How to combine chemotherapy, targeted agents and radiotherapy in locally advanced NSCLC?

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Combining chemotherapy and radiotherapy of the chest
Better survival with concurrent chemoradiotherapy vs. sequential (Pre-PET era; 2D radiotherapy...)

Aupérin et al. J Clin Oncol 2010

The overall survival benefit is associated with improved local control

Local tumour control better still 30-40% local progression

Same incidence of distant metastases

Aupérin et al. J Clin Oncol 2010
Most series used
- 60-66 Gy in 2 Gy/day fractions, 5 times per week
- Concurrently with
  - cisplatin-etoposide (“optimal schedule unknown”)
  - cisplatin-vinorelbine
  - carboplatin-paclitaxel

Much improvement is needed for systemic and local control

“Radioresistance does not exist”

If no prolif.

Radiation dose escalation with concurrent chemotherapy and prolongation of the overall treatment time

RTOG 0617, NCCTG N0628, CALGB 30609
Conventional vs. High Dose RT

Randomize

RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin X2 +/- Cetuximab

Overall Survival

Patients at Risk
60 Gy 213
74 Gy 204

Months since Randomization
0 3 6 9 12

Overall Survival (%)

Dead Total
60 Gy 58 213
74 Gy 70 204

HR = 1.45 (1.02, 2.05) p* = 0.02

*One-sided p-value, left tail
But,… RTOG0617 shows

- That the OS with “current 60 Gy” is better than in the past (patient selection, staging, imaging integration in radiotherapy planning, planning and delivery ...)
- ... which leads to “reasonable” median survival rates of 21 months

Dummy run shows that many centres could improve their results by emphasising the quality of the whole treatment chain!

Many ongoing dose-intensification trials

- Biological dose escalation ➔ dose intensification
  - Standard total doses, shorter overall time
- Individualisation
  - Physical
  - Biological, including molecular imaging
Influence of overall treatment time of radiotherapy on survival in stage I-III NSCLC without concurrent chemo-radiotherapy

**INDividualised Accelerated Radiotherapy (INDAR)**

- Escalate the dose to the maximum tolerance
- Delivered in a short overall treatment time
- Directed to areas that are 18F-deoxyglucose (FDG) positive
Survival by stage (large volume, multi-level N+, 25% WHO PS 2), sequential chemo-radiation

van Baardwijk et al. J Clin Oncol 2010
Individualised, accelerated iso-toxic radiotherapy with concurrent chemotherapy in stage III NSCLC

Median OS: 25 months; estimated 4-year survival: 30%

Isolated local recurrence: 5%; isolated regional recurrence: 4%; combined local and regional recurrence: 5%; distant relapse only: 27% (57% brain only)

van Baardwijk et al. Eur J Cancer 2012

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Individualised, accelerated iso-toxic radiotherapy with concurrent chemotherapy in stage III NSCLC

Single nodal stage cT4N0-1

Median OS: 33 months (2.7 years) Median OS: 55 months (4.6 years)

Median OS Region 7 nodal disease: 24 months
Median OS for other nodes: not reached

Reymen et al. Submitted 2012
Early response: FDG changes during first week of chemo-RT and survival

- **FDG-PET:**
  - Cut-off: 15% (EORTC response)
  - Changes in maximum SUV and mean SUV significant predictive for 2-year overall survival
    - HR 1.26 (95% CI: 1.09 – 1.45) per 5% decrease of SUV
- **CT (volume)**
  - Tumour volume pre RT is predictive for survival
    - HR 1.040 (95% CI: 1.005 – 1.076) per 10 cm³ increase
  - Change in tumour volume (CT) is not correlated to survival

*Van Elmpt W et al. J Nucl Med 2012*

Conclusions

- Radiotherapy to a dose of 60-66 Gy in 2 Gy per day, 5 days per weeks remains the standard when delivered concurrently with chemotherapy (*arguments in favour of high-dose, accelerated radiotherapy in non-concurrent schedules*)
- Individualised (accelerated, isotoxic) radiotherapy schedules are being investigated in many clinical trials and are still of much importance
- Improvement the quality of the *whole* diagnostic and treatment chain most probably improves overall survival
Combining targeted agents and radiotherapy of the chest

Rationale

- Improved local tumour control leads to increased overall survival at 5 years
- Dose-limiting organs (e.g. main bronchi, blood vessels, lungs, oesophagus, ...) remain problematic for optimising radiation dose
- Concurrent chemo-radiotherapy is toxic and for many patients already now too heavy [De Ruysscher et al. 2009]
Rationale

- Ideally agents targeting intracellular pathways that are known to modulate the RT response, enhancing tumour cell killing while having moderate effect on normal tissues should be considered in combination with thoracic RT


Choice of the drug does matter: Cetuximab, but not gefitinib, blocks nuclear transport of pEGFR.

Nyati MK et al. Nature Reviews Cancer 2006
EGFR inhibition: Influence of cell line type

Uptake of $^{89}$Zr – cetuximab is heterogeneous


(*) van Dongen, Nuclear Medicine VUMC, The Netherlands
Uptake of $^{89}$Zr – cetuximab is heterogeneous

EGFR Intermediate HT29

Heart
Liver

(48 hours after injection)

General conclusions

- Combining radiotherapy with targeted agents: Highly rational
- Selection of patients, treatment technique of utmost importance
- Resistance mechanisms for targeted agents alone may not be the same when these drugs are used as radiosensitisers
- Not yet in standard practice!