial (n=358) involving previously untreated, inoperable, locally advanced SCCHN in combination with Cisplatin & 5-FU prior to RT



RESULTS

Arm A – Docetaxel + Cisplatin + 5-FU

Arm B – Cisplatin + 5-FU

	<u>Overall Survival</u>	<u>Time to Disease Progression / Death</u>
Arm A	18.6 months	14.2 months
Arm B	11.4 months	8.3 months

Toxicity = enhanced (hair loss, mucositis, diarrhoea, fall of blood counts, neurosensory abnormalities)



• Paclitaxel

It is being used as monotherapy or multidrug combination with significant cytotoxic activity in SCCHN

• Gemcitabine

Nucleoside analogue
Innovative cytostatic action
Favourable toxicity profile

Combination is active and well tolerated

• Vinorelbine

Antimicrotubule agent
Reports of better response in SCCHN but evidence not yet convincing



IMPORTANT TRIALS

- TAX 323 trial

(Performed by EORTC & updated by Remenar et al in 2006)

Mostly T4N2 or 3, unresectable, n = >300, TPF vs PF

*Survival significantly better with TPF vs PF
29% decline in mortality with TPF*

- TAX 324 trial

(Induction Chemotherapy ; TPF vs PF)

More than 80% Stage IV disease, n = >500

3 cycles TPF or PF + CRT with weekly Carboplatin (low dose)

*3 year survival : TPF = 62%
PF = 48%*

Overall mortality reduction 30%



Contd.

- University of Pennsylvania trial

2 cycles of high dose PCL & carboplatin, then weekly PCL CRT

Survival = >60% at 3 years

- GORTEC trial

(Ca larynx & hypopharynx)

3 cycles of TPF or PF

Responders = RT :: Non-responders = Laryngectomy

More responders in TPF arm

TPF offers better laryngectomy-free survival

TPF 80% vs PF 60%



MONOCLONAL ANTIBODY

MAB is a protein made in the laboratory from a single copy of human antibody. Antibodies are immune system proteins killing germs in the body. Scientists can design a monoclonal version that can target growth factor receptors on cancer cells to stop the growth signal.



CETUXIMAB (ERBITUX)

Designed to block EGFR on the surface of cancer cells that trigger growth and thereby blocking these receptors will stop the signal that induces cancer cell proliferation

This drug is now approved for use alongwith RT in locally advanced unresectable SCCHN

Also approved as monotherapy in metastatic, first line chemotherapy failure cases



CLINICAL TRIALS EVIDENCE (Safety and Effectiveness)

Multicenter, randomised clinical trial (n=424)

Overall survival

- Cetuximab + RT = 49.1 months
- RT alone = 29.3 months

Delay in disease progression also observed

2nd study on 103 patients with recurrent/metastatic SCCHN

Refractory to platinum based therapy had tumour shrinkage.

(since tumour growth is associated with pain, difficulties in swallowing, speaking and eating control of tumour growth as long as possible is important for patients' well being)



NIMOTUZUMAB

3 clinical trials (n = 70)
All well tolerated, good response

Currently being evaluated in 24 SCCHN patients trial.
12 patients 100mg weekly + 6 weeks RT
12 patients 200mg weekly + 6 weeks RT

Complete tumour response in
8/12 and 9/12 patients



CANCER GROWTH FACTOR BLOCKERS

Growth factor receptors direct the cells to grow and divide into two new cells. Cancer cells have too many of these receptors (EGFR) causing abnormal cell growth.

EGFR when triggered activate the enzyme Tyrosine Kinase. Researcher are developing drugs (Tyrosine Kinase Inhibitors =TKI) that can block growth factor receptors and probably stop cancer cells from growing.

Geftinib currently being evaluated in head & neck cancer.

Erlotinib as single agent prolongs survival in refractory SCCHN as shown in phase II trial.

Lapatinib is a dual inhibitor of EGFR and *erb*-B2 tyrosine kinase and has shown efficacy in recurrent or metastatic SCCHN.



Nasopharyngeal cancer

Growth factor receptors identified

- C-kit (CD 117)
- C-erb-2 (HER 2)
- Vascular Endothelial Growth Factor (VEGF)

Whether this will lead to newer treatment strategy in Nasopharyngeal Cancer is still unanswered



GENE THERAPY

Still in very nascent stage.

Study is on for oncogenes and tumour suppressor genes, which control cell growth.

In SCCHN gene therapy trials are on in UK and USA.

UK – Onco VEX trial

USA – ONYX-15 trial (*Genetically engineered Adenovirus causing Common cold is used to infect and kill cancer cells without normal healthy cells.*)

These trials showed some promising results.

Researchers aim at using this form of therapy alongwith standard therapy.



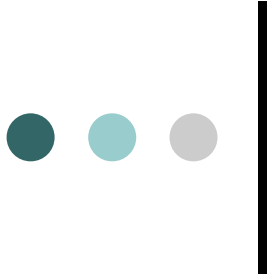
CONCLUSION

Use of new drugs increases response rate and amends side effect of chemotherapy.

Phase III studies documenting an improved overall survival lacking.

Targeted therapies broaden therapeutic armament.

Possibly EGFR inhibition will help overcoming chemotherapy resistance.



STILL A LONG WAY TO GO