UPDATE
Autologous Stem Cell Transplantation for Lymphoma and Myeloma

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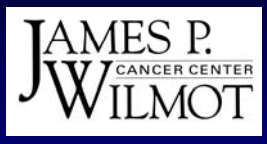
Autologous stem cell transplant



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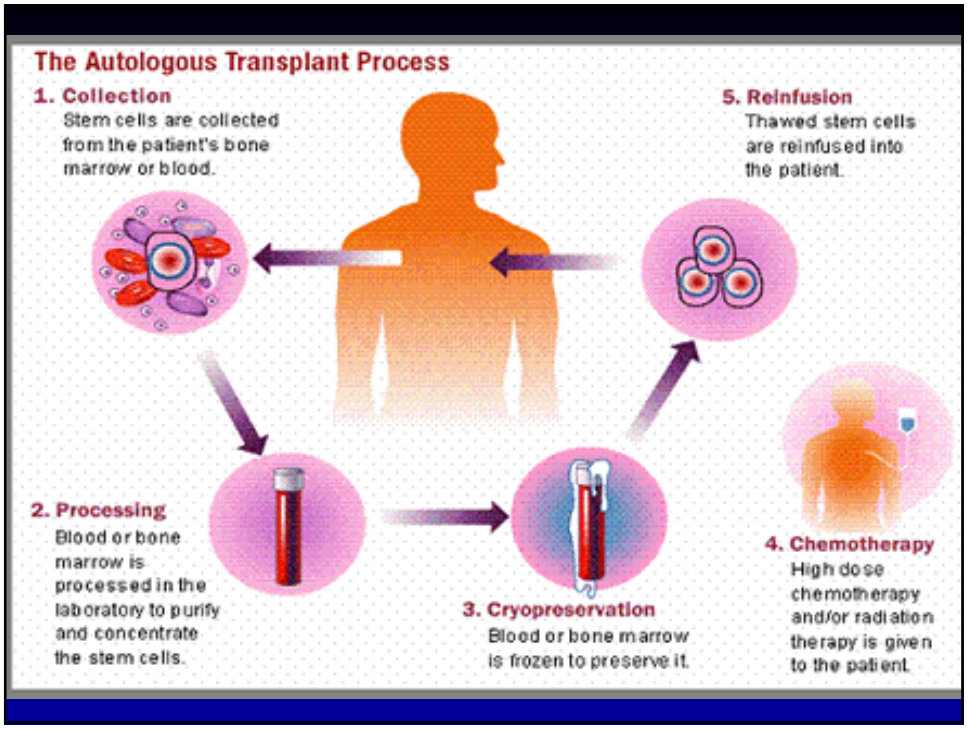
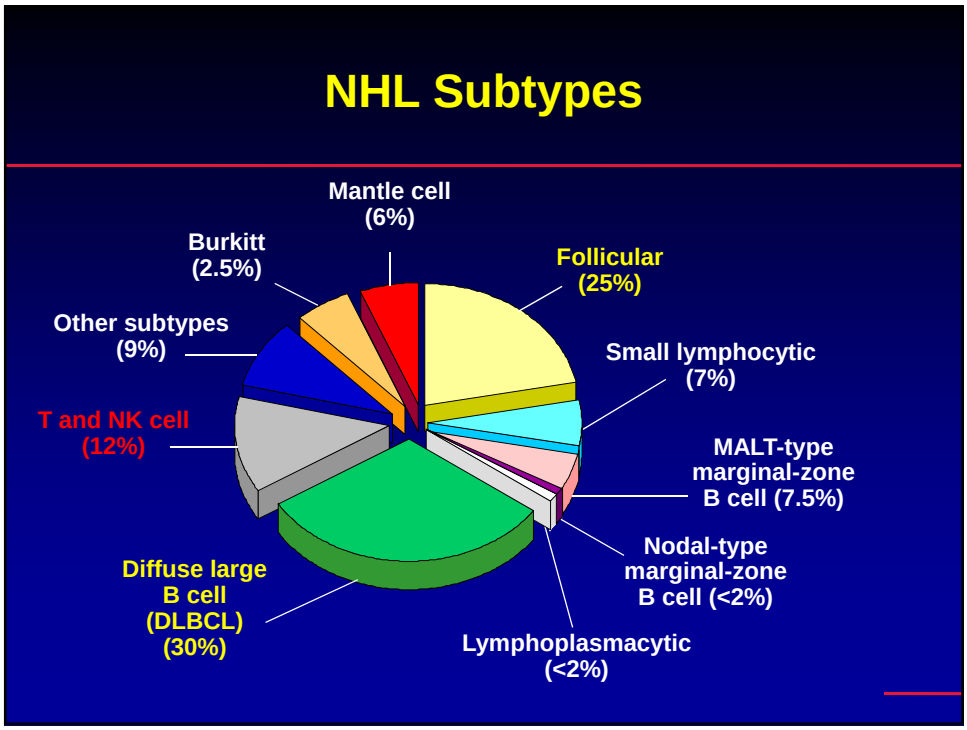

The Autologous Transplant Process
1. Collection
Stem cells are collected from the patient's bone marrow or blood.
5. Reinfusion
Thawed stem cells are reinfused into the patient.
2. Processing
Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.
3. Cryopreservation
Blood or bone marrow is frozen to preserve it.
4. Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient.


NHL Subtypes
Mantle cell (6%)
Burkitt (2.5%)
Follicular (25%)
Other subtypes (9%)
Small lymphocytic (7%)
T and NK cell (12%)
MALT-type marginal-zone B cell (7.5%)
Nodal-type marginal-zone B cell (<2%)
Diffuse large B cell (DLBCL) (30%)
Lymphoplasmacytic (<2%)

Issues with autologous stem cell transplantation in lymphoma

- **Types of lymphoma**
  - Diffuse large B-cell lymphoma
  - Mantle cell lymphoma
  - Follicular (and other indolent lymphomas)
  - Transformed lymphoma
  - Hodgkin lymphoma
- **Goals of transplantation**
  - Cure
  - Prolonged disease control
- **Timing of transplantation**
  - Remission consolidation
  - Relapsed disease

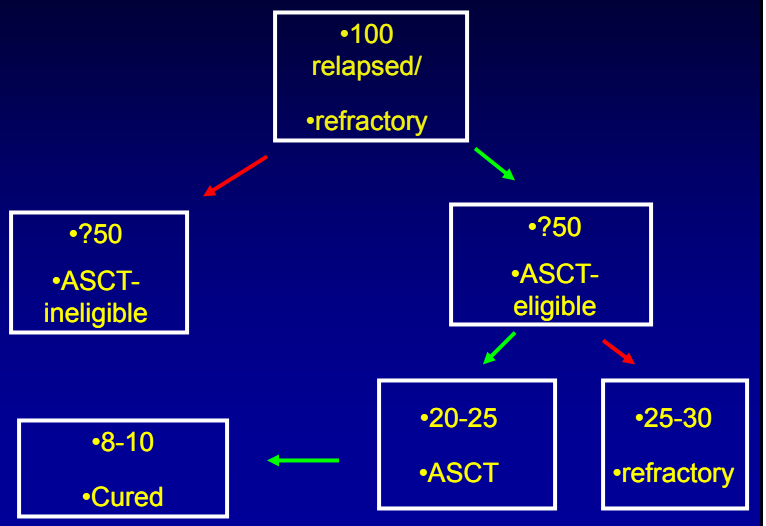
Autologous stem cell transplantation in lymphoma: Challenges

- **Age of patients and co-morbid medical problems limit eligibility**
- **Many patients are not able to achieve adequate disease control prior to ASCT, limiting eligibility**
- **“Contamination” of stem cell product with lymphoma**
- **Early toxicity**
  - Current mortality rate less than 2%
- **Late toxicity**
  - Second cancer risks
  - Organ damage: heart and lung toxicity

Improvements in autologous stem cell transplantation for lymphoma

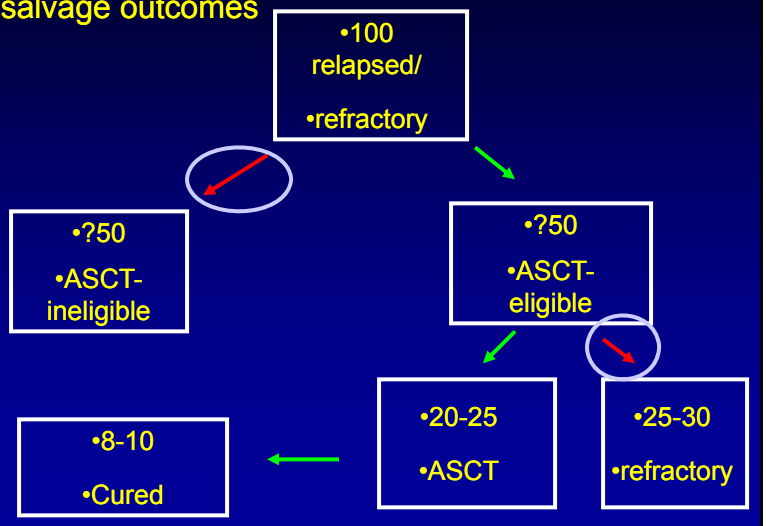
- **"Conditioning" approaches**
  - Chemotherapy vs. radiation
  - Incorporation of rituximab
  - Growth factor support
  - Outpatient transplantation
- **Novel agents**
  - Part of conditioning
  - "Maintenance" after transplantation
- **Recognition of toxicity**

Outcome of relapsed DLBCL and ASCT in the rituximab era



To impact relapsed DLBCL:

1. ASCT ineligible => novel agents
2. Improve salvage outcomes



Conclusions

- ASCT remains an important modality in treatment of lymphomas
  - Cures diffuse large B-cell lymphoma and Hodgkin lymphoma
  - Prolongs remission in follicular lymphoma
- Novel targeted treatments represent an important opportunity to:
  - Improve outcomes of ASCT
  - Avoid ASCT entirely (the ultimate goal)

Role of Bone Marrow Transplant in the Treatment of Myeloma

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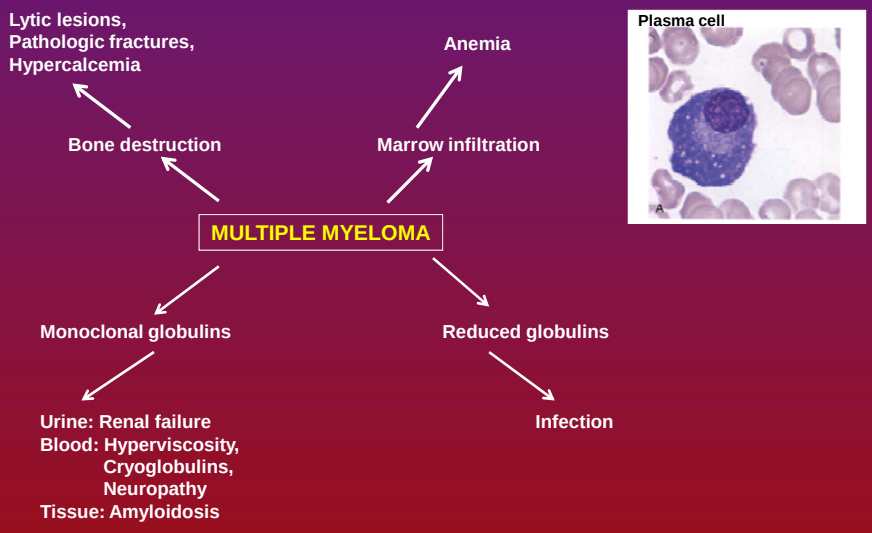
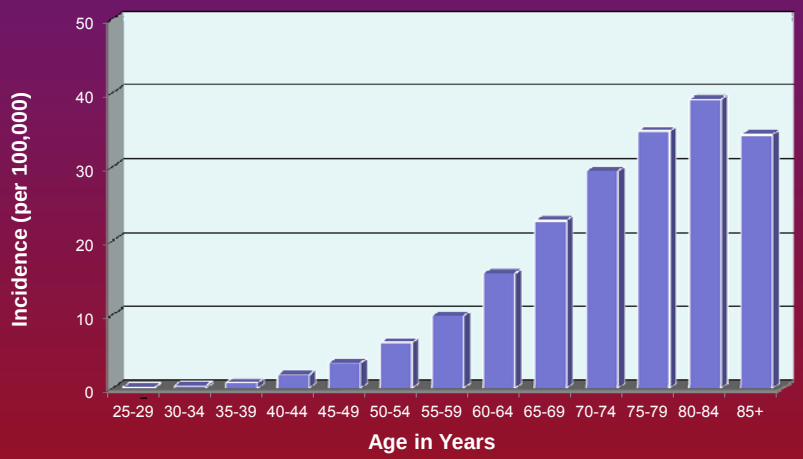
Hallmarks of MM



Carr et al, 1999.

Incidence Rates

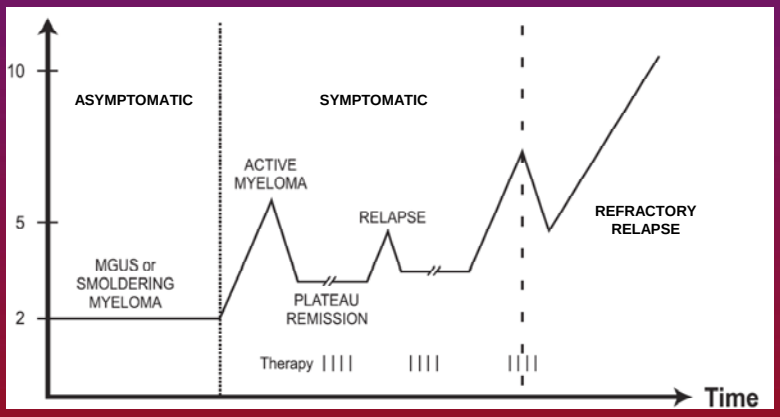
Age-Specific Incidence Rates for Myeloma, 2005–2009



*<16 cases for each age and time interval, SEER 18 areas

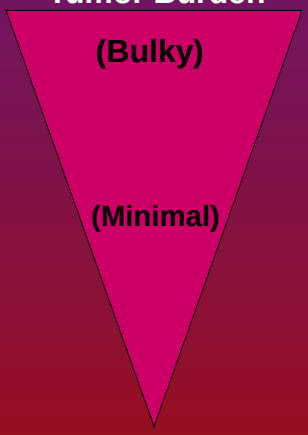
Source: SEER Cancer Statistics Review, 1975-2009, National Cancer Institute; 2012.

Challenges of Treating Multiple Myeloma



Durie. International Myeloma Foundation. 2007. www.myeloma.org.

Multiple Myeloma: Strategy for Cure?



Induction or Initial Therapy

↓

High Dose Melphalan + Autologous Stem Cell Transplant

↓

Immunotherapy + anti-myeloma Vaccines or Consolidation therapy

↓

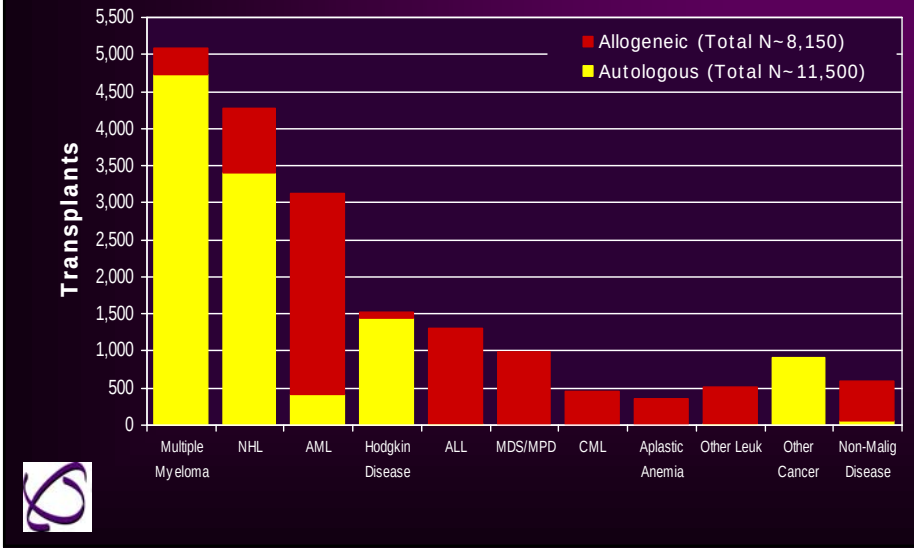
Targeted Maintenance Therapy

Genetic Abnormalities in Multiple Myeloma Affects Prognosis

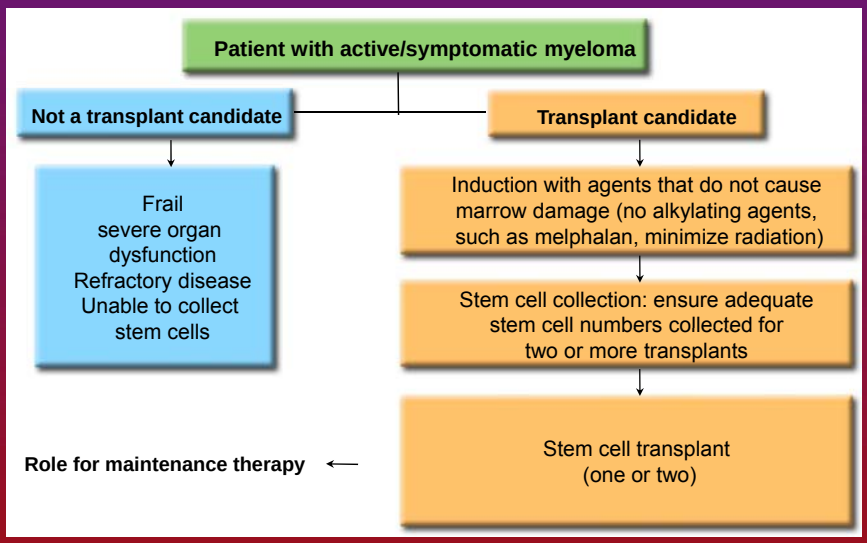
- Chromosomal changes and abnormalities present in 80%-90% patients in fluorescent in situ hybridization (FISH) analysis
- FISH looks at genes, chromosomes, and their aberrations
  - Patients with the t(4;14),t(14;16) translocation, deletions of 17p, or chromosome 13 abnormalities had statistically significant lowered survival
- Genomics used to understand the disease
  - Still too early to aide in treatment decisions

Dewald et al. *Blood.* 2005;106:3553.

Indications for Hematopoietic Stem Cell Transplantation in the US



Initial Approach for Myeloma Patients Requiring Disease-Specific Therapy



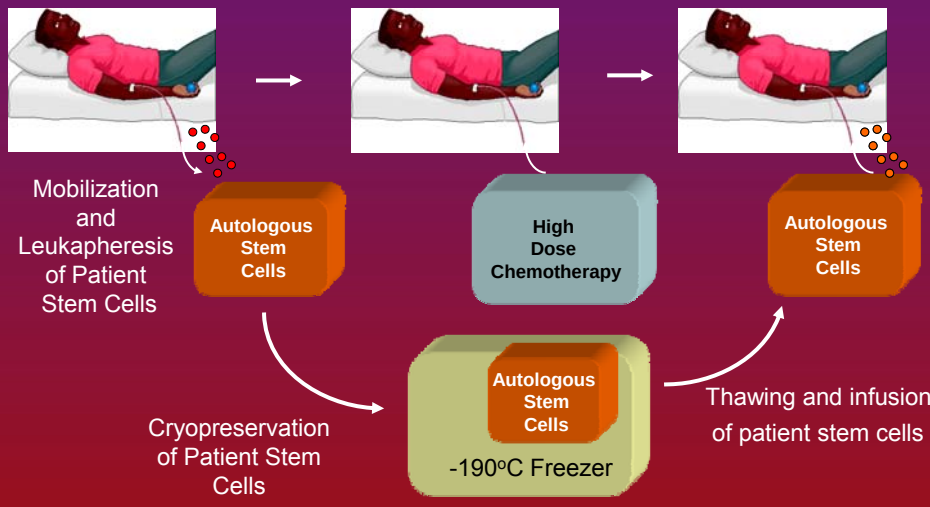
Types of Stem Cell Transplant

Type	Source of Stem Cells	Role in Myeloma Treatment
Autologous	Patient's blood or marrow	Current standard of care
Allogeneic	Sibling or Unrelated Donor blood or marrow or umbilical cord blood	Under study in clinical trials

Autologous Stem Cell Transplant

- An important treatment for patients with myeloma
- Generally must have adequate lung, liver and heart function
- More than one transplant can be performed at various stages
- Consider benefits vs. risks

Autologous Stem Cell Transplantation

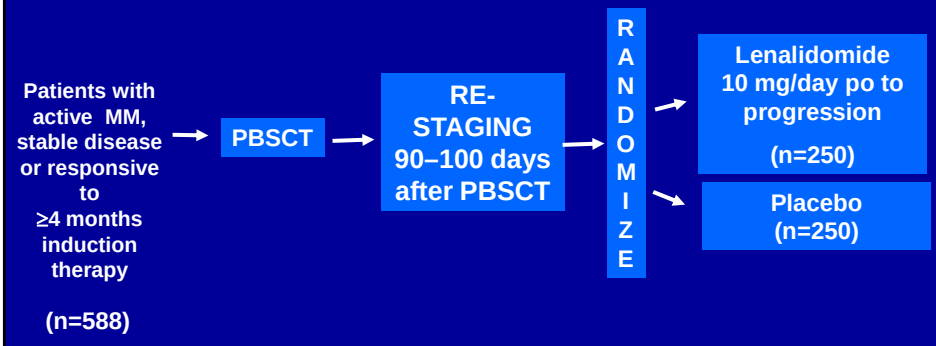


High-dose Melphalan and Autologous Stem Cell Transplant

- A number of studies show improved overall survival when auto-transplant is compared to standard dose chemotherapy
- A number of studies show the survival benefit of 2 auto-transplant (tandem transplant) compared to a single auto-transplant (mainly those still with disease after one)
- A number of studies now show the benefit of new (novel) therapy (lenalidomide) followed by auto-transplant over a lenalidomide based regimen without auto-transplant

Ongoing Study of Lenalidomide As Maintenance Therapy Following Autologous PBSCT for MM

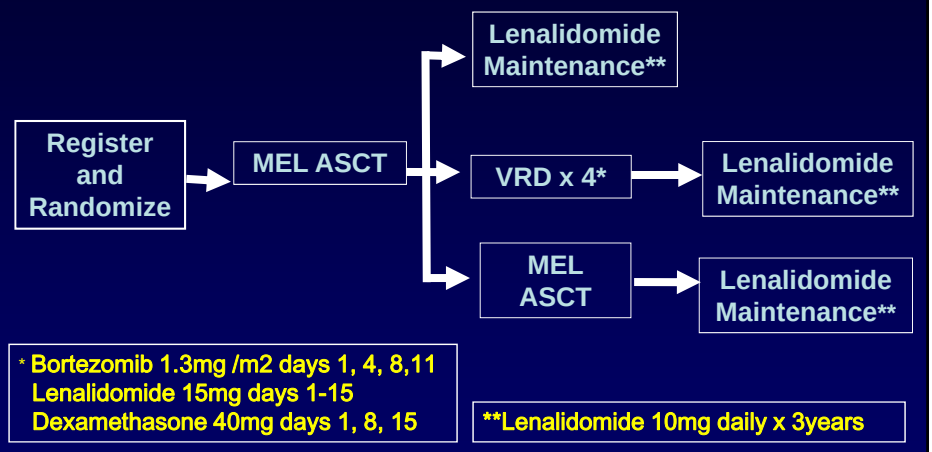
CALGB/ECOG 100104: Phase III Randomized, Placebo-Controlled Trial



1° Endpoint: Time to disease progression after autologous PBSCT

2° Endpoints: CR rate, PFS, overall survival, feasibility of long-term lenalidomide

BMT CTN 0702: SCHEMA

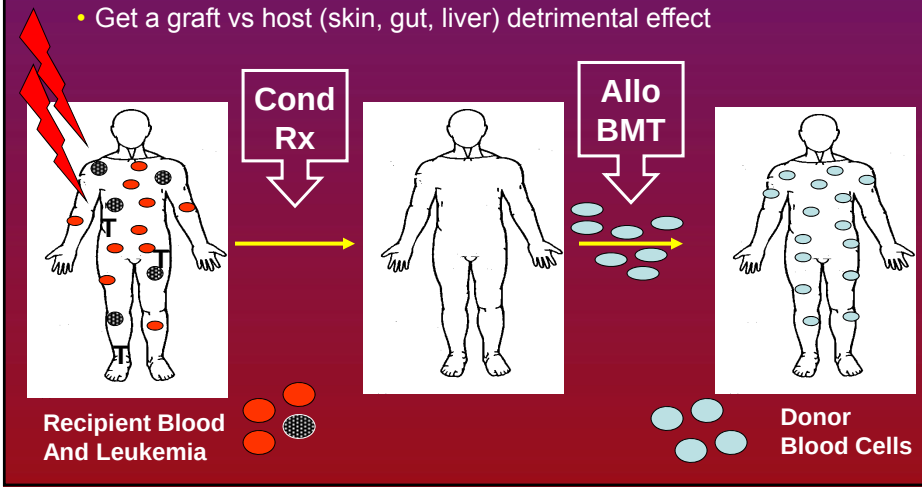


* Bortezomib 1.3mg /m2 days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15

**Lenalidomide 10mg daily x 3years

Allogeneic Bone Marrow Transplantation

- High dose chemotherapy ± XRT:
  - Antitumor effects, immunosuppression, myeloablation
- Replace with normal donor hematopoietic cells
- Get a graft versus tumor immune beneficial effect
- Get a graft vs host (skin, gut, liver) detrimental effect

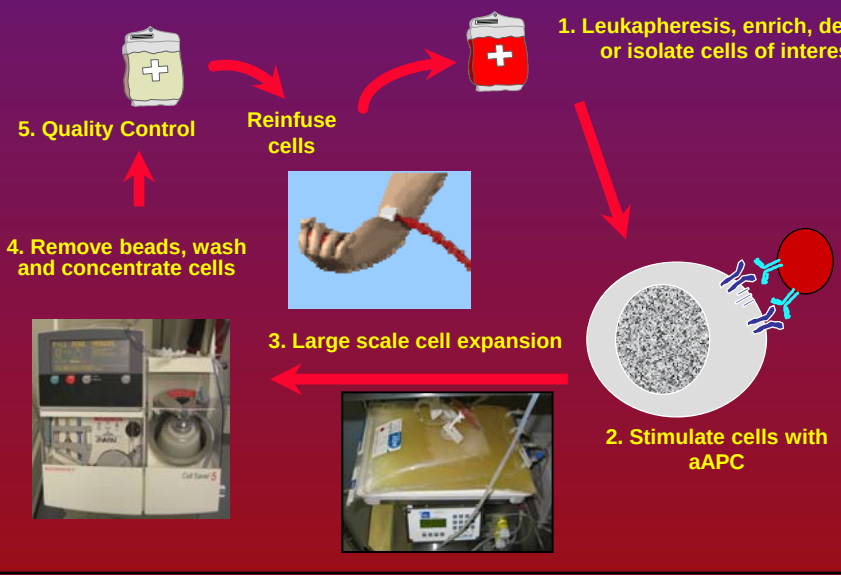


BMT CTN #0102

710 enrolled
last 3/07
endpoint 3 y PFS

- MM Meeting Eligibility
- Mel 200 Autograft
- Recovered at least 60 days post autograft
  - HLA-matched Sibling
    - 200cGy TBI Allograft CSA + MMF
  - No HLA-matched Sibling
    - Mel 200 Autograft
      - Observation
      - Thalidomide + Decadron for 1 yr

Ex Vivo Activated T-cell Production (Cellular Vaccine Production Facility)



Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer

Aaron P Rapoport[1,4], Edward A Stadtmauer[2,4], Nicole Aqui[2,4], Ashraf Badros[1], Julio Cotte[2], Lisa Chrisley[1], Elizabeth Veloso[2], Zhaohui Zheng[2], Sandra Westphal[1], Rebecca Mair[2], Nina Chi[2], Bashi Ratterree[1], Mary Francis Pochran[1], Sabrina Natt[1], Joanne Hinkle[2], Cheryl Sickles[2], Ambika Sohal[2], Kathleen Ruehle[1], Christian Lynch[3], Lei Zhang[1], David L Porter[2], Selina Luger[2], Chuanfa Guo[1], Hong-Bin Fang[1], William Blackwelder[1], Kim Hankey[1], Dean Mann[1], Robert Edelman[1], Carl Frasch[3], Bruce L Levine[2,4], Alan Cross[1,4] & Carl H June[2,4]

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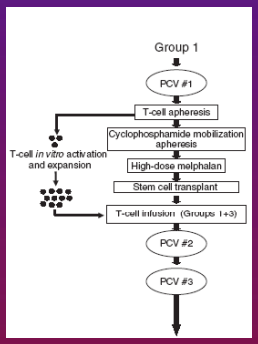
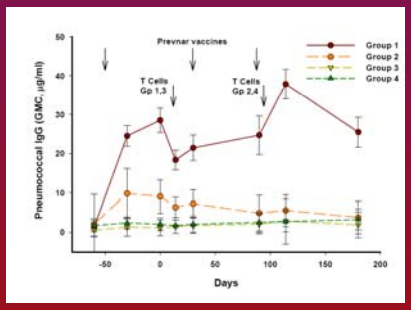
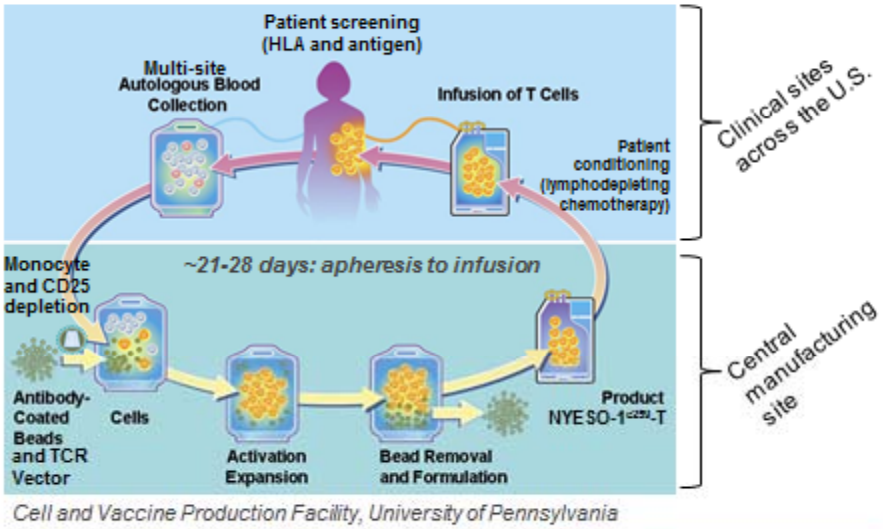


Results: 54 patients with MM treated

- Combination immunotherapy
  - A single early post-transplant infusion of in vivo vaccine primed and ex vivo costimulated autologous T-cells
  - Post-transplant booster immunizations
- Results
  - Improved the severe immunodeficiency associated with high-dose chemotherapy
  - Led to the induction of clinically relevant immunity (pneumococcal IgG) in adults within a month after transplantation
  - Accelerated restoration of CD4 T-cell numbers and function, significantly improved T-cell proliferation



Engineering Tumor Antigen Specificity to Patient Cells



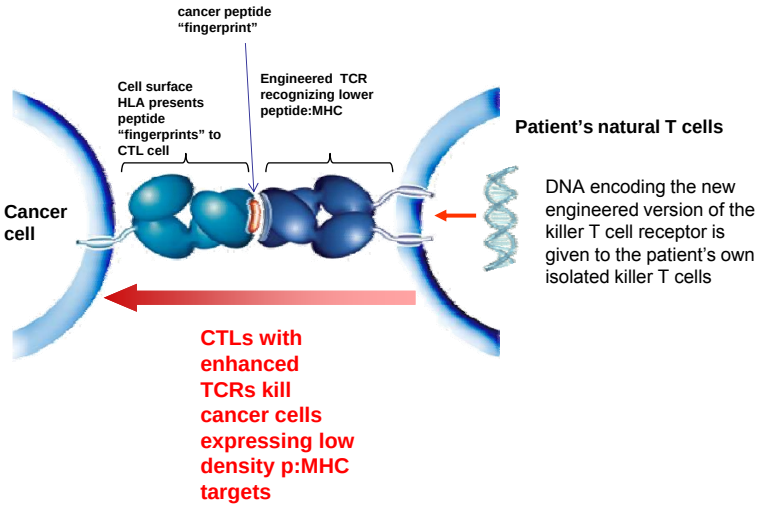
Cell and Vaccine Production Facility, University of Pennsylvania

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Perelman School of Medicine UNIVERSITY of PENNSYLVANIA

ADAPTIMMUNE transforming T cell therapy

Rationale for Therapy with Natural and Genetically Retargeted T-cells



Conclusions

- Survival in myeloma has improved, particularly in patients under age 70 due at least in part to Autologous Stem Cell Transplant
- The potential for longer survival and cure exists
  - Clinical trials are in progress to assess novel combination therapies with transplant (lenalidomide, bortezomib, etc)
  - Role of donor (allogeneic) transplant
  - Continue to improve autologous stem cell transplant
    - Induction
    - Tandem transplant
    - Maintenance
    - Targeted cellular therapies
- Side effects of therapies are manageable but must consider individual patient characteristics (biological factors, age, performance status, organ function)

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LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers

Question and Answer Session

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fighting blood cancers

The Leukemia & Lymphoma Society's (LLS) Co-pay Assistance Program offers financial assistance to qualified lymphoma and myeloma patients to help with treatment related expenses and insurance premiums. Patients may apply online or over the phone with a Co-pay Specialist.

- WEBSITE: www.LLS.org/copay
- TOLL- FREE PHONE: (877) LLS-COPAY

For more information about ASCT for lymphoma and myeloma or for other LLS programs, please contact an LLS Information Specialist.

- TOLL- FREE PHONE: (800) 955-4572
- EMAIL: infocenter@LLS.org