Chapter 9
Adolescent and Young Adult Concerns

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Introduction

Since the publication of the National Cancer Institute Progress Review Group report, Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer, there has been an increasing effort to address the unique needs of patients between the ages of 15 and 39 diagnosed with cancer, who often feel isolated between the worlds of pediatric and adult oncology. This group of individuals is now identified in clinical trials and in clinical care as the adolescent and young adult (AYA) population.

Historically, hematopoietic cell transplant (HCT) has been applied selectively to younger, healthier patients, and hematologic malignancies are among the most common cancers of the AYA population. Therefore, attention to their age-specific needs constitutes quality care. Each domain of AYA cancer care (Table 9.1) should be approached with the patient's age and developmental status in mind. An ideal AYA team consists of medical providers, nurse specialists, social workers,

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Table 9.1 Domains of AYA cancer care

Domain	Examples
Medical	Oncology, palliation, nutrition, endocrinology, etc.
Emotional/ Psychological	Psychology, coping, distress
Physical	Exercise, activities of daily living, myopathy
Neurocognitive	Education, vocation
Social	Relationships with peers and providers; family roles (parent, child) and relationship with significant others
Reproductive	Fertility preservation, parenting options
Financial	Disability, insurance
Lifestyle issues	Environment, risky behaviors, balance with treatment
Late effects	Prevention, monitoring
Care community	Caregivers, family, friends

AYA adolescent and young adult

vocational counselors, fertility experts, physical and occupational therapists, and community-based services with peer support.

Priority concerns for these domains are listed below.

Medical

1. Leukemias, lymphomas, and germ cell tumors are common cancers among AYA-aged patients. HCT may play an important role in the therapy of these malignancies.
    a. Compared to children, the treatment-related morbidity and mortality may be increased for AYAs, but less so than for older adults. Consequently, survival often varies inversely by age group, especially in leukemias [2–4].
    b. Changes in initial treatment, such as pediatric-inspired therapies for acute lymphoblastic leukemia, have led to a reconsideration of the role of HCT in first remission in some circumstances [5]. The presence of minimal residual disease (MRD) may predict the benefit of transplant [6]. Thus, the efficacy of initial therapy, which may be higher with pediatric inspired regimens, is especially important.
    c. An increased understanding of the prognostic importance of specific molecular features, and their prevalence in the AYA population relative to other age demographics, may improve the ability to tailor the role and timing of HCT for the AYA patient.
2. Attention to issues related to growth, development, and nutrition in the AYA patient may optimize short- and long-term medical care, including screening for late effects. These issues include the impact of preparative regimens and the

HCT process upon growth hormone, thyroid hormone, gonadotropin production, adrenal function, and other aspects of nutrition and metabolism.

3. A variety of genetic syndromes may present with cancer in the AYA age range including Fanconi anemia, Li–Fraumeni syndrome, dyskeratosis congenita, and others. A careful physical examination and family history is always warranted for an AYA with cancer, especially when a cancer presents with an earlier than expected age onset.

Emotional/Psychological

HCT in the AYA patient carries a significant risk of emotional and psychological dysfunction [7]. The adverse experiences endured during and post-HCT, along with disruptions to their daily life routine, can impact the emotional well-being and development of AYA patients.

1. Adolescent HCT survivors report more somatic problems compared to controls and siblings [7].
2. An AYA patient's physical and sexual development, sense of identity, ability to have achieve independence, and social development may be delayed due to the diagnosis and treatment of cancer and undergoing HCT.
3. AYA survivors of HCT are at higher risk of mood disorders that include depression and anxiety.
    a. Depression and anxiety are associated with longer hospital admissions, higher reporting of pain symptoms, and decreased adherence to medications and other elements of medical care.
4. Social anxiety and posttraumatic stress disorders can also be seen in this population.
    a. Both diagnoses are associated with social withdrawal, low self-esteem, and poor quality of life.
5. Medical providers should recognize the potential for altered emotional and psychological outcomes. Referrals to mental health professionals should be placed early to allow patients to receive appropriate psychological counseling and help with coping mechanisms.

Physical

Many AYAs who undergo HCT also experience physical changes as a result of treatment. These alterations may include changes in appearance and sexual development and function, as well as limitations in their normal activities. It is important for

patients to be encouraged to speak with their healthcare team about these changes and learn ways to cope or to identify changes that warrant treatment or referral.

1. Changes in appearance
    a. Chemotherapy, radiation, and treatment for acute and chronic graft-versus-host disease (GvHD) such as steroids are associated with changes in appearance including alopecia, weight gain or loss, scars, and/or changes in pigmentation.
    b. AYA patient's body image and identity can be negatively affected by these physical changes, and for some patients may lead to social isolation.
2. Sexual development and function [8]
    a. Sex and intimacy are an important part of many AYAs' lives.
    b. Conditioning regimens, GvHD, medications, and psychosocial issues can contribute to physical and psychological sexual dysfunction.
    c. Consequences can include decreased libido, hormonal dysregulation, erectile dysfunction, dyspareunia, and infertility.
    d. Often, sexuality is a difficult topic for patients and their significant others to discuss. Moreover, many healthcare providers may not feel comfortable or think about addressing it with patients.
    e. Since sexual dysfunction can have a negative impact on a patient's quality of life, it is important for healthcare providers to perform assessment of sexual function to identify changes and issues that may warrant treatment or referral.
3. Activity limitations
    a. Patients can be limited in their activities due to a myriad of causes that include physical isolation recommended due to their immunocompromised status, fatigue/low energy as a consequence of therapy, and possible cardiovascular or pulmonary complications. In addition, severe chronic GvHD can restrict patient's movements.

Neurocognitive

Neurocognitive dysfunction in AYA patients undergoing HCT can be a consequence of various factors such as systemic chemotherapy, intrathecal chemotherapy, cranial radiation, total body irradiation (TBI), immunosuppressive therapies, and GvHD. Symptoms of neurocognitive dysfunction can include impaired attention/concentration, memory impairment, and problems with executive function [9]. Although it is possible to regain many of these domains, 40% of HCT survivors may have persistent deficits [10].

1. The domains of neurocognitive function include the following
    a. Attention and concentration
    b. Perceptual processing
    c. Learning and working memory
    d. Abstract thinking and working memory
    e. Language
    f. Information processing speed
    g. Motor function
2. Neurocognitive dysfunction can have a major effect on activities of daily living
    a. Return to work or school and reintegration into society may be affected.
    b. Patients have reported poor self-image, physical and social functioning.
    c. Compliance to medication and post-HCT follow-up care may be affected [11].
3. Treatment effects and risk of neurocognitive impairment
    a. Systemic chemotherapy
        i. Patients treated with chemotherapy alone have greater deficits in neurocognitive function than controls.
    b. Intrathecal chemotherapy
        i. Both triple intrathecal (methotrexate, hydrocortisone, and cytarabine) and single intrathecal (methotrexate) had comparable neurocognitive deficits [12].
    c. Conditioning regimen
        i. Preparative regimens may include chemotherapy, TBI, or both in addition to cranial or cranio-spinal radiation.
        ii. Chemotherapeutic agents with risk of neurocognitive dysfunction include, but are not limited to [13]:
            - Busulfan
            - Carboplatin
            - Carmustine
            - Cytarabine
            - Etoposide
            - Ifosfamide
            - Thiotepa
        iii. TBI
            - Late neurocognitive dysfunction has been reported in patients who receive high-dose chemotherapy with TBI up to 12 Gy [14].

4. Other risk factors for neurocognitive impairment [13]
    a. GvHD and immunosuppressive therapies
        i. Calcineurin inhibitors (cyclosporin and tacrolimus) can cause tremors, posterior reversible encephalopathy syndrome (PRES), and thrombotic microangiopathy (TMA).
    b. Infections
        i. Cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human herpesvirus 6 (HHV6) can affect attention and speed of cognitive performance [15].
5. Neuropsychological assessments
    a. Consider neurocognitive evaluation prior to HCT for baseline assessment and during follow-up post HCT as indicated.
    b. Timely awareness of neurocognitive impairment is crucial for referral for psychosocial support and neurocognitive intervention.
6. Vocational training
    a. AYA patients may benefit from vocational training.

Social

1. Cancer treatment and HCT occur over protracted time periods, with physical and psychological complications and side effects from disease and treatment leading to repeated and prolonged hospitalizations and frequent clinic visits. Cumulatively, this leads to disruptions in school, work, and family life. Peer relationships often change, and it is critical not to neglect exploration of patient's social support systems.
2. Relationships with coworkers and employers may also change as patients experience prolonged time off work. Concerns related to disability, loss of employment, and reduced income are particularly important in this population.
3. For similar reasons, family relationships with a spouse, children, or parents often change as a result of disease and treatment.
    a. AYA patients may experience a loss of autonomy related to physical and psychological effects of disease and treatment.
    b. AYA patients may find that their roles and responsibilities within their family dynamics change over time. Understanding and discussing these concerns may alleviate psychological distress and promote resilience.
4. Many healthcare providers are also young adults and develop particularly intense relationships with AYA patients. Support for patients and providers is an important component to patient-centered care in this population.

Reproductive (see also Chaps. 39 and 40)

Reproductive health is a common concern for AYA patients undergoing HCT. AYA patients with cancer often rank having children as an important life goal. Thus, loss of fertility can have a negative impact on the reproductive and quality of life of young survivors of HCT [16]. Chemotherapy (alkylating agents) and radiation (TBI/testicular/cranial) adversely effect gonadal function and can lead to infertility. In particular, the factors that influence the risk of infertility include dose of radiation, age at treatment, and dose of chemotherapy. For example, TBI with 10–13 Gy can result in azoospermia in 85% of males undergoing HCT [17]. Cranial radiation, which is often utilized in patients with CNS leukemia and brain tumors, can also lead to secondary gonadal failure.

1. Guidelines from the American Society of Clinical Oncology (ASCO) recommend that a discussion of the possibility of infertility be part of education and informed consent for all patients of reproductive age [18]
    a. Discussion should include risks, fertility preservation options, and appropriate referrals to reproductive specialists:
        i. Every effort should be made to discuss fertility as early as possible at the time of cancer diagnosis.
        ii. Published guidelines also state that fertility preservation should be readdressed prior to HCT.
        iii. In addition to fertility preservation options, alternative parenting methods including adoption or surrogacy should be discussed.
2. Males
    a. Risk: Rates of azoospermia after high-dose conditioning regimens are as high as 90%; rates for patients treated with busulfan and cyclophosphamide are 50% and with cyclophosphamide alone 10%.
    b. Assessment: Semen analysis for quantitative analysis and motility.
    c. Fertility preservation options:
        i. Sperm banking [19]:
            - This method provides the highest likelihood of having biological children and should be discussed with postpubertal males prior to undergoing HCT.
            - Semen is generally obtained by masturbation, which can be uncomfortable or embarrassing and can lead to inability to ejaculate.
            - It is important to provide adolescent males with careful counseling with age-appropriate instructions as these patients are at risk for emotional distress from sperm banking.

- If possible, offer patients a private and relaxing environment or option to sperm bank at home. However, the specimen must remain at room temperature and return to the lab within 1 hour of collection.
- This method can be hampered by findings of decreased sperm motility or azoospermia.

ii. Testicular tissue cryopreservation

- This is the only current method available for preserving fertility in prepubertal males.
- It involves surgically removing a small portion of the testicular tissue, cryopreserving, and storing the specimen.
- In postpubertal males, the tissue is later thawed and transplanted via intratesticular grafting or by infusion into seminiferous tubules.
- As this method is investigational, it should be performed only as part of a clinical trial.
- There is a theoretical risk of reseeding tumor cells after reimplantation of tissue.

3. Females

a. Risk: Rates of ovarian failure after high-dose conditioning regimens are as high as 65–85%. However, this statistic may not be accurate as studies do not account for whether patients are trying to conceive. Younger age at the time of HCT may be associated with lower risks of infertility.
b. Assessment: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), estradiol level, and ovarian follicle assessment by ultrasound
c. Fertility preservation options [20]:

i. In vitro fertilization (IVF) and embryo cryopreservation:

- Advantages:
  - This approach is a well-established therapy that is available to most women.
  - Involves hormonal stimulation of ovaries and collection of oocytes to create embryos using IVF.
  - Success rates vary, with pregnancy rates as high as 59% and 50% live births [21].
- Disadvantages:
  - Requires two-three weeks from initiation of therapy for oocyte retrieval.
  - Requires a partner for sperm donation or willingness to accept banked sperm.
  - Females must be postpubertal.
  - This method is costly and may not be covered by insurance.

ii. Oocyte cryopreservation:

- This method involves hormonal stimulation of ovaries and collection of oocytes for cryopreservation. The unfertilized oocytes are later fertilized to produce embryos.
- Advantages:
  - Success rates are comparable to procedures using fresh embryos [22].
  - This method does not require a sperm source.
- Disadvantages:
  - Oocytes are more susceptible than embryos to damage during freezing/thawing.
  - Requires two-three weeks from initiation of therapy for oocyte retrieval.
  - This method is costly and may not be covered by insurance.

iii. Ovarian tissue cryopreservation:

- This approach is an experimental option to preserve fertility among prepubertal females.
- An ovarian cortical biopsy or oophorectomy is done laparoscopically with the goal of preserving eggs within the primordial follicles of the ovarian cortex.
- The cortical tissues are then frozen and later thawed and transplanted back to the patient.
- Advantage:
  - This is the only current option available for prepubertal girls.
- Disadvantages:
  - This approach is not recommended for females with hematologic malignancies or ovarian cancers due to the higher risk of cancer recurrence.
  - This option is an investigational treatment and should only be done in the setting of a clinical trial.

iv. Hormonal suppression with gonadotropin-releasing hormone (GnRH) analogue:

- Available to postpubertal females to help maintain ovarian follicles in a dormant state.
- Advantages:
  - It is relatively easy to administer with no delay in therapy.
- Disadvantages:
  - The efficacy of this method is not well established, and it is not sufficient alone to preserve fertility in HCT recipients.
  - GnRH is associated with bone loss, which may cause other long-term complications.

Financial

Undergoing HCT can have a significant impact on the socioeconomic well-being of patients and their families [23]. Financial toxicity or financial distress refers to the treatment-related financial burden experienced by patients with cancer. Financial toxicity can negatively influence a patient's quality of life, adherence to treatment plan, and perception of pain and symptoms.

1. Insurance
    a. HCT may be associated with high out-of-pocket costs despite insurance coverage.
    b. It is important for AYA patients and their families to meet with a financial navigator who can help them better understand the health insurance plans and their out-of-pocket costs for treatment and payment options.
    c. Patients should evaluate and budget coverage for their living, determining which expenses can be reduced or eliminated.
    d. Patients should consider applying for financial assistance programs if they qualify.
2. Employment
    a. Patients who are employed will need to take time off from their job during pretransplant treatment, transplantation, and posttransplant recovery.
    b. During this employment break, there will be a loss of income, but the cost of living and household bills will continue to incur.
    c. Patients may need to consider whether they qualify for disability insurance or other benefits through their employer or state.
3. Housing and transportation
    a. Some patients and families many need to temporarily relocate and move closer to the transplant center.
    b. Costs may be incurred due to new living arrangements as a result of relocation.
    c. Patients and families may also need to travel long distances to transplant centers and incur costs for gas and transportation.
4. Financial loss or bankruptcy
    a. Many families suffer large financial loss or file for bankruptcy as a result of significant out-of-pocket costs for medical care, loss of wages, and ongoing housing and transportation costs.
    b. Khera et al. showed that 73% of recipients of allogeneic HCT reported financial losses in some manner with a large percentage needing to sell or mortgage their home or prematurely utilize their retirement savings [24].

Lifestyle Issues

Young adults are particularly vulnerable to engaging in risky health and lifestyle behaviors [25]. Substance use/abuse may be common in this patient population and includes alcohol, tobacco, marijuana, or illicit drugs. Cigarette smoking is widely known to be linked to many adverse healthy problems and increases the risk of developing a secondary neoplasm. Some studies show that cancer survivors who smoke are more likely to fail cessation attempts [26]. The rate of marijuana use (medical and/or recreational) is increasing with rates climbing due to legalization in many states. The risk of marijuana and illicit drug use is higher in males, patients with lower socioeconomic status, and patients who report depressive symptoms. It is important for healthcare providers to screen and ask patients about their health behaviors.

Late Effects (see also Chap. 49)

1. Prevention
2. Monitoring

Care Community

Young adults have a variety of life situations that include living at home, being employed, attending school, or caring for a family of their own. Having a cancer diagnosis and going through transplant is a heavy burden for AYAs to bear alone. Thus, it is crucial for AYA patients undergoing HCT to have a support community to rely on. This care community may consist of family, partner, peers, community groups, or professionals who can help them navigate through the complex journey of a transplant.

1. Family (parents, spouse, siblings) or significant other
    a. AYAs should enlist family and partners early in the HCT process.
    b. Can serve as support persons during important discussions with the medical team as it can be difficult to remember everything being discussed.
    c. May assist with logistics such as transportation, meals, and financial issues.
2. Peers (friends, AYA organizations)
    a. Friends can be a source of support and comfort through the HCT process.
    b. Patients can also connect with other AYAs who have been through transplant and can better relate with their experience. However, it is important for healthcare providers to remind AYAs that each patient's experience is different.

3. Professional help (case coordinator, patient/nurse navigator, social worker)
    a. These individuals can assist with medical insurance issues such as patient's out-of-pocket costs and help apply for financial assistance programs if patients qualify.
    b. For patients who are employed outside of the home, they may provide information on employer benefits and disability insurance.
    c. Professionals can also help AYAs navigate through student loans and forbearance for those who are in college and need to take a leave of absence.
4. Community
    a. Support can also be found through religious organizations, clubs, and social networks.

AYA-Specific Resources

1. National Cancer Institute (http://www.cancer.gov/cancertopics/aya)
2. NCCN Guidelines for Patients – Adolescents and Young Adults with Cancer (https://www.nccn.org/patients/guidelines/aya/files/assets/common/downloads/files/aya.pdf)
3. Livestrong: Young Adults with Cancer (https://www.livestrong.org/we-can-help/just-diagnosed/young-adults-with-cancer)
4. Stupid Cancer (https://stupidcancer.org/)

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