What’s new in the systemic treatment of SCLC?

Jan.van.meerbeeck@uza.be
Antwerpen, 17 October 2014

Disclosures

- Conflict of interests: none
SCLC: no progress for many years

- app 15% of all lung cancers
- associated with heavy smoking
- Eto-Cis standard of care in first-line therapy (ORR 65-70%, OS 10 months)
- Topotecan standard of care in second-line therapy (PFS app 3 months!)
- No new approval in past 10 years (except oral topotecan)

Testing of novel agents in SCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Type of Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP</td>
<td>Marimastat</td>
<td>Phase III</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Tanomastat</td>
<td>Phase III</td>
<td>Negative</td>
</tr>
<tr>
<td>c-kit</td>
<td>Imatinib</td>
<td>Phase II (multiple)</td>
<td>Negative</td>
</tr>
<tr>
<td>EGFR</td>
<td>Gefitinib</td>
<td>Phase II</td>
<td>Negative</td>
</tr>
<tr>
<td>mTOR</td>
<td>Temsirolimus</td>
<td>Randomized Phase II</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>BEC-2</td>
<td>Phase III</td>
<td>Negative</td>
</tr>
<tr>
<td>Ganglioside</td>
<td>Thalidomide</td>
<td>Phase III (multiple)</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunologic, angiogenesis</td>
<td>Pemetrexed</td>
<td>Phase III</td>
<td>Negative</td>
</tr>
<tr>
<td>Antifolate</td>
<td>AT-101</td>
<td>Phase II</td>
<td>Negative</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Navitoclax</td>
<td>Phase II</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Obatoclax</td>
<td>Phase II</td>
<td>Negative</td>
</tr>
</tbody>
</table>
What’s new?

- Weekly topotecan
- Not so new agents
  - Temozolomide
- New agents
  - Amrubicin
  - Picoplatin
- Not so targeted agents
- Genomics of SCLC and its implications
- Conclusions

Figure 5: Simplified algorithm for the management of relapsing SCLC
SCLC = small-cell lung cancer. CAV = cyclophosphamide, doxorubicin, and vincristine.
**Weekly topotecan**

- Topotecan only approved agent for second line
  - Equal to CAV but superior palliation of symptoms
  - Oral administration equivalent to iv
  - T d1-5 q3w schedule comes with significant hematol toxicity
- **TOWER trial** ([Sehouli, JCO 2011; 29:242-8](#))
  - Platinum resistant ovarian cancer
  - T weekly (4 mg/m\(^2\)/wk administered on days 1, 8, and 15) q4w vs. T conventionally (1.25 mg/m\(^2\)/d on days 1 to 5) q 3w
  - Comparable OS
  - Tw significantly lower risks of
    - anemia (RR, 0.35; 95% CI, 0.16 to 0.79),
    - neutropenia (RR, 0.38; 95% CI, 0.23 to 0.65)
    - thrombocytopenia (RR, 0.23; 95% CI, 0.09 to 0.57)
- Weekly topotecan new SOC?

**Not so (new) agents**

- Thalidomide
- Statines
- Nitroglycerine
- Metformin
- Chloroquine
- Azithromycine
- Beta blockers
- ACE inhibitors
- Antidepressants
- …
- **EORTC randomized trial of PE +/- repurposing drug**
- **Temozolomide**
  - Alkylating agent
  - Oral precursor drug of 5FU, crosses BBB
  - SOC in GBM and astrocytoma
  - Mild toxicity profile
    - 6% gr 3-4 hematol tox.
  - Expression of MGMT prognostic and predictive of efficacy
A multicentre randomized phase 2 study of temozolomide versus topotecan in patients with relapsed or refractory SCLC (PI B Hiddinga)

- Inclusion criteria
  1. Patients with metastatic SCLC
  2. Relapsing after or refractory to first line platinum-based treatment
  3. Measurable disease according to RECIST 1.1
  4. Performance status WHO 0, 1 or 2
  5. Informed consent

- Endpoints
  1. progression free survival (PFS) at 12 weeks
  2. overall survival (OS)
  3. correlation of MGMT expression and promoter methylation in blood & tissue with activity and outcome
Trial schema

1. Metastatic SCLC
   1 prior line chemotherapy
   Measurable disease
   PS 0 – 2 ≥ 18 y

2. Temozolomide 75 mg/m²/day 1 – 21 of each 28 d cycle

3. Topotecan 2.3 mg/m²/day 1 – 5 of each 21 d cycle

Amrubicin

- Synthetic anthracycline
- Doxorubicin-like
  - Also camptothecine activity: stabilises topoisomerase II
- Amrubcinol accumulates in tumour cell
  - Less (cardio-)toxicity?
  - NADPH oxidase critical enzyme in metabolism
    - polymorphism in Asian influences pharmacogenomic profile
- Promising phase 2 trials in 1st and 2nd line in Japan
- Randomized trials in 1st line, combined with cisplatin (PA)
  - Vs. cisplatin etoposide (PE) EORTC 08062
  - Vs. cisplatin irinotecan (PI) JCOG 0509
- Phase 3 trials in 2nd line ACT-1
  - vs. Topotecan (T)
Amrubicin (conclusion)

- Outcome in Caucasian population
  - 1st line: equal to etoposide and inferior to irinotecan
  - 2nd line: equal to topotecan, superior in refractory pts

- Toxicity
  - Higher rate of (febrile) neutropenia

- No valid alternative for current SOC’s in Caucasian pts

Picoplatin

- Platinum analogue not avid for thiol groups (e.g. G-SH) responsible for platinum resistance
- Promising single agents phase 2 studies in sensitive en refractory pts

- SPEAR: picoplatin vs BSC in relapsed SCLC
  - N= 401
  - No difference in outcome but for PFS in subgroup of refractory pts
  - Imbalance in 3th line treatment
Not-so targeted agents

- SCLC highly angiogenic tumour
  - High microvessel density and levels of VEGF
- Bevacizumab: Mab against VEGF
  - IFCT-0802 trial (Pujol, ASCO 2014)
    - Randomized phase 2 in 147 ES SCLC; no biomarker selection
    - Chemo x 6 +/- bevacizumab: no difference in outcome
- Aflibercept: VEGF trap
  - SWOG S0802 (Allen, JCO 2014)
    - Randomized phase 2 in 189 pretreated SCLC: no biomarker selection
    - Topotecan weekly +/- aflibercept
    - Improved PFS @ 3m; similar OS; increased rate of grade 3-5 toxicities
- Sunitinib: oral tyrosine kinase inhibitor of VEGFR-2/3
  - CALGB 30504 (ALLIANCE) – (Ready, ASCO 2014)
    - Randomized phase 2 in 144 ES SCLC: no biomarker selection
    - Maintenance treatment with sunitinib or placebo until progression
    - Improved PFS; trend to improved OS

Not-so targeted agents (2)

- Vandetanib: oral TKI of VEGFR-2/3, EGFR and RET
  - Hoosier Oncology LUN06-113 (Sanborn, ASCO 2014)
    - Randomized phase 2 in 74 ES SCLC: no biomarker selection
    - Carbo etoposide +/- vandetanib
    - No difference in outcome, higher incidence of grade 3/4 toxicities
- Insuline growth factor (IGF-R) frequently overexpressed
  - Vismodegib and cixutumumab inhibit IGF-R
    - ECOG 1508 (Belani ASCO, 2012)
      - Cisplatin/etoposide +/- either V or C
      - No difference in outcome
- Check point inhibition: blocking antibodies of CTLA4
  - Chemotherapy +/- ipilimumab (Reck, Ann Oncol 2013)
    - Trend for improved OS at long follow up
Aurora A kinase inhibition

- Serine/threonine kinases with critical function during mitosis
  - Overexpression associated with increased cell proliferation via aneuploidy, supernumerary centrosomes, defective mitotic spindles, and resistance to apoptosis.
  - Not yet a proper biomarker

- Given the obligatory role of mitosis in tumor proliferation, an Aurora A kinase inhibitor would have potential applications across a broad range of human solid tumors
  - Alisertib: selective small-molecule inhibitor of Aurora A kinase
    - additive or synergistic antitumor activity in vivo when combining with tubulin inhibitors paclitaxel or docetaxel in SCLC xenograft models
    - predominant toxicities reflect the mechanism of action in proliferating tissues (bone marrow, GI epithelium, and hair follicles)

Alisertib

STUDY DESIGN SCHEMA

Primary endpoint: PFS
Target 67% improvement 3 to 5 mos.
Number of Patients: 166
Somatic mutation frequency in lung cancer

Pfeifer et al., *Nat Genet* (2012)

From exomes to 100 genomes...

- Pilot study: Whole exome sequencing on 29 T/N pairs

- WGS on 77 T/N pairs

<table>
<thead>
<tr>
<th></th>
<th>TP53</th>
<th>RB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations</td>
<td>95 % (73/77)</td>
<td>82 % (63/77)</td>
</tr>
<tr>
<td>CN Changes - Deletions</td>
<td>61 % (47/77)</td>
<td>69 % (53/77)</td>
</tr>
<tr>
<td>Genomic Rearrangements (translocations, inversions, larger deletions within the gene or gene region)</td>
<td>6.5 % (5/77)</td>
<td>12 % (9/77)</td>
</tr>
</tbody>
</table>

Julie George
Fundamental Issue in SCLC biology

*No “driver” mutation!*

---

**Many interesting genes, but…**

- No smoking gun mutation
- No link yet with characteristic phenotypes
  - Universal sensitivity to chemo
  - Rapid development of resistance
  - Highly metastatic disease
  - Small cells
  - Neuroendocrine features
- Are there infrequent actionable alterations?
SCLC and DNA damage

- Paradoxical and unique sensitivity to chemo (RR first line >60 %) despite...
- …universal biallelic loss of p53!
- Therapeutically amenable DNA damage dependency?
- High expression of PARP in SCLC (Byers et al., Cancer Discov 2012)
- Trials testing PARP inhibitors in SCLC are ongoing (10% RR with BMN673, abstract 7522)

Conclusions

- Weekly topotecan acceptable alternative in second line treatment
- No real progress in cytotoxic or targeted agents
- Despite many TSG mutations, no obvious ‘smoking gun’
- Need to explore multi-mutational, complex biology in detail to identify novel therapies
- Several interesting phase 2 trials ongoing
  - Repurposed drugs
  - Immune checkpoint inhibition
  - Aurora kinase A inhibitors
Programme
11th Thoracic Oncology Winter Symposium
Saturday 17 January 2015

09:00 Registration
09:30 Welcome
Jan van Meerbeeck, UZ Antwerp, Belgium

09:35 Research Lecture
CHAIR: Jan van Meerbeeck, UZ Antwerp, Belgium
10:00 Resistance in lung cancer: recognizing a genetic disease?
Kevin Stamm, UZ Gent, Belgium

09:55 – 10.00 Session 1: Can loco-regional therapy benefit a systemic disease?
Challenges in the treatment of small cell lung cancer, all other tumours, and the role of consolidation therapy in ES-SCLC
Ben Olthuis, VU University Medical Center, Amsterdam, the Netherlands
10:30 Early prediction of clinical inflammation in ES-SCLC
Rohan Tang, National University Hospital, Singapore, Singapore

10:15 Break

11:00 Session 2: The evolving role of care in metastatic NSCLC
Chair: Sigfrid van Meer, UZ Antwerp, Belgium
11:00 Lung cancer: a model for survival or for bone metastasis?
Stefan Nothnagel, CHUV University Hospital, Switzerland
11:05 3rd generation EGFR TKI: how do we use them successfully?
Christian Muller, UZ Antwerp, Belgium
11:30 Second generation EGFR TKI: progress in refractory disease
Jean-Yves Fang, Klinikum, Germany
11:45 Use of molecular biomarkers in the management of SCLC
Benjamin Reuss, UCL, Paris, France
12:15 What are our next-generation EGFR TKI?
Eugénie Spruyt, KUL-Antwerp, Belgium

13:00 Lunch