Stem Cell Transplant in Adolescent and Young Adult Patients

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Objectives

- Describe the pharmacologic and physiologic factors that may impact cancer treatment efficacy.
- Review available literature using stem cell transplant as a treatment option for adolescent and young adult (AYA) patients.
- Discuss the medical and psychosocial issues that AYA patients may encounter while receiving a stem cell transplant.

Introduction

- In the U.S., 2% of all invasive cancers occur in patients between the ages of 15 and 30 years
- 2.7 times more patients diagnosed with cancer during the second 15 years of life
- In 2000 - nearly 21,400 AYA (15 to 29 yo) diagnosed with invasive cancer

Bleyer A, et.al. *Oncologist* 2006.

Introduction

- Lack of progress in survival improvements among AYA patients with cancer
  - Patients between 15 – 39 years of age
- Lack of improvement is multifactorial
  - Low rate of participation in clinical trials
  - Differences in disease biology
  - Inconsistent treatment approaches
  - Lack of compliance or intolerance of therapy
  - No health insurance
  - Delays in diagnosis
  - Physicians not familiar with the management of AYA cancers

Bleyer A. available at: http://seer.cancer.gov/publications.
Bleyer A. *CA Cancer J Clin* 2007.
A report of the Adolescent and Young Adult Oncology Progress Review Group 2006.

Introduction

- Distinct age group
  - Unique medical and psychosocial needs
- AYA Oncology Progress Review Group (PGR)
  - Population-based cancer incidence, mortality, and survival data
  - Impetus for further research to improve survival outcomes and quality of life

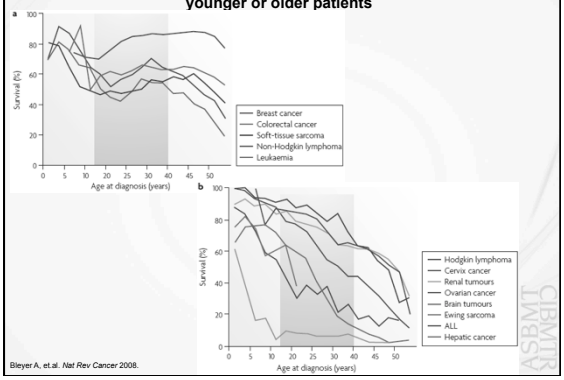
A report of the Adolescent and Young Adult Oncology Progress Review Group 2006.

Age-specific SEER incidences[c] of cancer by age group and sex in the AYA population (2004-2008)[d]

Cancer Type	Ages 15-19		Ages 20-24		Ages 25-29		Ages 30-34		Ages 35-39	
	M	F	M	F	M	F	M	F	M	F
Bone sarcomas	2.1	1.3	1.2	0.9	0.7	0.7	0.6	0.6	0.7	0.6
Breast cancer	-	-	-	1.4	-	7.8	-	26.1	0.1	59.5
CNS tumors	2.2	2.1	2.2	2.3	3.1	2.2	3.6	2.6	4.2	3.0
Carcinoma of cervix and uterus	-	-	-	1.7	-	6.3	-	14.3	-	20.9
Colorectal cancer	0.3	0.3	0.9	1.0	2.1	1.9	4.4	4.5	9.3	8.3
Carcinoma of respiratory tract	-	-	0.3	0.3	0.5	0.6	1.1	1.3	2.8	3.1
Germ cell neoplasms	4.3	1.1	10.6	1.2	14.0	1.1	13.4	0.9	11.1	0.7
Leukemias	3.7	2.6	3.0	2.3	3.0	2.2	3.4	2.8	4.2	3.2
Lymphomas										
HL	3.0	3.1	4.3	4.7	4.0	4.5	4.0	3.8	3.4	2.7
NHL	2.1	1.5	2.9	1.9	3.8	2.8	5.5	4.0	8.6	5.5
Melanoma	1.2	1.9	2.5	6.0	4.7	9.9	7.4	12.3	10.9	16.5
Soft tissue sarcomas	1.4	1.5	2.0	1.7	3.1	2.1	4.2	2.8	5.9	3.7
Thyroid cancer	0.7	3.4	1.3	8.8	2.7	14.2	4.0	20.2	5.3	24.6

c. Rates are per 100,000
d. Data from Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds.) SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER website, 2011.

Cancers with 5-year relative survival rates that are lower in AYAs than in younger or older patients



Bleyer A, et.al. *Nat Rev Cancer* 2008.

Cancer biology – Breast Cancer

- Larger tumor size
- Higher grade tumor
- Greater lymph node positivity
  - More lymph nodes involved
- Less hormone sensitive
  - Higher incidence of "triple-negative" tumors
  - Fewer treatment options
- Increased familial risk when diagnosed at early age
  - Higher incidence of BRCA1, BRCA2 and TP53 mutations

Bleyer A, et.al. *Nat Rev Cancer* 2008.
Anderson WF, et al. *J Clin Oncol* 2007.
Lalloo F, et al. Eur J Cancer 2006.

Cancer biology - Colorectal

- Highest incidence of microsatellite instability
- Highest incidence of familial adenomatous polyposis
  - Mutations in the adenomatous polyposis gene
- Hereditary non-polyposis colon cancer
  - Mutations in mismatch repair genes
    - mutS homologue 2 (*MSH2*)
    - mutL homologue 1 (*MLH1*)
    - postmeiotic segregation increased 2 (*PMS2*)
  - Sporadic forms of colorectal cancer in AYAs are missing
    - KRAS mutations
    - Loss of heterozygosity at chromosome 17p or 18q
    - Other mutations common in colon cancer of older patients
- Histopathological types
  - Mucinous adenocarcinoma
  - Signet-ring pathology

Bleyer A, et.al. *Nat Rev Cancer* 2008.

Cancer biology – Acute Lymphoblastic Leukemia (ALL)

- Higher adverse biological characteristics
  - Philadelphia (Ph) chromosome t(9;22) BCR-ABL translocation
    - 3 – 26% of AYAs with ALL
  - t(12;21) TEL-AML1 translocation
    - Favorable genotype
    - 10% of adolescents
- Cytogenetics
  - Hyperdiploid DNA content less common

Bleyer A, et.al. *Nat Rev Cancer* 2008.
Mulligan CG, et al. *Journal of Adolescent and Young Adult Oncology* 2011.
Mohan SR, et al. *Journal of Adolescent and Young Adult Oncology* 2011.

Cancer biology – ALL

- T-cell ALL phenotype
  - Approximately 25% of AYA patients
- Hypermethylation
  - Growth regulating kinase genes (p57 and p15)
  - Tumor suppressor gene (TP73)
    - DNA-hypomethylating agents
- ALL outcomes among AYA patients
  - Better outcomes when pediatric regimens used
  - Different drug selection and higher dose intensity

Bleyer A, et.al. *Nat Rev Cancer* 2008.
Mohan SR, et al. *Journal of Adolescent and Young Adult Oncology* 2011.
Boissel N, et al. *J Clin Oncol* 2003.

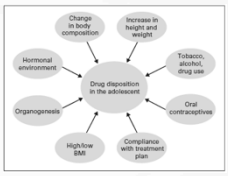
Cancer biology – Non-Hodgkin Lymphoma

- Diffuse large B-cell lymphoma (DLBCL)
  - Adult DLBCL classified by gene expression profiling
    - Germinal center B-cell type (GCB)
    - Activated B-cell type (ABC)
    - Type 3 DLBCL
  - Translocation t(14;18) in the *IGH* chain and *BCL2* genes
    - Adverse prognostic factor
    - Noted in 15% of adult patients
    - Not detected in children
- When do translocations start to appear?
  - Early- to mid-adulthood

Bleyer A, et.al. *Nat Rev Cancer* 2008.
Oschlies I, et al. *Blood* 2006.

Pharmacologic and physiologic factors

- Epigenetic effects
  - Hormonal changes
  - May alter drug metabolism
- Physiologic changes
  - Volume of distribution
  - Protein binding
  - Hepatic function
  - Renal function
- Obesity
  - Inferior outcomes in both ALL and AML
  - Increases drug disposition
  - Chemotherapy dosing



Bleyer A, et.al. *Nat Rev Cancer* 2008.
Veal GJ, et al. *J Clin Oncol* 2010.

Pharmacologic and physiologic factors

- Toxicities
  - Higher incidence of osteonecrosis among ALL patients
    - Dexamethasone dosage schedule adjustments
- Size and maturity of organs
  - Drug metabolism
  - Liver and kidney increase in absolute size
- Greater renal and hepatic capacity
  - Under dosed when treated on adult regimens

Bleyer A, et.al. *Nat Rev Cancer* 2008.
Veal GJ, et al. *J Clin Oncol* 2010.

Which unfavorable biological characteristic(s) is/are more common among AYA patients with acute lymphoblastic leukemia?

a. t(12;21)
b. Hyperdiploid DNA content
c. t(9;22)
d. None of the above
e. b. and c.

Stem Cell Transplant

Hematopoietic Cell Transplantation (HCT)

- Allogeneic stem cell transplant effective treatment for ALL
  - Significant toxicities
- Reduced-intensity preparative regimens and alternative donors
  - Increased accessibility to this treatment option
- Unknown if factors leading to poor outcomes in AYA patients translate to transplantation outcomes.

Kebriaei P, et al. *Curr Hematol Malig Rep* 2012.
Burke MJ, et al. *Biol Blood Marrow Transplant* 2013.

Outcomes of HCT for AYAs compared to children and older adults with AML

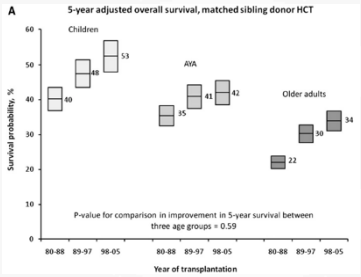
- Patients and Methods
  - Multi-center, retrospective review from 1980 to 2005
  - N = 900 children (<15 years), 2,708 AYA (15-40 years) and 2,728 older adults (>40 years)
  - Disease status
    - Most patients in complete remission (CR) 1
  - Cytogenetic risk
    - Similar incidence of poor cytogenetic risk in all groups
  - HLA match & conditioning regimen
    - 1980-1997: most received HLA-identical sibling myeloablative transplants
    - 1998-2005: most received unrelated, well or partially matched myeloablative transplants

Majhail NS, et al. *Biol Blood Marrow Transplant* 2012.

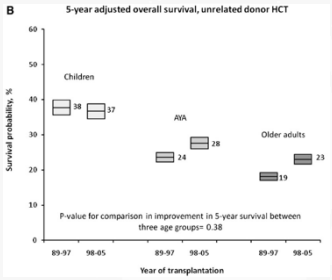
Outcomes of HCT for AYAs compared to children and older adults with AML

- Patients and methods
  - Median follow-up
    - 1980-1988: ~ 13 years
    - 1989-1997: ~10 years
    - 1998-2005: 4 to 5 years
- Outcomes
  - Overall survival (OS),
  - Leukemia-free survival (LFS),
  - Relapse,
  - Treatment-related mortality (TRM)
    - Assessed over three time periods
      - Matched sibling donor (MSD): 1980-1988, 1989-1997, 1998-2005
      - Unrelated donor (URD): 1989-1997, 1998-2005

Results



Results



Results

- Leukemia-free survival
  - Five-year LFS improved over time for all age groups, P=0.76
    - Children > AYAs > Older adults
  - Multivariate analysis: Older adults worse LFS rates (HR 1.47, 95% CI (1.24-1.75), P=<0.01)
- Treatment-related mortality
  - Cumulative incidence of TRM decreased over time, P=0.01
  - Multivariate analysis: Strong age correlation with relative risk of TRM
    - AYAs twice the risk, P=<0.01
    - Older adults three times the risk, P=<0.01
- Relapse
  - There were no statistically significant changes

Discussion

- Survival for AYAs with AML following an allogeneic HCT has improved over time
  - Due to decreasing risks of TRM
  - Parallel those of other age groups
- Relapse rates did not improve over time
  - Possibly due to changes in transplantation practices
  - Relapse continues to be a major reason for treatment failure
- Limitations
  - Retrospective cohort study
  - Data specific to allogeneic HCT and AML
  - Selection bias at the level of Cancer Centers
  - Did not address issues related to access to allogeneic HCT for AYAs

Survival differences between AYAs and children with B-ALL after HCT

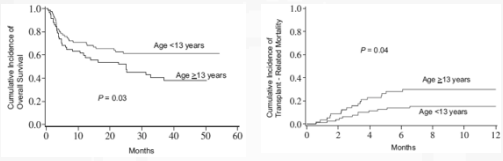
- Patients and Methods
  - Single-center, retrospective review from 1995 to 2010
  - n = 127 patients
    - 74 (58%) children age < 13 years
    - 53 (42%) AYAs age 13-30 years
  - Donor source
    - Cord blood > Bone marrow > Peripheral blood
  - Remission status
    - Age <13 years – 27% in CR1, 60% CR2, 12% CR3
    - AYAs – 42% in CR1, 47% CR2, 11% CR3
  - Cytogenetic risk
    - Low incidence of Ph^+ or mixed lineage leukemia rearrangement mutations in both groups

Burke MJ, et al. *Biol Blood Marrow Transplant* 2013.

Survival differences between AYAs and children with B-ALL after HCT

- Patients and Methods
  - Graft versus host disease (GVHD) prophylaxis
    - Cyclosporine-based in 122 patients (95%)
  - Median follow-up
    - Age < 13 years
      - 5.96 years (range, 1.0 – 13.61 years)
    - Age 13-30
      - 4.16 years (range, 14.07 years)
- Outcomes
  - OS
  - Disease-free survival (DFS)
  - Transplantation-related mortality (TRM)
  - GVHD
  - Relapse

Results



- Five-year DFS was not significantly different
  - Univariate analysis (52% [95% CI, 40%-63%] vs 40% [95% CI, 26%-53%]; P=0.18)
  - Multivariate analysis (relative risk [RR], 1.39; 95% CI, 0.85-2.25; P=0.18)
- Older age associated with a 2-fold increase in TRM (P=0.05)

Results

- GVHD
  - In univariate or multivariate analyses, age was not a factor in the development of GVHD
    - Grade II-IV acute GVHD (31% [95% CI, 21%-42%] vs 41% [95% CI, 27%-55%]; P=0.26)
    - Grade III-IV acute GVHD (11% [95% CI, 4%-18%] vs 8% [95% CI, 1%-15%]; P=0.59)
    - Chronic GVHD (7% [95% CI, 1%-12%] vs 15% [95% CI, 5%-25%]; P=0.06)
- Relapse
  - No significant difference in relapse at 1 year (P=0.72)
  - Disease status most significant risk factor for relapse in multivariate analysis (RR, 5.72; 95% CI, 1.37-23.81; P=0.02)

Discussion

- Inferior OS in the AYA patients due to greater TRM
  - Increased risk of TRM not likely due to more treatment
  - Increased TRM due to unique biological factors?
- Further investigation in methods to reduce TRM among AYA patients is warranted
- Limitations
  - Single-center, retrospective study cohort
  - Small sample size

Similar outcomes between AYAs and children with AML after HCT

- Patients and Methods
  - Single-center, retrospective study from 1995 to 2010
  - n = 168 AML patients
    - 101 (60%) were age < 15 years
    - 67 (40%) were age 15-30 years (AYA)
  - Conditioning regimen (P=0.03)
    - Cyclophosphamide and TBI most common regimen
  - Donor source
    - Cord blood > Bone marrow > PBSC
  - Remission status
    - Age <15 years – 38.6% in CR1, 34.7% CR2, 27% CR3/ refractory
    - AYAs – 47.8% in CR1, 37.3% CR2, 14.9% CR3/refractory

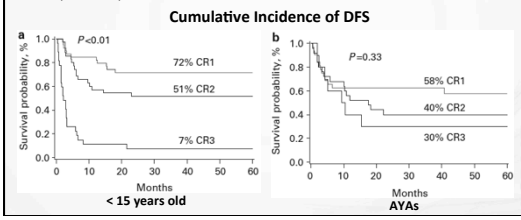
Burke MJ, et al. *Bone Marrow Transplantation* 2013. [Epub ahead of print].

Similar outcomes between AYAs and children with AML after HCT

- Patients and Methods
  - High-risk cytogenetics (age < 15 vs AYA, respectively)
    - FLT3/ITD – 5.9% vs 4.5%
    - MLL-R - 21.8% vs 11.9%
    - Monosomy 5 or 7 – 5% vs 7.5%
  - Median follow-up after HCT
    - Age < 15 years
      - 6.09 years (range, 0.56– 14.22 years)
    - Age 15-30
      - 5.75 years (range, 1.84-12.46 years)
- Outcomes
  - Same as the B-ALL study

Results

- Five-year OS
  - 50% [95% CI, 40%-59%] vs 43% [95% CI, 35%-39%]; P=0.89
- Five-year DFS
  - 47% [95% CI, 37%-57%] vs 47% [95% CI, 35%-39%]; P=0.89
- Similar OS and DFS in multivariate analysis
- Patients <15 yo and in ≥ CR2 had worse 5-year OS (P<0.01)



Results

- TRM
  - Non-significant trend toward more TRM in AYA patients (Relative risk 1.91, 95% CI 0.97-3.77; P=0.07)
- GVHD
  - Higher incidence of grade II-IV acute GVHD in AYA patients
    - 31% [95% CI, 22%-41%] vs 48% [95% CI, 35%-61%]; P=0.01
  - AYA patients also developed more chronic GVHD
    - 7% [95% CI, 2%-12%] vs 22% [95% CI, 12%-33%]; P<0.01
- Relapse at 2 years
  - No significant difference between the two age groups (P=0.30)
  - Patients in CR1 had the lowest relapse rate (P<0.01)

Discussion

- Similar survival regardless of age
- Differences noted between AYAs and <15 year-old AML patients were the rates of grade II-IV acute and chronic GVHD
- Outcome findings in AML patients different from ALL patients
  - Differences possibly due to:
    - Shorter duration of treatment in AML patients
    - CR status at time of transplant
- Limitations
  - Retrospective cohort study
  - Small sample size
- Further studies on how to minimize TRM in AYAs and increase OS in all patients are warranted

A young 25 year old female with AML in CR2 is the clinic today being evaluated for an allogeneic HCT. The patient is very anxious about receiving a transplant and she asked you if there's any data on outcomes in patients her age after a HCT? What's your response to her question?

a. There are multiple studies reviewing how well patients your age responded to a HCT for AML and in those studies most patients died from transplant-related toxicities.
b. Currently there's no information on how your disease will respond to a HCT or about transplant-related toxicities in patients your age.
c. Based on the limited data on outcomes of allogeneic HCT for patients with AML in your age compared to younger patients you may have a higher risk of developing acute GVHD.
d. Since you are currently in CR2, there's a lower incidence of relapse 2 years after receiving a HCT.

Medical and Psychosocial Issues

Unique AYA challenges

- Literature about issues/challenges AYA cancer patients experience while receiving treatment
  - AYA HCT patients may face similar issues, possibly more
- Vulnerable population
  - Social
  - Psychological
  - Developmental
- Rates of psychological distress higher among AYAs compared to older cancer patients

Cooke L, et al. *J Psychosoc Oncol* 2011.
Mor V, et al. *Cancer* 1994.

Unique medical challenges

- Access to medical care
  - Restricted or delayed
    - Highest uninsured rate compared to other age groups
    - AYA patients ignore or minimize symptoms
    - Low suspicion of cancer in this age group
    - See various health care providers prior to seeing an oncologist
  - Ability to make follow-up visits
- Survivorship concerns
- Health education access
- Healthy lifestyle habits while experiencing their developmental need for autonomy and independence

A report of the Adolescent and Young Adult Oncology Progress Review Group 2006.
Zebrack B, et al. *J Clin Oncol* 2012.
Cooke L, et al. *J Psychosoc Oncol* 2011.

Unique psychosocial issues

- AYA patients experience distinct psychosocial challenges from pediatric and adult patients
- Psychosocial needs based on the following areas:
  - Individual aspects
  - Relationships
  - Socioeconomic issues
  - Supportive care

Zebrack BJ. *Cancer* 2011.

Unique psychosocial issues

- Individual aspects
  - Developmental issues
    - Identity development
    - May not be developmentally ready to manage their care
  - Emotional Issues
    - Fear of death
      - Personal death
      - Loss of AYA cancer friends undergoing treatment
    - Loss of fertility
    - Depression and anxiety
      - Recurrence of disease

Cooke L, et al. *J Psychosoc Oncol* 2011.
Zebrack BJ. *Cancer* 2011.
Abrams AN, et al. *Cancer Treat Rev* 2007.

Unique psychosocial issues

- Relationships
  - Autonomy and independence throughout HCT
    - Previously living on their own
    - Dedicated caregiver throughout transplant
  - Isolation and alienation when receiving treatment
  - Difficult for health care providers to communicate information to AYA
- Socioeconomic issues
  - Financial
    - Higher unemployment
    - Lower incomes
    - Difficulty paying for medical bills and other finances

Cooke L, et al. *J Psychosoc Oncol* 2011.
Abrams AN, et al. *Cancer Treat Rev* 2007.
Morgan S, et al. *J Clin Oncol* 2010.

Unique psychosocial issues

- Supportive care
  - Late physical effects
    - Medical
    - Cognitive impairments
      - Among adult survivors of transplant more cognitive symptoms seen in those treated with total body irradiation
      - May affect school and work performance
- Behavioral issues
  - Substance abuse
  - Poor compliance

Cooke L, et al. *J Psychosoc Oncol* 2011.
Eiser C. et al. *J Can Surviv* 2007.
Andrykowski MA, et al. *Bone Marrow Transplant* 1990.

Interventions

- Offer more information on health access
  - Age appropriate
  - Timely
- Competent health professionals in AYA health
- Better communication within health care team
  - AYAs prefer information communicated in a positive, respectful and nonjudgmental manner
- Current technology
  - Distraction
  - Communication
  - Education
  - Treatment adherence

Cooke L, et al. *J Psychosoc Oncol* 2011.
Morgan S, et al. *J Clin Oncol* 2010.
Zebrack B, et al. *J Clin Oncol* 2012.

Interventions

- Peer support
  - Access to other AYA patients and/or survivors
  - Reduce feelings of isolation
  - Emotional support
- Educational resources
  - Promote healthy lifestyle
  - Adherence education
  - Provide guidance on appropriate and relevant information
- Flexible treatment options to allow normal school/work activities

Cooke L, et al. *J Psychosoc Oncol* 2011.
Morgan S, et al. *J Clin Oncol* 2010.
Zebrack B, et al. *J Clin Oncol* 2012.

AYA Oncology (AYAO) PRG Recommendations to Improve Outcomes

- Identify the characteristics that distinguish the unique cancer burden in the AYAO patient.
- Provide education, training, and communication to improve awareness, prevention, access, and quality cancer care for AYAs.
- Create the tools to study the AYA cancer problem
- Ensure excellence in service delivery across the cancer control continuum.
- Strengthen and promote advocacy and support the AYA cancer patient.

A report of the Adolescent and Young Adult Oncology Progress Review Group 2006.

Sexuality/Fertility Issues

- Uncomfortable discussing sexual concerns
  - With physicians
  - When parents are present
- Fertility and sexuality issues to expect after HCT
- Family planning
  - Younger patients may not have considered starting a family
  - AYA patients may be planning a family
    - Fertility preservation major concern

Cooke L, et al. *J Psychosoc Oncol* 2011.
A report of the Adolescent and Young Adult Oncology Progress Review Group 2006.

Fertility Preservation

- Following the diagnosis of cancer
  - Discussion of risks of infertility associated with cancer treatment
  - Options for fertility preservation
  - Provider initiate referral for fertility preservation clinics
- Fertility preservation options are costly
  - May not be covered by many insurance companies or Medicaid plans

Lee SJ, et al. *J Clin Oncol* 2006.
Levine J, et al. *J Clin Oncol* 2010.

Fertility Preservation

- Infertility may occur in both males and females after receiving cancer treatment
  - Age at time of treatment
  - Duration, dose intensity and type of treatment
  - Alkylating agent-based therapies
  - Total body irradiation or radiation to a field that includes the ovaries/testis
- Ovarian protection during chemotherapy
  - Gonadotropin-releasing hormone (GnRH)
- Oophoropexy and embryo cryopreservation
- Semen cryopreservation

Lee SJ, et al. *J Clin Oncol* 2006.
Levine J, et al. *J Clin Oncol* 2010.

AYA HCT program at MD Anderson Children's Cancer Hospital

- Medical care
  - Multi-disciplinary team
    - Leukemia/Lymphoma physician with special interest in AYA patients
    - AYA HCT service
    - Child life specialist specializes on AYA patients
    - AYA exercise group with physical therapist
    - Dedicated chaplain to our pediatric and AYA patients
    - Clinical pharmacy specialists
  - Outpatient treatments
  - Innovative surgical techniques
  - Sexuality and fertility counseling
  - Hospital facilities – AYA lounge, library and recreational center

AYA HCT program at MD Anderson Children's Cancer Hospital

- Psychosocial Care
  - Career and vocational counseling
    - Social worker
  - Education and Creative arts program
    - Dedicated school teachers
  - Special events
  - Psychological counseling
    - Psychologist consulted on admission for HCT
    - May provide counseling to parents/caregivers when needed
  - AYA support group

All of the following are examples of unique medical and psychosocial issues that AYA patients more commonly encounter throughout cancer treatment, except for?

a. Anxiety about not undergoing fertility preservation prior to starting chemotherapy
b. Fear of personal death
c. Distress about not being able to swallow tablets
d. Isolation from friends and family

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