**Adolescents and Young Adults, Late Effects**

1. A 19-year-old man is referred to your clinic after 1 week of fevers and increased fatigue. His CBC reveals a WBC count of 75,000/µL, hemoglobin of 5.5 g/dL, and platelets of 15,000/µL. On peripheral blood smear, 86% of the WBCs are large, immature cells with scant cytoplasm and prominent nucleoli.

Which cytogenetic finding is more likely to occur in this teenage patient compared with an infant or young child with a similar presentation?

A. t(12;21)

B. High hyperploidy (51-65 chromosomes)

C. t(4;11)

D. t(9;22)

E. t(1;19)

**Explanation**

Adolescents and young adults (AYAs) with acute lymphoblastic leukemia have different cytogenetic abnormalities compared with infants and young children, which may be a factor in their decreased survival. Philadelphia chromosome–positive leukemia with t(9;22) is rare in young children (approximately 5% of diagnoses); however, the rate increases with age, with an incidence of 10% to 25% in AYAs. Patients with this translocation are considered to be at very high risk. Current treatment includes tyrosine kinase inhibitors.

More favorable cytogenetic factors, such as t(12;21) and high hyperdiploidy, are more common in young children than AYAs. MLL rearrangements, particularly t(4;11), are the most common cytogenetic abnormality in infants and are associated with poor prognosis. The t(1;19) translocation was originally associated with an unfavorable prognosis; however, treatment with more intensive approaches has improved results, and it is no longer thought to be a prognostic factor. This translocation occurs in most age groups at approximately the same rate.

2. A 25-year-old girl with a history of Hodgkin lymphoma presents to the oncology late effects clinic. She was treated with nitrogen mustard, vincristine, procarbazine, and prednisone followed by 25.5 Gy modified mantle radiation at age 15.

What screening is needed for subsequent malignancies?

A. Annual CBC

B. Annual urinalysis

C. Annual mammography and breast MRI

D. Colonoscopy every 5 years

E. Annual thyroid ultrasounds

**Explanation**

Subsequent malignancies are the leading cause of nonrelapse late mortality for childhood cancer survivors. The incidence of subsequent malignancies increases with age, and Hodgkin lymphoma survivors are at particularly high risk. Female patients who have received radiation to the breast are at increased risk for breast cancer. The Children’s Oncology Group Long-Term Follow-Up Guidelines recommend annual mammography and MRI starting at age 25 or 8 years after breast radiation exposure, whichever occurs last. Although procarbazine and nitrogen mustard increase the risk of myelodysplasia/acute myeloid leukemia, the recommendations are to perform an annual targeted history and physical examination. In addition, the patient is at elevated risk of thyroid cancer due to exposure to radiation. Monitoring for thyroid cancer should be performed annually with a physical examination. The risk of thyroid cancer should be discussed with patients, and decisions about screening with ultrasound made through shared decision making. If screening thyroid ultrasounds are performed, they should be repeated every 3 to 5 years. Early screening for colon cancer is recommended for patients who received abdominal radiation. This patient received mantle radiation, which includes the neck, chest, and axilla, not the abdomen.

3. A 14-year-old girl presents to survivor clinic for her first visit after transferring care from another institution. She was treated for acute lymphoblastic leukemia (ALL) at 2 years of age. She has been doing well since that time, but her family reports that she is struggling in school, especially with concentration and math.

Which of the following treatments that she received places her at greatest risk for neurocognitive deficits?

A. Dexamethasone

B. Asparaginase

C. Daunorubicin

D. High-dose methotrexate

E. Vincristine

**Explanation**

Neurocognitive deficits can occur in survivors treated with high-dose cytarabine, high-dose methotrexate, intrathecal methotrexate, and cranial radiation. These deficits are typically functional deficits in executive function, attention, memory, processing speed, visual-motor integration, and fine motor dexterity. Survivors also may have learning deficits, particularly in math and reading comprehension. New deficits may emerge over time. A meta-analysis of childhood acute lymphoblastic leukemia survivors treated with chemotherapy-only treatment regimens showed a significant impairment in IQ and other neurocognitive domains. Survivors with concerns may benefit from a formal neuropsychological evaluation.

4. An 18-year-old man with history of multiply relapsed leukemia is interested in discussing his risk of infertility due to cancer treatment. He underwent two hematopoietic stem cell transplants as part of his treatment.

After reviewing his previous treatment, which of the following agents contributes to his risk of azoospermia?

A. Cytarabine

B. Methotrexate

C. Busulfan

D. Fludarabine

E. Etoposide

**Explanation**

Risk of infertility is one the most common concerns voiced by young adult survivors of childhood cancer. Survivors treated with hematopoietic stem cell transplant have a high risk of gonadal dysfunction due to conditioning regimens and previous treatments. Surgery, radiation, and chemotherapy that affect the hypothalamic-pituitary-gonadal axis and reproductive organs increase the risk of infertility. Treatment factors that affect this axis and may lead to infertility include surgical removal of reproductive organs (oophorectomy/orchiectomy), alkylating agent chemotherapy, hypothalamic-pituitary radiation, and radiation to the reproductive system. Pelvic or spinal surgery may also lead to sexual dysfunction, including retrograde ejaculation in men after retroperitoneal lymph node dissection. Radiation fields that may affect reproductive organs in women include abdominal, pelvic, lumbosacral spine, and total body. In men, these fields include pelvic, testicular, sacral spine, and total body. Alkylating agents used for treatment of childhood cancer include busulfan, carmustine, chlorambucil, cyclophosphamide, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, thiotepa, cisplatin, carboplatin, dacarbazine, and temozolomide.

5. A 23-year-old woman with a history of rhabdomyosarcoma at age 4 years comes to the survivor clinic to discuss late effects. She is worried about her risk of infertility. Which of the following factors is *not* known to affect the risk of infertility for female survivors of childhood cancer?

A. Age at treatment

B. Dosage of alkylating agent chemotherapy

C. Location of radiation

D. Current age

E. Race

**Explanation**

Many factors can affect the risk of infertility. Surgery, radiation, and chemotherapy that affect the hypothalamic-pituitary-gonadal axis and reproductive organs increase the risk of infertility. In general, female patients maintain ovarian function at higher cumulative alkylating agent dosages than testicular function in male patients. However, the risk of infertility increases with increased dosage of alkylating agents and radiation. Female patients are at high risk for premature ovarian insufficiency when they receive ovarian radiation dosages greater than 20 Gy. Compared with postpubertal girls, prepubertal girls are able to tolerate higher dosages of gonadotoxic chemotherapy and radiation before development of premature ovarian insufficiency. All girls are born with a finite number of primordial ovarian follicles that decrease over time until the number approaches 1,000 follicles, and menopause ensues. In female survivors of childhood cancer who have received gonadotoxic therapy, there may be an abrupt drop in the primordial follicle pool, leading to premature ovarian insufficiency or ovarian failure. However, women with a decreased ovarian reserve due to cancer therapy may have a window of time between the end of cancer treatment and the onset of ovarian insufficiency in which they are fertile and could conceive or undergo fertility preservation measures. There are no data supporting a difference in risk for infertility due to cancer treatment based on race.

6. A 15-year-old girl with a history of osteosarcoma presents to survivor clinic for her first evaluation. Her mother complains that she does not listen well and is wondering if she may have trouble hearing. Which of the follow is true regarding platinum-associated hearing loss?

A. Platinum chemotherapy is most often associated with conductive hearing loss.

B. Low-frequency volumes are affected first.

C. Older age at exposure increases risk.

D. Platinum-associated hearing loss is due to destruction of the cochlear hair cells.

E. Carboplatin is more ototoxic than cisplatin.

**Explanation**

Platinum-associated sensorineural hearing loss is due to the destruction of cochlear hair cells. The hair cells are arranged tonotopically; therefore, the high-frequency hair cells (>2000 Hz) are affected first. As cumulative dose increases, injury progresses toward the cochlear apex, where lower frequencies in the audible range are affected. Cisplatin is more ototoxic than carboplatin. Younger age at exposure (younger than 5 years), higher doses, receipt of multiple ototoxic agents, and combination treatment with cisplatin and cranial radiation places patients at increased risk for hearing loss. Radiation is associated with both conductive and sensorineural hearing loss; however, platinum agents are typically associated with sensorineural hearing loss only.

7. An 18-year old male patient with acute lymphoblastic leukemia recently started maintenance therapy and is complaining of increased hip pain. The pain increases during weight-bearing activity; however, it occasionally hurts at night as well. His CBCd is normal. Which of the following risk factors is most commonly associated with this process?

A. Younger age at diagnosis

B. Non-White race

C. Low body-mass index

D. Dexamethasone exposure

E. Male sex

**Explanation**

Avascular necrosis (AVN) is a well-known complication of therapy for acute lymphoblastic leukemia and can lead to significantly impaired quality of life. AVN can develop during treatment or after therapy completion and is associated with exposure to glucocorticoids. Dexamethasone has more bone toxicity compared with equivalent doses of prednisone, and continuous exposure increases this risk. Weight-bearing joints are affected in 95% of patients with AVN, with the femoral head as the most commonly involved joint, though often it is multifocal. The mechanism of injury is thought to be multifactorial, including disruption of osteoblasts, intramedullary lipocyte proliferation impacting circulation, and fat embolization to subchondral arteries. Common risk factors include female sex, radiation exposure, White race, and obesity. Teenagers are more likely to develop AVN compared with younger patients; therefore, current treatment protocols limit the exposure to long courses of dexamethasone in adolescents.

8. A 19-year old male patient with a history of acute lymphoblastic leukemia, currently 13 years from completion of therapy, presents for a fertility consultation. He is interested in his risk for infertility. Which of the following statements is true?

1. A semen analysis at this point would provide accurate information about future fertility.
2. Males can maintain gonadal function at higher cumulative alkylator dosages compared with females.
3. He should have been offered sperm cryopreservation at diagnosis.
4. His risk for testosterone deficiency is greater than his risk for infertility.
5. Prepubertal status at diagnosis is protective from gonadal injury in males.

**Explanation**

Adolescents and young adults are often concerned about their risk for future infertility. Risk for gonadotoxicity and fertility preservation options differ for males and females. Males are more sensitive to gonadotoxic exposures and have a higher risk of infertility compared to females with equivalent treatment. The Leydig cells that secrete testosterone are fairly resistant to gonadotoxic injury; therefore, males are often able to produce normal levels of testosterone even if they have Sertoli/germ cell damage leading to infertility. In females, the stromal and germ cells are equally affected by therapy; therefore, after girls receive highly gonadotoxic therapy, they are more likely to need hormone replacement to proceed through puberty or maintain menstrual cycles. Prepubertal status is protective from gonadal injury in females; however, this is not true in males. In males, gonadal recovery after therapy can take up to 5 years. After recovery, gonadal function is stable with aging. On the other hand, females may have recovery after treatment leading to a reproductive window prior to premature menopause. A semen analysis is the best method for fertility evaluation in males and would be appropriate to pursue at this time if the patient is interested. Semen cryopreservation is only possible in postpubertal males. Prepubertal males can undergo testicular tissue cryopreservation; however, it is still considered experimental.