Immunotherapy

Inspire to Live

CCA

Bob Pinedo

8 februari 2018
Immunity is required to successfully reject cancer

Discovered that bacterial infections sometimes coincide with tumor rejection.
Treated ~900 patients with bacterial extract known as ‘Coley’s Toxin’ (1915)
Achieved up to 40% success rate in cancer patients.
Poorly understood and (too) toxic.

Immunity is the key to curing cancer
Science breakthrough of the past year: Immunotherapy

Evolving insights over the years at VUmc

1) Autologous whole tumor-cell immunization
2) Chemo-immunotherapy: in vivo vaccination
3) Allo-GVAX with ipilimumab/CTLA-4 blockade
4) Antibodies
5) Cytolytic virusses
Immunotherapy

Active Specific Immunotherapy

Intradermal Injection

Addition of Immuno stimulant

tumor cell suspension

Colon cancer

The Lancet, 1999
Autologous vaccination in the thigh
Autologous vaccination in colon cancer

Vaccines 1 and 2: $10^7$ autologous tumor cells + $10^7$ BCG organisms
Vaccines 3 and 4: $10^7$ autologous tumor cells
Recurrence Free Interval
All Randomized Patients

Vermorken et al, The Lancet 1999
Recurrence-Free Interval following Adjuvant Autologous Vaccination (AV)

p-value 0.033

254 randomized patients

De Weger et al, *Clin Cancer Res* 2012; 18: 882-889
Study design

Original study Vermorken and colleagues N = 254
  (Control, n = 126)
  (ASI, n = 128)

Analyzed for microsatellite status N = 196
  (Control, n = 100)
  (ASI, n = 96)

Not analyzed for microsatellite status N = 58
  (Not traced back, n = 37)
  (Poor quality, n = 21)

MSI
  N = 34
  (MSI-Control, n = 20)
  (MSI-ASI, n = 14)

MSS
  N = 162
  (MSS-Control, n = 80)
  (MSS-ASI, n = 82)
RFS in 2010 analysis: MSS+MSI
DSS in 2010 analysis: MSS+MSI

![Graph showing survival rates with different markers for MSS and MSI]
DTH response
Autologous Vaccination in Melanoma
COURSE OF DISEASE AFTER REMOVAL OF METASTASES OF MELANOMA

• 58 yr old man presented with multiple metastases in right lung underwent resection of 8 metastases
• Autologous immunization (AV) every 3 months for 2 years
• At 60 yrs new metastasis removed
• AV resumed every 3 months for 2 more years
• At 68 yrs he died of unrelated disease
Melanoma (8 metastases at thoracotomy)
Melanoma: Metastectomy and Successful Use of the Cancer Cells as Autologous Vaccine (AV)

Resection of 8 lung mets
AV q 3 mths during 2 yrs
At 2 yrs new lung lesion resected
AV resumed q 3 mths for 2 more yrs

PD in right groin after treatment-free period
Resistance to chemotherapy
Intra-metastatic Lymphoid Follicles

HE
CD3+
CD4+
CD8+
Survival according to remaining disease following surgery in melanoma stage III-IV

Rembrandt’s Batseba
Phase 2 study of neoadjuvant AC + GM-CSF in LABC OS according to number of cycles

Honkoop et al. The Oncologist 2000
Neoadjuvant Chemo-immunotherapy in LABC
Change in Multidisciplinary Approach

Mastectomie
Radiotherapie

GM-CSF

AC
The Pre-existent idea...

Breast cancer

Lymph vessel

chemotherapy induced tumor cell death and tumor-antigen release

GM-CSF recruits and stimulates DC

bone marrow

Axillary lymph nodes

kill of micrometastases

CTL

Th

DC
DC infiltration following GM-CSF injection in skin

Increase of number of DC’s (HLA-DR+) in skin
Phase 1 study anti-CTLA4 Treatment schema

**GVAX** every 2 weeks for a total of 13 i.d. doses

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose</th>
<th>Patient #</th>
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<tbody>
<tr>
<td>w0</td>
<td>0.3</td>
<td>1-3</td>
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<tr>
<td>v1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>w4</td>
<td>1.0</td>
<td>4-6</td>
</tr>
<tr>
<td>v3</td>
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<tr>
<td>w8</td>
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<td>7-9</td>
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<td>v5</td>
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<td>w12</td>
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<td>v7</td>
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<td>w16</td>
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<td>fu1</td>
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* blood sampling for immunomonitoring

Skin reactions at the GVAX injection sites

GVAX IT alone

GVAX IT + MDX-010 (0.3 mg/kg)

GVAX IT + MDX-010 (3 mg/kg) After 1 week
PSA curves – Dose Level 3 (3 mg/kg)

a: 13Mar06: Hypophysitis (7m)
b: 03Feb06: Hypophysitis (5 mo)
c: 09Feb06: Hypophysitis (5 mo)
Bone Scan Improvement in Patient 8 (3 mg/kg)

15 Sept 05

29 Mar 06
# Breakthrough: Guidance by T-Cell Profiling in Blood, Tumor and Lymph nodes

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>STAGE</th>
<th>TREATMENT</th>
<th>IMMUNOSTIMULANT</th>
<th>PREDICTIVE FACTOR</th>
<th>REFERENCE</th>
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<tbody>
<tr>
<td>MELANOMA</td>
<td>METASTATIC</td>
<td>EXCISION METS + AUTOLOGOUS TUMOR CELL VACCINATION</td>
<td>BCG</td>
<td>MELANOMA-SPECIFIC TILs, BUT NOT CIRCULATING CD8+ T CELLS, DTH</td>
<td>Haanen, Baars, Cancer Imm.Immunother. ‘06</td>
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<tr>
<td></td>
<td>DISEASE</td>
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<td>Baars, Ann Oncol, 2000</td>
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<tr>
<td>COLORECTAL CANCER</td>
<td>PRIMARY STAGE 2</td>
<td>SURGERY PLUS AUTOLOGOUS TUMOR CELL VACCINATION</td>
<td>BCG</td>
<td>MSI/MSS, CD8, CD8 T-CELL INFILTRATION</td>
<td>De Weger et al., Clin Cancer Res, ‘11 Turksma</td>
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<tr>
<td>BREAST CANCER (LABC)</td>
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<td></td>
<td></td>
<td></td>
<td>Van Cruijsen et al, in pr DeNardo, Cancer Discovery, ‘11</td>
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<tr>
<td>PROSTATE CANCER</td>
<td>ADVANCED</td>
<td>ALLO-GVAX VACCINATION</td>
<td>IPILIMUMAB/GM-CSF</td>
<td>Teff/Treg ratio and CTLA-4 activated Th CELLS; High DC, low MDSC frequencies</td>
<td>Santegoets, Cancer Imm. Immunother, ‘13 and submitted.</td>
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<td>HORMONE RESISTANT</td>
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….. Studies on profiling following anti-PD1 and others running…….