Is Maintenance Therapy Useful in Head & Neck Cancer?

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For LOCALIZED disease, adjuvant systemic treatment given after primary surgery/XRT failed to demonstrate benefit, mainly because of low dose-intensity delivered.

For ADVANCED disease, maintenance systemic therapy may be discussed in the case of residual disease = situations in which complete pathological response is unlikely to occur.
Do we have much experience of maintenance therapy in H&N Cancer?

NO

EXTREME: Study design

Group A
Cetuximab 400 mg/m² initial dose then 250 mg/m² weekly + EITHER carboplatin (AUC 5, d1) OR cisplatin (100 mg/m² IV, d1) + 5-FU (1000 mg/m² IV, d1-4): 3-week cycles

Group B
EITHER carboplatin (AUC 5, d1) OR cisplatin (100 mg/m² IV, d1) + 5-FU (1000 mg/m² IV, d1-4): 3-week cycles

Randomized

No treatment

Progressive disease or unacceptable toxicity

6 chemotherapy cycles maximum

Cetuximab maintenance up to PD


Results of EXTREME phase III randomized study

Improvement of Overall Survival with Cetuximab + platinum + 5FU versus platinum + 5FU

WHY?

1. LIMITED SURVIVAL (median OS 6-9 months):
   initial response to treatment is rapidly followed by broad acquired resistance to several classes of conventional chemotherapy agents

2. LIMITING TOXICITY: Low therapeutic index with conventional cytotoxics
   - general toxicity / comorbidities
   - neurological/renal cumulative toxicity of cisplatin

Can we prevent acquired resistance and improve therapeutic index?

PROBABLY YES

1. Prevent acquired resistance
   Select therapeutic agents that are active in the context of resistance to platinum
Functional role of EGFR

Intracellular domain
Cellular membrane
Extracellular domain

Tyrosine kinase
EGF EGF-R

Tyrosine kinase

Differenciation
Modulation
Cell Survival
Proliferation
Angiogenesis
Chemo- and Radiation therapy
Resistance

Cetuximab demonstrates marked synergy with cisplatin in A431 xenograft growth inhibition

Cetuximab + Cisplatin
Cetuximab
Cisplatin
Control (PBS)

A431 cells implanted

Tumor size (cm)

Days


Cetuximab single agent in platinum-refractory patients

Baseline After 7 injections After 13 injections
2. Improve therapeutic index

Decrease toxicity while improving efficacy

Therapies must take into account H&N patients characteristics...

- **High blood pressure**: careful monitoring during hyperhydration for cisplatin administration.
- **Cardiac disease**: careful monitoring of blood pressure and respiratory status during hyperhydration for cisplatin administration.
- **Coronary disease**: if uncontrolled, contra-indication to 5FU administration.
- **Diabetes mellitus**: screening for impaired glucose tolerance during chemotherapy, particularly if corticosteroids are administered (+ occult symptoms of coronary insufficiency).
- **Pulmonary disease**: high incidence of obstructive chronic bronchitis and infections (pneumonia).
- **Renal insufficiency**: careful monitoring of biological renal function and potential side effects of nephrotoxic drugs (cisplatin +++).
- **Alcohol addiction**: increased risk of acute syndrome (delirium tremens) and of gastrointestinal (gastric ulcer, bleeding, pancreatitis) or liver complications (steatosis or cirrhosis decompensation).

Limited side effects of EGFR inhibitors: Skin toxicity

- Acne-like rash... 80% (including 5-20% severe)
- Topical treatments or systemic antibiotherapy
- Positive correlation with efficacy
  - No myelosuppression
  - No infection
  - No cardiovascular toxicity
  - No renal toxicity
  - No neurological toxicity
Antitumor agents inhibiting EGFR

Monoclonal Antibody
Cetuximab

Tyrosine Kinase Inhibitors
Gefitinib
Erlotinib

Inhibition of signaling pathways

Overcoming CYP1A1/1A2 Mediated Induction of Metabolism by Escalating Erlotinib Dose in Current Smokers
Andrew N. Hughes, Mary E.B. O’Dea, W. Jeffrey Petty, Jonathan H. Choh, Jennifer Bubin, Priscilla J. Weil, David Drapkin, Marianne Nicolini, Barbara Soupartly, Julie Wolff, and Allen Prise

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“Steady-state trough plasma concentrations and incidence of rash and diarrhea in smokers at 300 mg were similar to those in former or never smokers receiving 150 mg in previous studies”

Can we learn from other malignant diseases?

PROBABLY YES

LUNG (chemotherapy)
COLORECTAL Cancer (CT)
GIST (imatinib)
Example of Lung Cancer

Sequential, Alternative, and Maintenance/Consolidation
Chemotherapy in Advanced Non-Small Cell Lung Cancer:
A Review of the Literature

"...Consolidation/maintenance chemotherapy may provide additional benefit for patients achieving disease control after standard first-line chemotherapy.
Better results are seen when maintenance consists of an agent that has proven active in the induction phase."

Example of Lung Cancer

Phase III Study of Immediate Compared With Delayed Docetaxel After Front-Line Therapy With Gemcitabine Plus Carboplatin in Advanced Non–Small-Cell Lung Cancer

N=566

No. of patients in good performance status (ECOG 0/1)

90% of patients in good performance status (ECOG 0/1)

Significant improvement of Progression-Free Survival with maintenance docetaxel after platinum-based CT

5.7 months versus 2.7 months, p=0.0001
Non-significant improvement of Overall Survival with maintenance docetaxel after platinum-based CT

Example of Lung Cancer

In patients with good PS, maintenance treatment with docetaxel (efficient doses 75 mg/m² q 3weeks):
- statistically significant improved PFS
- nonstatistically significant increased OS
- after front-line platinum-based regimen, without increasing toxicity or decreasing QOL

Example of GIST

Prospective Multicentric Randomized Phase III Study of Imatinib in Patients With Advanced Gastrointestinal Stromal Tumors Comparing Interruption Versus Continuation of Treatment Beyond 1 Year: The French Sarcoma Group

J Clin Oncol 25:1107-1113. © 2007
Example of GIST

*Imatinib interruption results in rapid progression in most patients with advanced GIST, and cannot be recommended in routine practice unless patient experience significant toxicity*

What is the next targeted therapy that could be an attractive candidate in H&N cancer?
RAPAMYCIN COMBINATIONS WITH CONVENTIONAL AGENTS

- To provide strong demonstration of synergistic effects
- To study the possible role of sequence exposure to respective agents

Rapamycin + Carboplatin + Paclitaxel

In HNSCC cell lines

CARBOPLATIN AND RAPAMYCIN IN HNSCC CELL LINES

Aissat et al, Cancer Chemother Pharmacol 2008

PACLITAXEL AND RAPAMYCIN IN HNSCC CELL LINES

Aissat et al, Cancer Chemother Pharmacol 2008
CONCLUSIONS

• The investigation of maintenance therapy in H&N cancers with conventional cytotoxics was impaired by limited survival and low therapeutic index.

• EGFR inhibitors represent promising drugs since they are active in platinum-resistant patients and display good toxicity profile.

• The role of maintenance therapy with EGFR inhibitors needs to be assessed in controlled trials.

• Other targeted therapies including mTOR inhibitors may be attractive agents for initial combinations followed by maintenance therapy.

**YES**

Maintenance therapy with targeted agents will be useful in advanced H&N Cancer
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