Lung Cancer Surgery in the Era of Immunotherapy

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Outline

- Introduction
- Adjuvant and neoadjuvant treatment before immunotherapy
- Potential advantages of neoadjuvant immunotherapy
- Brief review of immunotherapy trials
- Surgical results, considerations, and takeaways from the published trial data
- Conclusions

Lung Cancer

- Remains the leading cause of cancer-specific mortality
- 85% NSCLC
- Up to 50% NSCLC diagnosed at advanced stage
- 5 year OS for locally resected NSCLC remains poor
- >50% of resected patients develop recurrence, often at distant sites, suggesting significant potential benefit of more effective systemic therapies

Adjuvant and Neoadjuvant Treatment before Immunotherapy

- LACE Collaborative Group 2008 (Pignon et al.)
  - Adjuvant chemo associated with decreased risk of death of 5.4% at 5 years
  - Significant benefit only in patients with stage II/III

- Neoadjuvant therapy not shown to benefit early stage cancers, certainly used for IIIA, and optimal treatment regimen on IIIA long debated
  - IIIA 5yr survival 10-15%, 5% with bulky N2 disease (Provencio et al.)

Immunotherapy Mechanism

Immune Checkpoint (PD-L1 and PD-1) Inhibitors (ICIs)

- Approved for metastatic and selected stage III NSCLC
- Data on safety and efficacy in resected NSCLC are emerging particularly in the last couple years
- Mechanism of action
  - PD-1 = protein on surface of activated T-cells
  - PD-L1 binds PD-1 and renders T-cell inactive as a way for body to regulate the immune system
  - Many cancers make PD-L1, inhibiting T cell response
  - ICIs block this from happening, allowing T-cells to attack the tumor

PACIFIC Trial (Antonia et al. NEJM 2017)

- Durvalumab vs placebo in Stage III NSCLC with no disease progression on chemoradiotherapy
- OS HR .72 median 47.5 vs 29mo, PFS HR .55 median 16.9 vs 5.6mo
- 5yr OS 43 vs 33%, PFS 33 vs 19% (Spigel et al. 2022)
- Surgeon perspective: Up to 50% of patients in this trial were IIIA, how many were potentially resectable?

Adjuvant Trials

IMpower010 (2021) (Felip et al.)

- Phase III
- N = 1280
- **Adjuvant atezolizumab** after resection+adjuvant chemo
- Significant DFS benefit (HR .81) in all patients stage II-IIIA, more benefit in patients whose tumors express PD-L1, especially in patients with PD-L1 >50%

Adjuvant Trials

PEARLS/KEYNOTE-091 (Paz-Ares et al.)

- N=1177
- **Adjuvant pembrolizumab compared with placebo** in patients who underwent resection and adjuvant chemotherapy for stage II to IIIA disease
- DFS of 54 mo vs 42 mo
- HR .76, p=.0014
- PD-L1 >50% group didn’t see added benefit

Potential Advantages of Neoadjuvant Immunotherapy

- Macroscopic tumor proving larger group of neoantigens to activate the immune system
- Concept supported by peripheral selective T-cell expansion seen in trials (Forde, NADIM, etc).
- Neoadjuvant chemotherapy produces an increase in PD-L1 positive tumor cells (poss synergy)
- Allows rapid and complete assessment of tumor sensitivity to systemic treatments
- Adjuvant therapy could allow faster surgery and void surgery delays due to treatment, but these concerns are not borne out in trial data

Neoadjuvant Trials

Forde et al. NEJM 2018

- Pilot study demonstrating safety of neoadjuvant nivolumab
- MPR 45% in resected tumors and treatment induced expansion of mutation associated neoantigen specific T-cell closed in peripheral blood

NADIM (**Phase II**) (46pts) (Provencio et al.)

- Single arm, open label, multicenter study
- **Neoadjuvant chemo + nivolumab** for patients with **stage III** cancer followed by adjuvant nivolumab
- OS 36 months 81.9% in intention to treat population and 91% in per protocol population. PFS at 36 mo: 69.6% and 81.1% respectively.
- 54% of these patients have multi-station N2 disease

Neoadjuvant Trials

LCMC3 (MSKCC) (Lee et al.)

- Phase II, N=181
- **Neoadjuvant atezolizumab** in stage IB-IIIB resectable NSCLC without EGFR/ALK+ mutations
- MPR 20%, pCR 7%
- Pathologic downstaging in 31%

NEOSTAR (MDAnderson) (Cascone et al.)

- Phase II
- **Neoadjuvant nivolumab or nivolumab + ipilimumab** followed by surgery for operable NSCLC
- MPR 24 and 50% respectively in patients resected
- pCR 10 vs 38% respectively
- Greater effector and memory T-cell frequency

Neoadjuvant Trials

Altorki et al. Lancet 2021

- Phase II
- **Neoadjuvant durvalumab** with or without **SBRT** in early stage NSCLC, randomized, single center
- N = 60
- Grade 3-4 adverse events 17 vs 20%
- MPR: 6.7 (durva) vs 53.3%(durva+SBRT), and 27% pCR in durva+SBRT group

Neoadjuvant Trials

Checkmate-816 (**Phase III**) (Forde et al NEJM 2022)

- First to show benefit of neoadjuvant immunotherapy + chemotherapy over standard chemotherapy
- Stage IB-IIIA
- **Neoadjuvant nivolumab + chemo vs chemo alone**
- pCR in 24% vs 2%
- Major pathologic response in resected patients: 47% vs 13%
- Event-free survival 31.6 months vs 20.8 months
- Benefit greater for IIIA (HR .54) than IB or II (HR .87). And greater for patients with PD-L1 >1% (HR .41 vs .85)

Surgical Considerations

- Risk of disease progression before surgery?
- Delays to resection?
- Perioperative morbidity and mortality?
- Intraoperative technical difficulty?

Surgical Timing Considerations

- Treatment Related Adverse Events (**TRAEs**) and the **potential to delay resection**
  - In each phase II trial of neoadjuvant ICIs, 82% **or more** of patients underwent successful surgical resection
  - Across the various ongoing neoadjuvant immunotherapy trials, patients are proceeding to surgery at a rate in line with previous neoadjuvant therapy trials.
- Optimal timing still undetermined
  - Most patients in the trials underwent resection 3-6 weeks after completing neoadjuvant ICI

Early Intraoperative Concerns?

- Have been concerns about technical difficulty associated with neoadjuvant immunotherapy due to significant inflammatory responses and fibrosis at the tumor site and lymph nodes associated with neoadjuvant immunotherapy
- IONESCU trial termination due to 9% 90-day postoperative mortality
  - Ultimately determined not to be surgery/treatment related
- Earliest ICI trials had relatively higher rates of thoracotomy (Bott et al. 2019)

Surgical Video

Robot-Assisted Left Upper Lobectomy After Immunotherapy - YouTube

Surgical Considerations

- Checkmate-816: Chemo-immunotherapy resulted in shorter operations, fewer pneumonectomies, higher rate of minimally invasive surgery, fewer conversions most notable in the IIIA cohort
    - R0 surgery 83 vs 73%
- LCMC3: Conversion to open surgery rate of 15% with complete resection rate of 82.3%
- NADIM: Downstaging rate of 90% and R0 surgery rate 89%
- Only one treatment related postoperative death in neoadjuvant ICI trials and that was in NEOSTAR (BP fistula after steroid-treated pneumonitis/ARDS.
- So although operation may be technically more challenging, it is safe in experienced hands.

Assessment of Treatment Response

- RECIST criteria - uses CT and PET criteria to assess treatment response
  - sens. 73%, spec. 55%, 41% discordance rate (pre-immunotherapy)
  - Immunotherapy response may be particularly difficult to assess due to **pseudoprogression**

- Area of research with radiomics and ctDNA studies, but for the moment response to therapy evaluated at the time of surgery after neoadjuvant therapy offers a reliable assessment of pathologic response to therapy

Pathologic Response Assessment

- Accurate assessment pCR and MPR represents a major advantage of neoadjuvant therapy
  - Prognosis
  - Guide adjuvant therapy

- Potential for pCR and MPR as surrogates for survival will speed trial progress
  - Time to obtain OS data on neoadjuvant therapy trials is 10-13 years from patient enrollment to data publication

Conclusions

Which patients benefit the most?

- Recognized that patients will actionable genomic mutations do not respond well to immunotherapy
  - Early molecular profiling is critical
- Yes benefit: Neoadjuvant chemoimmunotherapy for patients with operable IIIA N2 NSCLC
  - Easy integration as it is not a dramatic change in treatment sequence
  - Fewer pneumonectomies, fewer conversions to open surgery
- Possibly benefit : In patients with stage II/tumors >4cm as well.
  - Benefit smaller (HR .87 Checkmate 816), and represents change in treatment algorithm. And adjuvant therapy also an option based on data, OS may be similar.
  - Coming data should be able to guide this…

Conclusions

- Potential surrogacy of pCR for OS to facilitate evidence based treatment decisions in surgical candidates
- Potential for changes in the populations of patients who stand to benefit from different treatment modalities at both early and late stages
- Surgery, systemic treatments, and radiotherapy all will have critical roles to plan in the investigation and treatment of NSCLC in the immunotherapy era
- Importance of multidisciplinary tumor boards and deciding treatment plan and what it resectable

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