Brave New World of Cancer Therapeutics
(Back to the Future)

Alexandra M. Levine, MD, MACP

Chief Medical Officer
Melinda & Norman Payson Professor of Medicine
Professor of Hematology/HCT
City of Hope National Medical Center

Distinguished Professor of Medicine, Emeritus
Keck School of Medicine of USC
FACULTY DISCLOSURE

I have no conflict of interests to disclose.
There is a relationship between Mind and Body
We have had Western medicines for less than 100 years, but doctors (healers, “medicine men”, etc.) have been present for THOUSANDS of years.

If they were not effective, we (ie the doctors) might not even be here today.
RE-INTRODUCE THE OLDEST ADVANCE IN MEDICINES.

It's called talking. Right or wrong, many older people today feel that doctors just don't spend as much time talking with their patients as they used to. Things seem more rushed and hurried.

But talking, especially about medicines, is more important than ever before. Your older patients may be taking several different medicines and seeing more than one doctor. And many older people are treating themselves with over-the-counter drugs.

Unfortunately, an older person's response to medicines is less predictable than a younger person's. They can experience altered drug actions and adverse drug reactions.

So, if they don't tell you first, ask them what they're taking and if the medicines are causing any problems. Take a complete medications history including both prescription and non-prescription medicines.

Make it a point to tell them what they need to know—the medicine's name, how and when to take it, precautions, and possible side effects. Give them written or printed information they can take home, and encourage them to write down what you tell them.

Good, clear communication about medicines can increase compliance, prevent problems, and lead to better health.

So re-introduce the oldest advance in medicines. Make taking a crucial part of your practice. It isn't a thing of the past. It's the way to a healthier future.

Before they take it, talk about it.

National Council on
Patient Information and Education
660 Eleventh St. NW, Suite 200
Washington, D.C. 20001
“…One of the essential qualities of the clinician is interest in humanity, FOR THE SECRET OF THE CARE OF THE PATIENT IS IN CARING FOR THE PATIENT.”

F.W. Peabody
Doctor and Patient
Harvard University Press
Cambridge, Mass, 1928
Can human caring / kindness / attention really work??

(Even in cancer or AIDS?)
Indolent Lymphoma (Follicular, grade 1)
March, 1989
Indolent Lymphoma (Follicular, grade 1)
June, 1990
Indolent Lymphoma (Follicular, grade 1)  
June, 1990 

NO THERAPY GIVEN
Natural History of Low-Grade, Indolent Lymphoma

Spontaneous regression in 20-30%

• Median duration = 15 mos
  (range 4+ to 72+ mos)

What about HIV/AIDS??
Effect of Psychological Distress on Progression to AIDS in 451 HIV+ IDU’s (ALIVE Study)

MULTIVARIATE ANALYSIS: Stress; CD4<200; Thrush

Potential Biologic Mechanisms for “Mind-Body” Connection

A. Immunologic

B. Stress catecholamines

C. Other
Macrophage Engulfing BCG

Natural killer cell
Attacking cancer cell
How Dendritic Cells Jump-Start the Immune Response

Activated Dendritic Cell
Cytotoxic T 8 Cells Attacking Cancer Cell
Mechanism Cell Death by Activated Cytotoxic T-Cells

Fundamentally, cancer requires at least two “errors / accidents”

- Error at level of DNA (“genomic” error), giving a growth / survival advantage to that cell and its progeny

- A failure of the host immune system to recognize the error, and destroy this new “foreign” cell
NOW,
to the FUTURE
(and PRESENT)
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
IMMUNOTHERAPY

The use of the immune system to treat disease

FIRST EXAMPLE

Coley’s Toxins - Injected purulent material from infected cancer material into other cancer patients, with clinical benefit

Coley, WB: Annals of Surgery 1891
Adoptive T cell transfer of autologous CTL’s for treatment of cancer

History of T Cell Therapy (Melanoma / Renal Cell Cancer)

- IL-2 infusions (T cell growth factor) → 6-7% complete remission; most sustained for > 30 years

- IL-2 plus autologous anti-tumor T cells → 56% response (52/93) 22% CR, all sustained from 5 to 11+ years

Therapeutic approaches to overcome immune tolerance to cancer cells

Cytokine Therapy
IL-2, IFN
IL-7, IL-15, IL-21

Therapeutic Vaccines
Dendritic cell vaccines
DNA, RNA, Engineered tumor cells

Checkpoint blockade
anti-CLTA4
anti-PD1
anti-PDL1

Tumor-specific T cell
MHC-peptide antigen

Chemotherapy

Antibody-drug conjugates
Gentuzumab ozogamicin

T cell clones
CAR-T cells
TCR engineered T cells

CELL-SURFACE ANTIGENS ON THE B CELL

Monoclonal Antibodies Currently in Use for Lymphoma (NHL)

“COLD” ANTIBODY = Rituximab Anti-CD 20

Fc

Fab

CD20

NHL
Monoclonal Antibodies Currently in Use for NHL

"COLD" ANTIBODY = Rituximab Anti-CD 20

MACROPHAGE in spleen

Fc Receptor
Bi-specific T cell Engager (BiTE) Rx for A.L.L. 
Mechanism of Action for Blinatumomab

History of T Cell Therapy (Melanoma / Renal Cell Cancer)

- LL-2 infusions (T cell growth factor) → 6-7% complete remission most sustained for > 30 years
- IL-2 plus autologous anti-tumor T cells → 56% response (52/93) 22% CR, all sustained from 5 to 11+ years

THE FUTURE IS NOW

Genetic modification of normal lymphocytes with receptors reactive against tumor antigens

Therapeutic approaches to overcome immune tolerance to cancer cells

Cytokine Therapy
- IL-2, IFN
- IL-7, IL-15, IL-21

Therapeutic Vaccines
- Dendritic cell vaccines
- DNA, RNA, Engineered tumor cells

Checkpoint blockade
- anti-CLTA4
- anti-PD1
- anti-PDL1

Tumor-specific T cell

Tumor cell

Chemotherapy

Antibody-drug conjugates
- Gentuzumab ozogamicin

T cell clones

CAR-T cells

TCR engineered T cells

Pathway for designing optimal Chimeric Antigen Receptor (CAR-T) cells for tumor cell kill

Schema: Personalized / Precision immunotherapy using gene modified cells

- Lymphocytes from patient
- Tumor sample from patient
- Viral vector encoding antitumor antigen receptor
- Cells expanded in culture
- Antitumor lymphocytes
- Cells + IL-2
- Reinfused

New generations of CAR-T cells

Method for generation of CAR-T cells against tumor associated antigens

1. Leukapheresis (Remove immune cells from blood)
2. Isolate and activate T cells
3. Genetically engineer T cells with tumor-specific chimeric antigen receptor (CAR)
4. Stimulate replication of tumor-specific engineered CAR T cells
5. Infuse engineered CAR T cells
Anti-CD19 CAR-T cell Rx in NHL

CD19 CAR-T cell Rx in 30 patients with relapsed / refractory ALL

Correlates of Cytokine Release Syndrome after CAR-T cell therapy

CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy
Therapeutic approaches to overcome immune tolerance to cancer cells

Cytokine Therapy
- IL-2
- IFN
- IL-7, IL-15, IL-21

Therapeutic Vaccines
- Dendritic cell vaccines
- DNA, RNA, Engineered tumor cells

Checkpoint blockade
- anti-CLTA4
- anti-PD1
- anti-PDL1

Chemotherapy

Tumor cell

Tumor-specific T cell

T cell clones

CAR-T cells

TCR engineered T cells

Immune Checkpoints: Convergence of Cancer Treatment & HIV Cure

BY PAUL VOLBERDING, MD

Cancer biology and the immune system have long been known to enjoy an intimate relationship. The increased incidence of some cancers in immunosuppressed individuals led to speculations that oncogenesis events are common but detected by “immune surveillance” systems that might recognize and eliminate newly formed malignant cells before they became an established and independent cancer. The dramatic increase in certain cancers in persons infected with HIV—especially ones with a viral co-infection—offered further support for the linkage of cancers with immune deficiencies. The frequent delay in relapse of cancer following primary therapy might suggest another facet of this immune system-cancer relationship with interesting parallels to HIV infection and the possibility of cure.

Continued on page 4
Immune checkpoints function to maintain self tolerance and limit collateral tissue damage during development of immune responses to infection and inflammation

- **PD-1** (Programmed death 1 receptor)
- **CTLA-4** (cytotoxic T-lymphocyte associated antigen-2)
- **BTLA** (B- and T-lymphocyte attenuator)
- **LAG-3** (Lymphocyte activation gene 3)
- **TIM-3** (T cell immunoglobulin and mucin protein 3)
• Engagement of PD-1 receptor by its ligands = T cell senescence and apoptosis

• Programmed death receptor 1 & 2 (PD-1 and PD-2)
  Modulates function of T cells in peripheral tissues, limiting collateral tissue damage during development of immune response
Cancer uses immune checkpoints to evade immune destruction

RESTING NAIVE T CELL

Activation by APC
Recognizing tumor antigens

ACTIVATED T CELL
against tumor antigen

Tumor antigen R

PD-1 or PD-2

CANCER CELL

PDL-1 or PDL-2

Melanoma
Ovarian
Non small cell lung
Renal cancer
Gastric cancer
Esophageal cancer
Pancreatic cancer
B cell lymphomas
Brain cancer
Etc, etc

IL-4

IFN-γ
IMMUNE CHECKPOINT INHIBITORS TO TREAT CANCER

• Do not directly target the cancer cells
• Do not activate the immune system to kill cancer, but eliminate the inhibitory pathways that prevent anti-tumor T cell responses

ACTIVATED T CELL

Anti-CTL4

NIVOLUMAB
PEMBROLIZUMAB

AMP – 224
AMP – 514
PDR – 001
BMS – 936559
Etc, Etc

PDL-1 or PDL-2

IPILIMUMAB

CTLA-4

CANCER CELLS

Tumor antigen
Checkpoint inhibitors currently licensed / USA 2016

<table>
<thead>
<tr>
<th>Anti-CTLA-4</th>
<th>Ipilimumab</th>
<th>Yervoy</th>
<th>Melanoma (2011)</th>
</tr>
</thead>
</table>

MANY more on the way
## Selected results: Phase 3 trials of PD-1/PD-L1/CTLA4 inhibitors

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>PD Inhibitor</th>
<th>Comparator</th>
<th>ORR%</th>
<th>CR%</th>
<th>PFS</th>
<th>OS @ 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 066</td>
<td>Melanoma, 1st line (N = 418)</td>
<td>Nivolumab</td>
<td>DTIC</td>
<td>40%</td>
<td>8%</td>
<td>5 mos</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14%</td>
<td>1%</td>
<td>2 mos</td>
<td>42%</td>
</tr>
<tr>
<td>CheckMate 037</td>
<td>Advanced melanoma, after progression on</td>
<td>Nivolumab</td>
<td>Investigator choice</td>
<td>32%</td>
<td>3%</td>
<td>5 mos</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ipilimumab (N = 405)</td>
<td></td>
<td>of chemo</td>
<td>11%</td>
<td>0</td>
<td>4 mos</td>
<td></td>
</tr>
<tr>
<td>CheckMate 017</td>
<td>Advanced non small cell lung cancer</td>
<td>Nivolumab</td>
<td>Docetaxel</td>
<td>20%</td>
<td>1%</td>
<td>4 mos</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>(N = 272)</td>
<td></td>
<td></td>
<td>9%</td>
<td>0</td>
<td>3 mos</td>
<td>24%</td>
</tr>
</tbody>
</table>

12-month Survival for Patients with Advanced Melanoma

- 1975: DTIC (36%)
- 1998: Interleukin-2 (46%)
- 2011: Ipilumumab (47%)
- 2013: Dabrafenib (70%)
- 2014: Trametinib
- 2015: Vemurafenib + Cobimetinib (83%)
- Nivolumab + Ipilimumab (85%)
- Pembrolizumab (69%)
- Dabrafenib + Trametinib (80%)
- Nivolumab (73%)
Oncolytic Viruses

Virus

- Cancer Cell
- Normal Cell
- Viral Replication Proceeds
- No Viral Replication
- Tumor Lysis
- Virus Spread
- Normal Cell Spared
Measles Killing Cancer

Modified measles virus targets and destroys cancer, study says

Los Angeles Times
Science / Science Now

By MONTE MORIN
contact the reporter

A single virus particle, or virion, of the measles virus. (Centers for Disease Control and Prevention)
Oncolytic Virus Therapy

Tumor selective due to deletion of genes crucial for viral replication in normal cells, but not necessary in cancer cells

EX: Oncolytic B18R Vaccinia Virus
- Deletion of thymidine kinase – enzyme needed for nucleic acid metabolism
- Deletion of B18R gene – encodes decoy receptor for Type 1 IFN’s

EX: T-VEC-genetically modified herpes I
- Insertion of GM-CSF gene, promoting local Ag presentation and systemic anti-tumor immunity
PVS – RIPO oncolytic virus

Attenuated, live oral (Sabin) polio vaccine

Remove disease causing genes and replace with gene from cold-causing rhinovirus

Cannot cause polio

Polio virus receptor = CD155
- Used for cell entry
- Cancer cells express CD155

Oncolytic virus causes cell death

Rx = One injection into tumor (1 x 10^7)
Phase I, 15 pts with recurrent glioblastoma

Results = Over-all Survival
12 mos = 70%
18 mos = 44%
24 mos = 29%

2 patients remain in CR > 3 yrs

Combining Oncolytic Virus Therapy with Checkpoint Inhibition

Another major frontier in cancer therapy seeks to elucidate the precise error at the level of the DNA which caused that cancer in that patient, and to reverse / stop that error.

↓

Small Molecule Signaling Inhibitors
Signaling cascades represent another mechanism to treat specific mutations causing a given cancer.
B cell signaling pathway

B cell receptor inhibitors

Precision (Personalized) Cancer Treatment

Matches patients with therapies based on specific biomarkers (mutations, neoantigens, cell surface antigens) in that cancer and that patient

- Using the immune system
- Using oncolytic viruses
- Using small molecular inhibitors to block signaling

MORE to come
Impact of Precision (Personalized) Cancer Treatment

Meta-analysis of 570 studies on 32,149 patients with diverse cancers on phase 2 trials

- Personalized strategy was an independent predictor of better outcomes and fewer toxic deaths
- Chemo had worse outcome than personalized approach
- Use of non personalized target agents was associated with poorer outcome than chemo

CANCER WILL BE CURABLE
(or, you can just live with it)
…was the “peace” of his presence augmenting the patient’s immune system??