Stem cell transplantation for AML

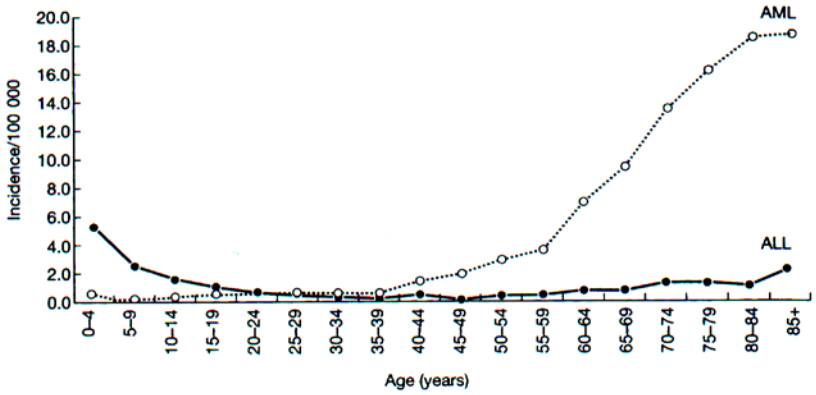
Peter Westervelt, MD, PhD
Professor of Medicine
Washington University School of Medicine

Overview of stem cell transplantation for AML

- Indications for transplant
- Essential elements of transplant
- Transplant complications

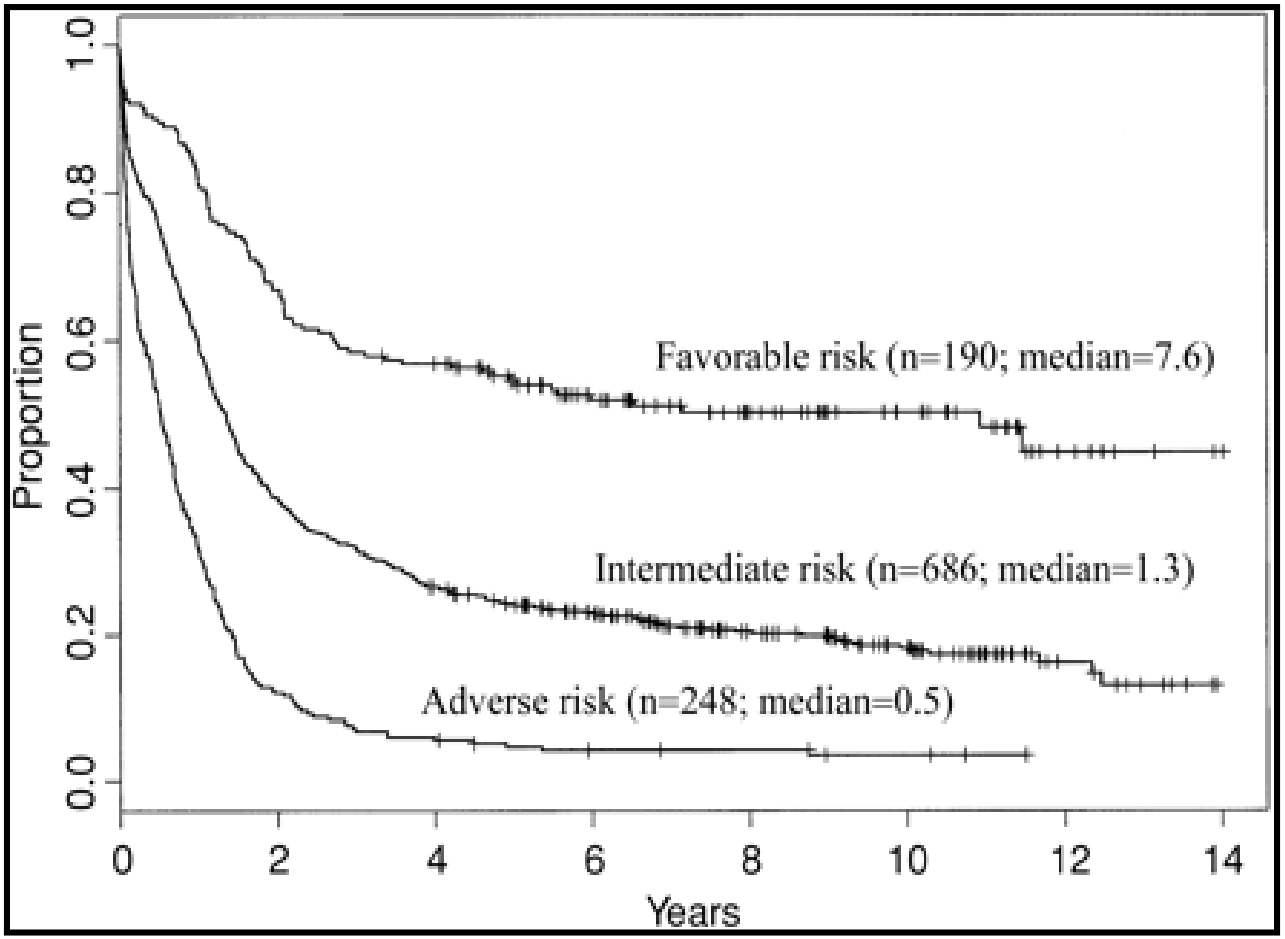
Epidemiology of AML

- 1.1% of US cancer incidence
- 0.5% lifetime risk
- Estimated 19,520 cases (2018)
- Estimated 10,670 deaths (2018)
- Median age at diagnosis: 68 years

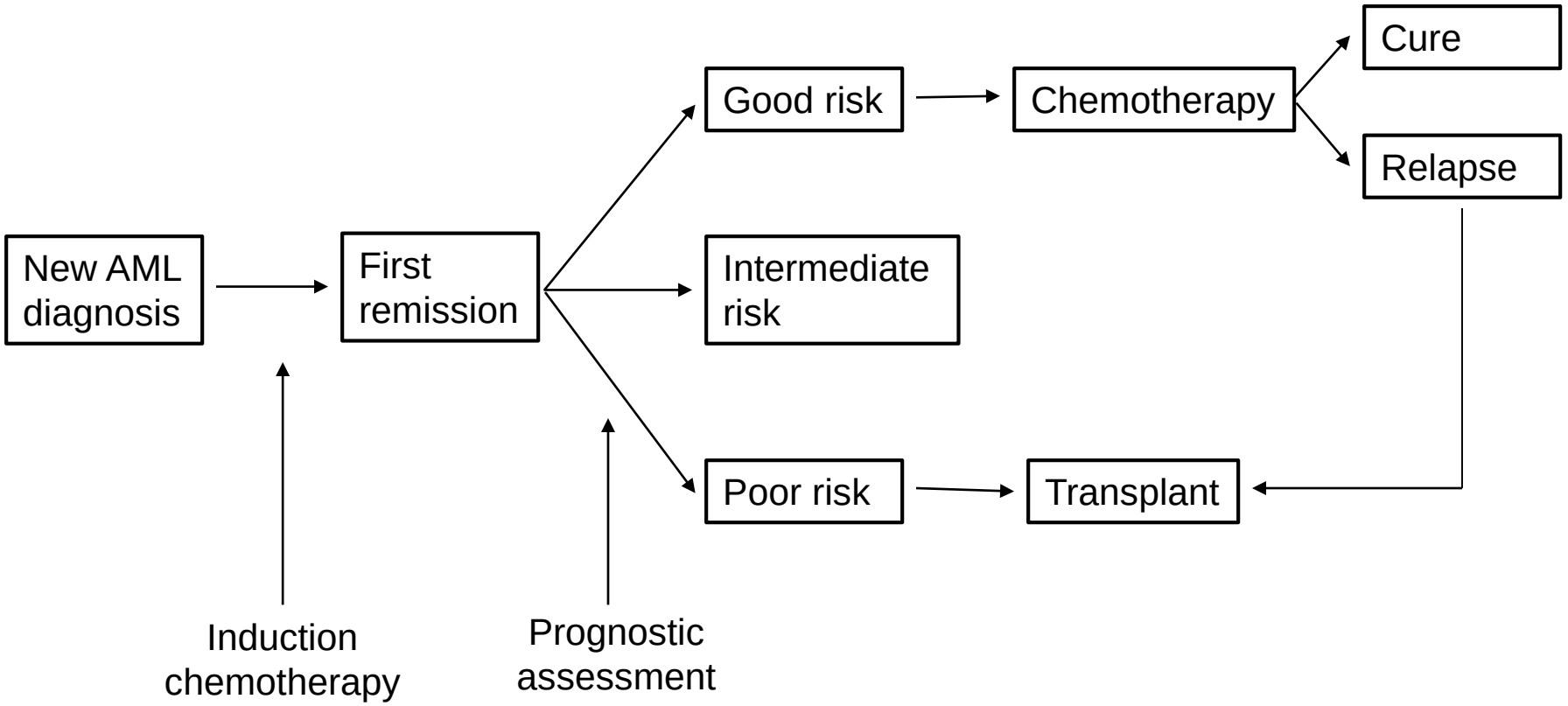


2018 SEER database:
https://seer.cancer.gov/statfacts/html

Overall survival in AML by prognostic subgroups



Treatment algorithm for AML



Transplant indications for AML

- Risk/benefit balance
- High risk/low probability of cure without transplant:
  - Adverse chromosomes
  - Mutational profile
  - Antecedent MDS/MPN
  - Treatment-related (chemo/radiation)
  - Prior relapse
  - Older age

Requirements for transplant

- Suitable donor
- Medically “fit” recipient
  - Co-morbidities
  - Performance status
  - Age
- Remission

Sources of hematopoietic stem cells for transplantation

- Autologous vs allogeneic
- Related vs unrelated allogeneic donors
- Haploidentical donors
- Umbilical cord blood (UCB)
- Bone marrow
- Mobilized peripheral blood stem cells (PBSC)

Stem cell apheresis

- 5 day growth factor administration
- 4-5 hour outpatient procedure
- May require central venous catheter

Bone marrow harvest

- 1-2 hour surgical procedure
- General anesthesia
- Overnight hospitalization
- 1-2 week recovery time

PBSC vs marrow

PBSC

- Shorter time to neutrophil and platelet recovery
- Less donor morbidity
- No difference in autologous transplant outcomes

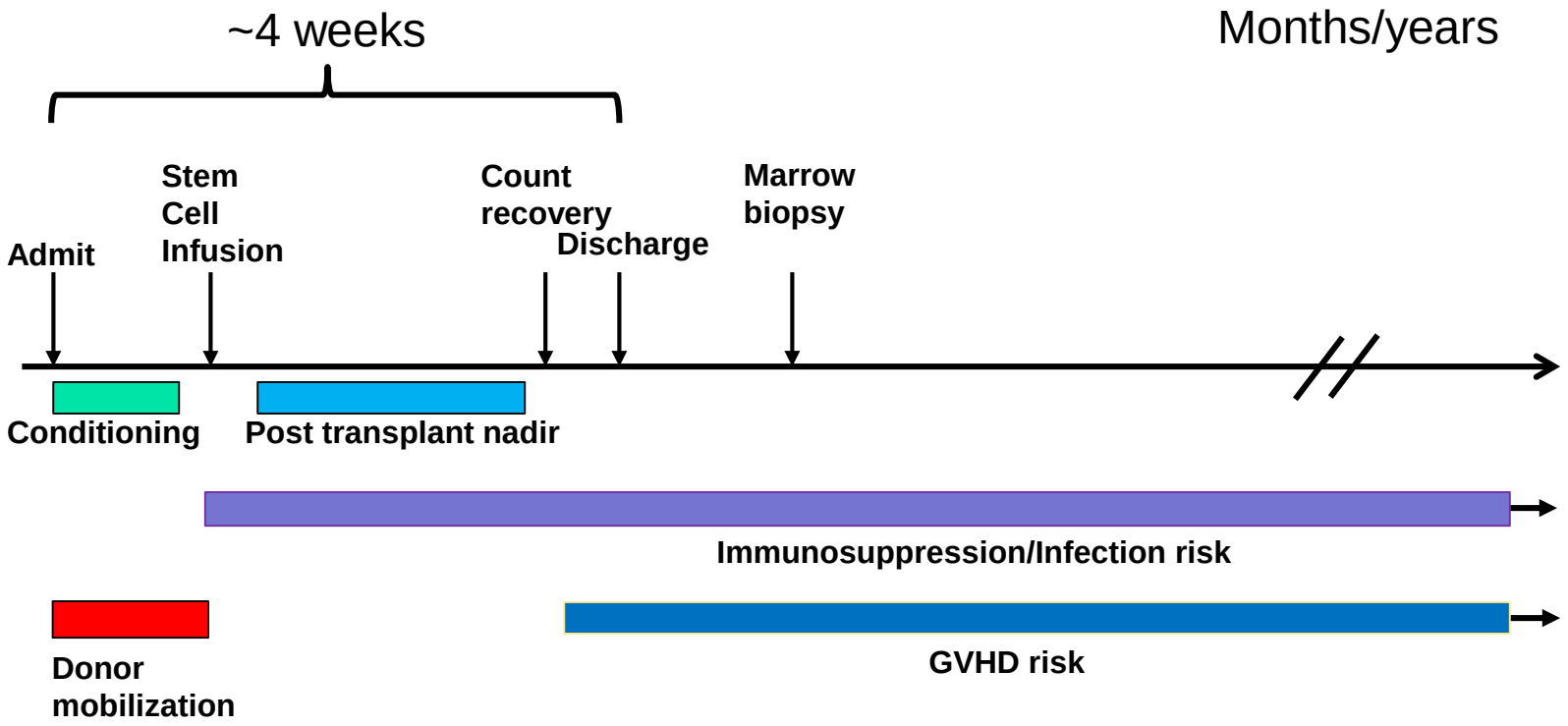
Bone marrow

- Decreased chronic GVHD
- Survival benefit in children with acute leukemia and aplastic anemia

Elements of allogeneic stem cell transplant process

- Conditioning regimen
- Hematopoietic stem cell infusion from suitable donor
- Immune system suppression
- Supportive care

Typical transplant timeline



Conditioning regimens

- Administered immediately pre-transplant
- Elements of conditioning
  - Chemotherapy, radiation, ATG
- Goals of conditioning
  - Ablation of recipient immunity to block rejection
  - Reduction of tumor burden
- Myeloablative vs reduced intensity conditioning

Myeloablative (MAC) vs reduced intensity (RIC) conditioning

- Higher toxicity with MAC
- MAC limited to younger healthier adults
- Host marrow ablation (MAC) not required for successful transplantation
- RIC extends transplant availability to a wider spectrum of patients in need

Reduced intensity conditioning regimens

- Provides immunoablation of host
- Facilitate donor immune system attack on residual AML cells (“Graft vs Leukemia”)
- Minimal toxicity
- Minimal tumor cell kill

Reduced intensity conditioning regimens (RIC)

- Advantages
  - Feasibility in older, sicker patients
  - Ideal in indolent malignancies sensitive to GVL
  - Suitable for outpatient procedure
  - Demonstrated efficacy in older adults
- Disadvantages
  - No impact on GVHD toxicity
  - Improved outcomes with MAC in selected “fit” AML patients over age 55

Complications of allogeneic stem cell transplantation

- Graft-versus-host disease (GVHD)
- Infection
- Graft failure
- Organ toxicity
- Treatment related mortality
- Relapse

GVHD in allogeneic stem cell transplantation

- Major cause of toxicity (and mortality) in allogeneic transplant
- Results from donor:host differences detected by donor immune system
- Requires post transplant immune suppressive medication for prevention and treatment
- Acute vs chronic GVHD

Acute GVHD

- Onset weeks-months post-engraftment
- Affects skin, GI tract, liver
- Incidence ~30-50%
- Substantial morbidity/mortality
- Treatment with escalation of immune suppressive medications

Risk factors for acute GVHD

- Age
- HLA match disparity
- Gender disparity
- Sub-optimal prophylaxis
- Higher total body radiation doses

Chronic GVHD

- Delayed onset (months/years)
- More varied presentation:
  - Mouth dryness/soreness
  - Eye dryness/irritation
  - Skin thickening
  - Joint immobility
  - Difficulty breathing

Risk factors for chronic GVHD

- *Acute GVHD*
- Older recipient age
- Donor/recipient gender disparity
- Unrelated donor
- HLA mismatching

Infectious complications

- Impaired immunity
  - Neutropenia
  - Immunosuppression
  - Mucosal barrier disruption
- Opportunistic infections
  - Bacterial
  - Fungal
  - Viral
  - Parasitic

Strategies for reduction in post-transplant infection risk

- Targeted antibiotic prophylaxis
  - Pneumocystis
  - Cytomegalovirus (CMV)
  - Herpes zoster
  - Fungal
  - Encapsulated bacteria
- CMV monitoring and pre-emptive therapy
- Immune globulin supplementation

Graft rejection

- Risk factors
  - Unrelated and HLA mismatched donors
  - T-cell depletion
  - Limited cell dose
  - Donor specific antibodies
- May require additional donor cell infusion (or second transplant)

Transplant related organ toxicity

- Liver
- Lungs
- Kidneys
- Myocarditis
- Mucositis
- GI tract
- Skin

Long-term transplant-related toxicities

- Second malignancies
- Infertility
- Skeletal complications
- Sexual dysfunction
- Psychological

Transplant survivorship

- Bone health maintenance
- Vaccinations
- Psychosocial support
- Cancer screening

Future directions in stem cell transplantation

- Improved prevention and treatment of GVHD
- Strategies for relapse risk reduction
- Improved transplant availability with alternative donor stem cell sources