Advances in Treatment of Malignant Pleural Mesothelioma: A Reason for Hope

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Action Mesothelioma Day
Liverpool, UK
July 5, 2013
Malignant Mesothelioma:

- Tumor of Serosal Surfaces of Pleura (80%), Peritoneum, Pericardium, Tunica Vaginalis
- Median Survival Varies Depending on Cell Type
- Morbidity Related To Local Invasion Of Vital Structures, Not Metastatic Disease
Mesothelioma Pathogenesis:

~80% of Pleural Mesotheliomas Are Associated With A Known Exposure To Asbestos
Occupational and Environmental Exposures

- Most exposures occupational: Asbestos mining, processing; Pipefitting /insulation; shipbuilding; brake repair; construction; plumbing
- Other exposures: Environmental (near asbestos site); Contact with clothes from exposed workers; Contaminated buildings.
Mesothelioma and Asbestos in North America
Asbestos production and mesothelioma incidence: asbestos production in the United States in the last century and mesothelioma incidence from 1980 projected to 2055

Increases in Mesothelioma in Asia

Trends of Malignant Mesothelioma Incidence in Korea

Projected Mesothelioma cases – Hong Kong males 2002–2027


Genes Have Been Identified That Predispose Individuals To Develop Mesothelioma

Germline BAP1 mutations predispose to malignant mesothelioma

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The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma

Matthew Bott¹², Marie Brevet¹, Barry S Taylor³, Shigeki Shimizu¹, Tatsuo Ito¹, Lu Wang¹, Jenette Creaney⁴, Richard A Lake⁴, Maureen F Zakowski¹, Boris Reva³, Chris Sander³, Robert Delsite⁵, Simon Powell⁵, Qin Zhou⁶, Ronglai Shen⁶, Adam Olshen⁶, Valerie Rusch² & Marc Ladanyi¹⁷

Nature Genetics, 2011
Advances in Early Detection of Mesothelioma
(New York University, Mount Sinai, Univ. of Hawaii, Univ. of Toronto)

• We may be getting closer to a blood test for the diagnosis of malignant mesothelioma.
• Ultimately, this may be a means to screen people at risk to allow for early detection and even prevention of mesothelioma.
Advances in Early Detection of Mesothelioma

Pass, et al, NEJM 2013
Advances in Surgery for Mesothelioma: Shift Towards “Lung-Sparing” Approaches
Advances in “Lung-Sparing” Surgery: Improved Survival in Advanced Stages

Photos Courtesy of Dr. Joseph Friedberg, M.D.
University of Pennsylvania, Philadelphia, USA
Advances in Chemotherapy:

“Personalized” Medicine and Targeted Therapies

Vogelzang, JCO, 2003
Advances in Radiation for Mesothelioma:
More Precise Tumor Targeting and Less Collateral Damage


Proton Beam Therapy
Principals of Cancer Immunotherapy

- There are differences in the composition of tumors that allow the immune system to recognize tumor cells as “foreign” and kill them.

- Tumors have “evaded” or “overwhelmed” this system and require a stimulus to enable the immune system to eliminate the tumor cells.
WT-1 Peptide Vaccine Trials
Memorial Sloan-Kettering and M.D. Anderson Cancer Centers

- Malignant Mesothelioma
- WT-1 positive
- 4-12 weeks post surgery & chemotherapy

Randomize

WT-1 vaccine / Adjuvant
Vs.
Adjuvant alone

Aim is to Improve Survival after Surgery for Mesothelioma
Antibody Therapy: *Mesothelin*

- Cell surface glycoprotein
- Normal expression in human tissues is limited to mesothelial cells of pleura, peritoneum & pericardium
- *Mesothelin* highly expressed in many cancers, esp. MPM

Targeting Mesothelin For Cancer Therapy

Recombinant immunotoxin

SS1P

Anti-mesothelin Fv -Toxin-

Chimeric mAb

MORAb-009

Human Gene Therapy

1. DNA (with chromosome and cell nucleus)

2. retrovirus
   - therapeutic DNA
   - vector
   - target cell
   - repaired cell
Gene therapy for malignant mesothelioma: beyond the infant years

RG van der Most¹², BWS Robinson¹ and DJ Nelson¹³

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- Localized to chest cavity
- Accessible for local drug delivery
- Current therapies inadequate
- Some response to immunotherapy
Interferon Gene Therapy - Biology

Direct Inhibition of Tumor Cell Growth And Survival

Activation of Anti-tumor Immune Responses

Blockade Of Tumor Blood Supply

Inhibition of Tumor Cell Growth
Tumor Cell Death

1) Insert tunneled pleural catheter and maximally drain fluid, if present.
2) Infuse adenoviral vector into pleural space
3) Sample pleural fluid to assess gene transfer, etc.
Pt 309 Post Gene Therapy PET Scan

Pre-therapy

Post-therapy (6 months)
Patient 304 Sailing to Victory in Portsmouth, England April, 2010
Design of Phase I/II Clinical Trial of ImmunoGene Chemo Combination

(University of Pennsylvania, Philadelphia)

Endpoints: Safety, ORR, PFS, OS

Pemetrexed/platin X 4-6 cycles

First Line

Second Line

Gemcitabine +/- Carbo X 4-6 cycles

Tunneled Pleural Catheter Insertion (Medical/Surgical)

Celecoxib 400 mg bid x 12 d

Catheter Removal

D-7/-14 D1 D4 D5 D14

IPI Ad.IFNα IPI Ad.IFNα
Adoptive T Cell Therapy for Mesothelioma
(Penn, Memorial Sloan-Kettering, NCI)

Hawkins, et al. HUMAN GENE THERAPY 21:665–672 (June 2010)
Regressions Of Massive Melanoma Tumor After Transfer Of Anti-Tumor T Cells
(National Cancer Institute, Bethesda, Maryland, USA)
Advances in Experimental Therapy: Gene-Modified T Cell Clinical Trial

Dr. Haas and T-Cell Recipient  
*(HIPPA Consent Obtained)*

Infusion Bag with $10^8$ Mesothelin-CAR T cells
Phase I Trial of Autologous Redirected RNA Meso-CIR T Cells

UPCC 17510 / NCT01355965

Abramson Cancer Center of the University of Pennsylvania

Estimated 57% decrease in volume
Overcoming Hurdles

- Increase federal research funding levels
- Foster inter-institutional consortia to maximize expertise and resources
- Encourage public-private partnerships with pharma and biotech
Together, We Can Work Towards a Cure!