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**
- Gefitinib
- 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

<table>
<thead>
<tr>
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<th>Overall Survival</th>
<th>Time to Disease Progression / Death</th>
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<tbody>
<tr>
<td>Arm A</td>
<td>18.6 months</td>
<td>14.2 months</td>
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<tr>
<td>Arm B</td>
<td>11.4 months</td>
<td>8.3 months</td>
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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
  Favoursble 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 along with 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

2\textsuperscript{nd} 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. Researchers are developing drugs (Tyrosine Kinase Inhibitors = TKI) that can block growth factor receptors and probably stop cancer cells from growing.

**Gefitinib** 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 along with 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