Historical overview of immunotherapy

Before introduction of immune checkpoint inhibitors

John B.A.G. Haanen, MD PhD
My disclosures

• I have provided consultation, attended advisory boards, and/or provided lectures for: **Pfizer, Bayer, MSD, BMS, IPSEN, Novartis, Roche/Genentech, Neon Therapeutics, Celsius Therapeutics, Gadeta BV, Immunocore, Seattle genetics** for which NKI received honoraria

• Through my work NKI received grant support from **BMS, MSD, Novartis** and **Neon Therapeutics**
Historical background
examples of immunotherapy and their impact on survival

• **Coley’s toxine and spin-off**

• **Allogeneic bone marrow and peripheral stem cell transplantations**
  – Hematological malignancies
  – (Solid tumors)

• **High dose interleukin-2 and LAK cell therapy**
  – Metastatic melanoma
  – Metastatic clear cell renal cell cancer

• **Adoptive cell therapy with TIL**
History of cancer immunotherapy

- **1863**: Coley’s toxin
- **1898**: Virchow: Immune infiltrates
- **1957**: Burnet: Immune-surveillance
- **1976**: Rosenberg: IL-2 and LAK cells
- **1985**: Maloney: Rituximab
- **1992**: Lejeune: Isolated limb perfusion
- **1995**: Slaman: Trastuzumab
- **1998**: Bendani: Anti-idiotype vaccination

Courtesy of R. Stahel
Coley’s toxin

Complete remission of a sarcoma in a patient after 2 episodes of erysipelas caused by streptococcus pyogenes

William Coley, 1893

Courtesy of R. Stahel
Coley’s toxin

- Induction of erysipelas by direct inoculation with streptococci

- Coley’s toxin: Heat inactivated mixture of streptococci and serratia
  About 900 patients treated, most inoperable sarcoma, 10% response rate. Treatment associated high fever

William Coley, 1909

Courtesy of R. Stahel
Coley's Active Career (1890-1936)

1890 - 1891 - 1894

Coley repeatedly calls attention to sarcomas as being comparatively sensitive to his treatment.

1909

Vaccine of undetermined origin used unsuccessfully to treat melanoma and sarcoma patients, half of which were inappropriately selected.

1931

Carswell et al. use a murine sarcoma in the discovery of TNF.

1936

Vaccine used improperly to treat unselected patient population; isolated, but dramatic response in ovarian carcinoma.

1962

Vaccine used concomitantly with chemotherapy to treat lymphoma patients; only modest effects.

1965

Berendt et al. use sarcomas to illustrate the importance of tumor immunogenicity to the curative effects of endotoxin.

1981

Demetri et al. empirically select sarcomas for treatment with TNF and γ-interferon.
Isolated Limb Perfusion With High-Dose Tumor Necrosis Factor-α in Combination With Interferon-γ and Melphalan for Nonresectable Extremity Soft Tissue Sarcomas: A Multicenter Trial


**Conclusion:** ILP with TNF, IFN, and melphalan is a safe and highly effective induction biochemotherapy procedure that can achieve limb salvage in patients with nonresectable extremity STS. TNF is an active anticancer drug in humans in the setting of ILP.

Immunotherapy with BCG

- **Raymond Pearl, Amer J Hyg 1929:** Lower incidence of cancer in patients with TB
- **Lloyd Old, Nature 1959:** Mice infected with BCG have resistance to transplantable tumors
- **Burton Zbar, JNCI 1971:** Suppression of tumor growth in mice at the site of infection with BCG
- **George Mathé, 1968:** Adjuvant BCG in children with acute lymphoblastic leukemia
- **Donald Morton, Surgery 1970:** Intrallesional treatment of melanoma metastases with BCG
- **Alvaro Morales, J Urol 1976:** Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors
Immune Surveillance of Tumours

- *Paul Ehrlich 1909*: the immune system might repress a potential overwhelming frequency of carcinomas

Courtesy of R. Stahel
Immune Surveillance of Tumours

**Lewis Thomas 1957:**
“… the primary function of cellular immunity is in fact not to promote allograft rejection but rather to protect from neoplastic disease, thereby maintaining tissue homeostasis in complex multicellular organisms”

**1982 Lewis Thomas:**
“the greatest trouble with the idea of immunosurveillance is that it cannot be shown to exist in experimental animals”

Courtesy of R. Stahel
Immune Surveillance of Tumours

Sir Macfarlane Burnet, 1964

“...in animals, ..., inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy.

It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character.”
Cancer Immunoediting

Schreiber et al., Science 2011
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• Adoptive cell therapy with TIL
Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT)

M Aoudjhane¹, M Labopin¹, NC Gorin¹, A Shimoni¹, T Ruutu¹, H-J Kolb¹, F Frassoni¹, JM Boiron¹, JL Yin¹, J Finke¹, H Shouten¹, D Blaise¹, M Falda¹, AA Fauser¹, J Esteve¹, E Polge¹, S Slavin¹, D Niedewieser¹, A Nagler¹ and V Rocha¹ on behalf of the Acute Leukemia Working Party of EBMT²

OS comparing RIC and MA PSCT from HLA identical siblings

Aoudjhane et al., Leukemia 2005;
Donor Lymphocyte Infusion in the Treatment of First Hematological Relapse After Allogeneic Stem-Cell Transplantation in Adults With Acute Myeloid Leukemia: A Retrospective Risk Factors Analysis and Comparison With Other Strategies by the EBMT Acute Leukemia Working Party

Schmid et al., JCO 2007
REGRESSION OF METASTATIC RENAL-CELL CARCINOMA AFTER NONMYELOABLATIVE ALLOGENEIC PERIPHERAL-BLOOD STEM-CELL TRANSPLANTATION

RICHARD CHILDs, M.D., ALLEN CHERNOFF, M.D., NATHALIE CONTENTIN, M.D., ERKUT BAHCECI, M.D., DAVID SCHRUMP, M.D., SUSAN LEITMAN, M.D., ELIZABETH J. READ, M.D., JOHN TISDALE, M.D., CYNTHIA DUNBAR, M.D., W. MARSTON LINEHAN, M.D., NEAL S. YOUNG, M.D., AND A. JOHN BARRETT, M.D.
Outcome of mRCC patients treated with allogeneic PSCT

Childs et al., NEJM 2000
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LAK cell therapy and Interleukin-2

Steven Rosenberg, NEJM 1985: Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer
LAK cell therapy in combination with interleukin-2

Steven Rosenberg, NEJM 1985: Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise</td>
<td>25</td>
</tr>
<tr>
<td>Fever</td>
<td>22</td>
</tr>
<tr>
<td>Chills</td>
<td>19</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
</tr>
<tr>
<td>Confusion</td>
<td>8</td>
</tr>
<tr>
<td>Weight gain (&gt;10%)</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>20</td>
</tr>
<tr>
<td>Erythema or rash</td>
<td>17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
</tr>
<tr>
<td>Glossitis</td>
<td>14</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>13</td>
</tr>
<tr>
<td>Serum creatinine &gt;2 mg/dl</td>
<td>12</td>
</tr>
<tr>
<td>Serum bilirubin &gt;2 mg/dl</td>
<td>16</td>
</tr>
<tr>
<td>Eosinophilia &gt;5%</td>
<td>24</td>
</tr>
<tr>
<td>Anemia requiring transfusion</td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50,000/mm³)</td>
<td>11</td>
</tr>
</tbody>
</table>
Tolerance and effectiveness of recombinant interleukin-2 and lymphokine-activated killer cells in patients with metastatic solid tumors

- 26 patients with metastatic solid tumors, including 14 renal cell carcinomas, seven melanomas, three extragonadal germ cell tumors refractory to chemotherapy and two colon carcinomas

- Capillary leak syndrome with hypotension and impaired renal function and CNS toxicity were the major reasons for dose modification

- Partial responses were documented in three renal cell carcinomas and one melanoma. The median response duration was 5.5 (range 1-6) months.

Stahel, Eur J Cancer Clin Oncol 1989
High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993


Randomized Study of High-Dose and Low-Dose Interleukin-2 in Patients With Metastatic Renal Cancer

By James C. Yang, Richard M. Sherry, Seth M. Steinberg, Suzanne L. Topalian, Douglas J. Schwartzentruber, Patrick Hwu, Claudia A. Seipp, Linda Rogers-Freezer, Kathleen E. Morton, Donald E. White, David J. Liewehr, Maria J. Merino, and Steven A. Rosenberg

Randomized Phase III Trial of High-Dose Interleukin-2 Versus Subcutaneous Interleukin-2 and Interferon in Patients With Metastatic Renal Cell Carcinoma

David F. McDermott, Meredith M. Regan, Joseph I. Clark, Lawrence E. Flaherty, Geoffery R. Weiss, Theodore F. Logan, John M. Kirkwood, Michael S. Gordon, Jeffrey A. Sosman, Marc S. Ernstoff, Christopher P.G. Treffer, Walter J. Urba, John W. Smith, Kim A. Margolin, James W. Mier, Jared A. Gollob, Janice P. Dutcher, and Michael B. Atkins

Atkins et al., JCO 1999; Yang et al., JCO 2003; McDermott et al., JCO 2005
Overall Survival of patients with metastatic RCC treated with high dose IL-2

Atkins et al., JCO 1999
Durability of Complete Responses in Patients With Metastatic Cancer Treated With High-Dose Interleukin-2

Identification of the Antigens Mediating Response

Steven A. Rosenberg, MD, PhD,* James C. Yang, MD,* Donald E. White, MS,* and Seth M. Steinberg, PhD†

Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Proportion Surviving</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td></td>
<td>27 (14.8)</td>
</tr>
<tr>
<td>Renal cancer</td>
<td></td>
<td>43 (19.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>70 (17.1)</td>
</tr>
</tbody>
</table>

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Cancer Regression and Autoimmunity in Patients After Clonal Repopulation with Antitumor Lymphocytes

Mark E. Dudley,1 John R. Wunderlich,1 Paul F. Robbins,1 James C. Yang,1 Patrick Hwu,1 Douglas J. Schwartzentruber,1 Suzanne L. Topalian,1 Richard Sherry,1 Nicholas P. Restifo,1 Amy M. Hubicki,1 Michael R. Robinson,2 Mark Raffeld,3 Paul Duray,3 Claudia A. Seipp,1 Linda Rogers-Freezer,1 Kathleen E. Morton,1 Sharon A. Mavroukakis,1 Donald E. White,1 Steven A. Rosenberg1*
Scheme for TIL therapy

1. Excise tumor
2. Plate tumor fragments
3. Culture with 6000 IU/mL IL-2
4. Select and expand to $10^{10}$ cells
5. Reinfuse post-lymphodepletion
Lymphodepletion prior to T cell transfer is followed by immune reconstitution

Peripheral blood cell count

- 6000 cells per mm$^3$

- Cyclophosphamide
- Fludarabine
- T cell transfer
- IL-2

Days from cell infusion

- White blood cell count
- Absolute neutrophil count
- Absolute lymphocyte count
Preparative Regimens for Cell Transfer

<table>
<thead>
<tr>
<th>Days</th>
<th>-7</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-myeloablative</td>
<td>Cy</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Cells</td>
<td>IL-2</td>
<td>IL-2</td>
<td>IL-2</td>
</tr>
<tr>
<td>Ablative</td>
<td>(200cGy)</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>TBI</td>
<td>Cells</td>
<td>IL-2</td>
<td>IL-2</td>
</tr>
<tr>
<td>Ablative</td>
<td>(1200cGy)</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>TBI</td>
<td>TBI</td>
<td>TBI</td>
<td>Cells</td>
</tr>
</tbody>
</table>

Current Opinion in Immunology

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**Cell transfer therapy.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>PR</th>
<th>CR</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TBI</td>
<td>43</td>
<td>17 (77+, 45+, 34+, 28, 28, 14, 13, 11, 8, 8, 7, 4, 3, 3, 2, 2, 2)</td>
<td>3 (75+, 70+, 60+, 59+)</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>200 cGy TBI</td>
<td>25</td>
<td>11 (45+.41+.35+.14 10, 6, 5, 5, 4, 3, 3)</td>
<td>2 (49+, 38+)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>1200 cGy TBI</td>
<td>25</td>
<td>11 (26+, 19+, 19+, 19+, 13, 7, 6, 6, 5, 4, 3)</td>
<td>7 (29+, 19, 25+, 25+, 19+, 19+, 18+)</td>
<td>18 (72%)</td>
</tr>
</tbody>
</table>

52 responding patients: 42 had prior IL-2, 21 had prior IL-2+ chemotherapy.

*All patients with metastatic melanoma received a preparative regimen of cyclophosphamide (60 mg/kg/day × 2d) and fludarabine (25 mg/m²/day × 5d) either with no total body irradiation (TBI) or with 200 or 1200 cGy TBI followed by the administration of autologous TIL plus IL-2 (720,000IU/kg q 8 h).*

Rosenberg and Dudley. Curr Opin Immunol 2009
Summary

• Over more than 100 years the role of the immune system in defense against cancer has established
• Immunotherapy of cancer has slowly developed into an effective treatment for few patients, sometimes with severe toxicities
• Currently, with the arrival of immune checkpoint blockers and new modalities of adoptive cell therapy (CARs), immunotherapy has led to a paradigm shift in the treatment of cancer
FDA approvals for immune checkpoint blockers, diagnostic tests, and treatment combinations

Courtesy of S. Topalian (JAMA 2017)