Progress of cancer immunotherapy and its future perspectives

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Cancer immunotherapy

Current status and future perspectives

• Cancer immunotherapy is now a promising therapy!
  – Durable responses for advanced cancer patients with multiple cancer types
  – Immune-checkpoint blockade (PD-1/PD-L1, CTLA4)
  – T-cell based adoptive cell therapy (TIL, TCR/CAR-T cells)

• The clinical issues to be solved;
  – Identification of biomarkers for personalized therapy
    • Selection of appropriate patients / Selection of appropriate immunotherapy
  – Development of combination immunotherapy
    particularly for non-responsive patients to the current immunotherapy

• Further understanding of immunopathology of cancer
  particularly in tumor microenvironment and it’s modulation!
  – Individual difference of immune status in cancer patients
  – It’s correlation with response to various cancer therapies
  – Multiple mechanisms of immune-evasion; Appropriate interventions!
  – Personalized immunotherapy based on the immune-evaluation!
  – Combination immunotherapy targeting multiple key regulation points!
Cancer immunotherapy

- Active immunization (Cancer vaccines)
  - Prophylactic vaccines for microbes
  - Adjuvant vaccines to prevent relapse
  - Immunotherapy to reduce tumors

- Non-specific immunomodulators
  (BCG, OK432, PSK, etc)

- Tumor Ags
  (peptides, proteins, DNA etc)

- Tumor extracted Ags

- Dendritic cells pulsed with tumor Ags

- Modified cancer cells

- Tumor Ag reactive T-cells

- PBMC
  + Tumor Ags
  + Cytokines
  + TCR/CAR transduction

- TIL
  + Cytokines

- Allogeneic lymphocytes
  (Allo-BMT, DLI)

- Reversal of immunosuppression
  (PD-1/PD-L1, etc)
Important issues for development of immunotherapy

- **Survival**
  - Months

Current immunotherapy (e.g. anti-CTLA-4 / PD-1 Ab)

Standard therapy (e.g. Chemotherapy / molecular target therapy)

- **Biomarkers for personalized therapy**
  - Selection of appropriate patients
  - Selection of appropriate immunotherapy

Further understanding of human cancer immunology!

- Improvement of immunotherapy by combination immunotherapy?
- Non-responders convert to responders

Immunomonitoring methods?

Clinical evaluation?
- irRC, irRECIST, delayed clinical effects
Positive and negative immune responses to cancer

- Oncogene triggered immunosuppression
- Anti-tumor T-cell triggered immunosuppression

**Immunosuppressive cells**

- **Oncogene triggered immunosuppression**
  - Myeloid derived suppressor cells (MDSC)
  - Regulator T-cells (Treg)

**Cancer cell**
- Passenger mutations
- Driver mutations
- Gene alteration

**Dendritic cell**
- Tumor Ags
- Chemokine, CXCL13, CCL4
- Cytokine, IL15
- HLA

**Cytotoxic T-cells**
- Tumor Ags
- T-cell receptor
- PD-1
- PD-L1
- IDO
- IFN-γ

**Immunosuppressive molecules** (e.g. TGF-β, VEGF, PGE2)

**Local negative immune-feedback Adaptive resistance**

**Environmental factors**
- smoking, diet/obesity
- microbiota, infection history
## Immunotherapy using Ab specific for targets on T-cells

### Anti-PD-1Ab (Nivolumab)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Response rate</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>26/94</td>
<td>28%</td>
</tr>
<tr>
<td>RCC</td>
<td>9/33</td>
<td>27%</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>14/76</td>
<td>18%</td>
</tr>
</tbody>
</table>

Durable responses (over 1 year or more) in 20 of 31 (65%) responders

*Topalian SL, et al, NEJM 2012*

### Anti-PD-L1Ab

<table>
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<tr>
<th>Condition</th>
<th>Response rate</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>3/16</td>
<td>19%</td>
</tr>
<tr>
<td>RCC</td>
<td>2/17</td>
<td>12%</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4/15</td>
<td>16%</td>
</tr>
</tbody>
</table>

Less immune-adverse effects than anti-CTLA4 Ab

*Brahmer JR et al, NEJM 2012*

### Anti-CTLA4 Ab (Ipilimumab)

- Median Survival: 10mo vs 6.4mo (n=676)

*Hodi FS, et al, NEJM 2010*

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**Diagram:**

- **Effector T cells**
  - PD-1
  - (-)
  - CTLA4
- **Cancer cells**
  - PD-L1
  - CD80/86
- **T reg**

CTLA-4/Treg is involved in peripheral tolerance → More autoimmune AE
Human tumor antigens recognized by tumor infiltrating T-cells

- **Mutated antigens derived from DNA alterations in cancer cells**
  (β-catenin, etc) SYLDSGIH\(\text{S}(F)\) \(\rightarrow\) acquire HLA-binding

- **Viral related antigens**
  (HPV-E6/E7)

- **Cancer-testis antigens**
  (MAGEs, NY-ESO-1)

- **Tissue specific antigens**
  (MART-1/Melan-A, gp100)

- **Over-expressed antigens**

- **Allo-antigens**

- **Others**

**Mechanisms for T-cell epitope generation**

- **Neo-antigens**

  - Cancer cell
  - T cell
  - Peptide splicing

  - Other components
Novel personalized immunotherapy targeting individual mutations

- Identification of mutations by exomic-sequencing of autologous cancer cells

- Prediction of HLA binding peptides by computer argorithsms

- Confirmation of T cell epitopes by
  - *in vitro* peptide induction of T cells
  - immunization of HLA transgenic mice
  - using HLA tetramers

- Active immunization with peptides / mRNA
- ACT with TIL / TCR-transduced T cells
Issues to be solved in the immuno-checkpoint blockade

• **When used?** Advanced cancer, frontline treatment, adjuvant setting

• **When stopped?** How long should be used? (high cost, economical issues)

• **Personalized immunotherapy**
  – Unresponsive cancer: pancreas ca., MSS-CRC, myeloma, prostate ca,
  – Non-responders convert to responders

  *Biomarkers* (PD-L1 exp, CD8+T cell infiltration, DNA mutations, MDSC, Treg, etc) through systematic analysis of clinical trials (Omics, microbiota, immuno-analysis)

  *Pretreatment, early on-treatment*

  *Biomarkers can be new treatment targets*

• **Combination immunotherapy with personalized interventions**
  – Immunogenic cancer cell death, adjuvant, vaccine, immune-regulators
  – Enhanced anti-tumor effects w/o increase of adverse effects?
  – Which combination? Concurrent vs sequential?
  – **Combination of chemotherapy / molecular target therapy**
    w/ checkpoint blockade: high immunogenic mutation (melanoma, NSCLC)
    w/ ACT: less immunogenic leukemia, NSCLC, etc,
Combined immunotherapy targeting multiple key regulation points in anti-tumor T cell response

Tumor antigen vaccine
- Mutated Ags
- Cancer stem cell Ags

Augmentation of dendritic cell function
- Adjuvant (TLR3, STING), Ab (CD40 agonist)

Cancer
- NKT/NK/γδT
- Tumor Ag
- HLA

Tumor Ag
- (-)
- T-cell activation / expansion
- Cytokines (IL2, IL7, IL15, IL21)
- Agonist Ab (4-1BB, OX40)

Dendritic cell
- Tumor Ag
- HLA
- T-cell activation / expansion
- Cytokines (IL2, IL7, IL15, IL21)
- Agonist Ab (4-1BB, OX40)

Anti-tumor T cells
- PD-1
- PD-L1

Cancer
- Cox2
- IDO/TDO

Immunosuppressive molecules /cells
- TGF-β, VEGF, IL10, IL6, PG-E2, T-reg, MDSC

In site tumor destruction
<Immunogenic cell death>
- Chemotherapy • Ab • physical • Virus, etc

Reversal of immunosuppression
- Signal inhibitors, Chemotherapy, IDO inhibitor, Ab (CTLA4, PD-1, LAG3, CCR4, TIM3, TIGIT), RNAi, etc
Adoptive cellular immunotherapy using tumor antigen specific *ex vivo* cultured T-cells

Tumor infiltrating T-cells

- cytokine

Blood T-cells

- Tumor Ag stimulation
- Gene transfer of tumor Ag receptor

TCR: T-cell receptor

CAR: chimeric Ag receptor

CD3

CD8

TCR

Melanoma

Cervical ca

HLA

Tumor Ag

Recognition w/o HLA
Important issues to be solved for developing effective immunotherapy

- Identification of Biomarkers?
- Further understanding of human cancer immunology in tumor microenvironments!
- Combination immunotherapy?

Personalized immunotherapy based on the immune evaluation

Survival

Standard therapy

Current immunotherapy

- Anti-PD-1/PD-L1 Ab +
  - Anti-CTLA4 Ab (Other costimulatory mole.)
  - IDO/TDO inhibitor
  - Molecular target / chemotherapy
  - Radiation
  - Cancer vaccine
  - T cell ACT
  - Novel therapies
日本における個別化・複合がん免疫療法開発の課題

＊日本での複合免疫療法の臨床試験実施と病態解析研究を！
・複合免疫療法臨床試験のための企業間連携はすでに進めている！
・新たな産学官連携の構築が必要（win-win situation, high cost, 得意分野）！

-アカデミアシーズ・ノウハウの効率的な企業への受け渡し
・日本医療研究開発機構(AMED)(Japan Cancer Research Project)でのシーズ開発
・複合免疫療法の医師主導臨床試験の実施を！（AMEDにも期待？）
・企業にとって 真に有用なシーズ、適切な組み合わせ、評価法と対策の提言！

-企業治験におけるアカデミアによる病態解析（治療効果・副作用機序）
・治験段階での免疫学的解析一＞次のステップのためのシーズ（診断・治療標的）！
・治験の空洞化問題（臨床研究中核病院）
・企業にとって 真に有用な評価法、臨床データとその解釈、さらにその検証！

・全国レベルでのがん患者ネットワークの構築、臨床検体収集システム、
各種システム生物学的解析拠点体制の構築 ＜AMEDへの期待！＞
・米国NCIの全国ネットワーク（e.g. 肺癌変異シークエンスシステム）
・米国GoogleのCancer Immunotherapy開発への参画？
・日本における産官学コンソーシアムの確立（議論の場の提供）
＜米国SITC / CRI, EU-CIMT＞
新しい医療の健全な均てん化・教育

・異なる治療効果判定基準
  • RECISTだけでは不十分（irRCやirRECISTの併用）

・化学療法や分子標的治療薬とは異なる副作用と対策
  • 免疫性副作用（皮膚炎、甲状腺炎、腸炎、肝炎など）
  • 間質性肺炎や下垂体炎、筋無力症などの重篤、致死的な副作用
  • 適正使用ガイドが作成されており、医療従事者は十分に熟知する必要

・多職種医療チームへの教育
  • ガイドライン
  • 医師はもちろんのこと、がんチーム医療において、薬剤師、看護師など広く各職種への教育体制も重要