**General Oncology: Principles of Radiation, Chemotherapy and Targeted Therapy**

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1. A 2-month-old girl is found to have a small, hard mass on her scalp. The mass increases in size over the next 4 weeks. A biopsy is performed that confirms a diagnosis of embryonal rhabdomyosarcoma. You initiate chemotherapy with vincristine, dactinomycin, and cyclophosphamide. The child presents to clinic for day 1 of cycle 3 of chemotherapy, and the mass on her scalp is smaller. She is afebrile, absolute neutrophil count is 1,405 cells/mcL, platelet count is 154,000/mcL, and total bilirubin is 0.8 mg/dL. Her mother reports she looks very tired because her eyelids have been “very droopy,” and she thinks she has a sore throat because her cry is hoarse. Her last bowel movement was 2 days ago.

What is the most appropriate chemotherapy plan?

A. Continue vincristine, dactinomycin, and cyclophosphamide at full dosage.

B. Do not administer any chemotherapy; rhabdomysarcoma is progressing and she needs different therapy.

C. Administer dactinomycin and cyclophosphamide but hold the vincristine and reevaluate weekly. If the ptosis and hoarse cry resolve, vincristine can be resumed with a dose reduction and, if tolerated, re-escalated to the full dose in the future.

D. Administer dactinomycin and cyclophosphamide but discontinue vincristine permanently.

E. Administer vincristine and cyclophosphamide but do not administer dactinomycin; the ptosis is due to dactinomycin.

**Explanation**

The correct answer is C. Vincristine causes peripheral neuropathy, which in infants presents as bilateral ptosis, hoarse cry, los of deep tendon reflexes, and constipation. In older children and adults, foot drop and paresthesia occur. If vincristine is temporarily held until symptoms resolve, it then can be resumed at partial or full dose. Dactinomycin causes myelosuppression and liver dysfunction. Cyclophosphamide causes myelosuppression.

2. A 5-year-old boy with history of stage III favorable Wilms tumor of the left kidney treated with vincristine, dactinomycin, and doxorubicin for 24 weeks and left flank radiation relapses in both lungs 9 months after completion of primary treatment. You plan to treat his relapse with ifosfamide, carboplatin, and etoposide chemotherapy. His measured glomerular filtration rate is 65 mL/min/1.73 m2.

What is the most appropriate measure to prevent prolonged thrombocytopenia?

A. Target area under the concentration-time curve (AUC) for carboplatin dosage.

B. Premedicate with dexamethasone and ranitidine before etoposide.

C. Administer ifosfamide as a continuous infusion.

D. Divide carboplatin over 3 days.

E. Reduce ifosfamide dosage by 25%.

**Explanation**

The correct answer is A. Carboplatin is cleared primarily by the kidneys, and myelotoxicity is dose limiting. Thrombocytopenia is directly proportional to carboplatin drug exposure as measured by the AUC.

3. A 4-year-old child being treated for acute lymphoblastic leukemia is found to be heterozygous deficient for the enzyme thiopurine methyl transferase (TPMT). Based on this finding, what would be the best dosing guidance for administration of mercaptopurine?

A. Administer no more than 10% of the usual dosage and observe closely for myelosuppression.

B. Administer 50% of the standard mercaptopurine dosage and observe closely for myelosuppression.

C. Monitor red blood cell thioguanine nucleotides to avoid toxic concentrations.

D. Consider a small dosage reduction of mercaptopurine and modify dosing based on peripheral blood counts.

E. Switch to thioguanine in place of mercaptopurine.

**Explanation**

The correct answer is D. Only patients who are homozygous-deficient for TPMT need major dosage reductions; usually no more than 10% of the usual dosage of mercaptopurine is then administered. Although tolerance to mercaptopurine is diminished in heterozygotes, overall the drug remains reasonably well tolerated and can be managed based on the peripheral blood counts.

4. A 15-month-old child is diagnosed with standard-risk acute lymphoblastic leukemia. On what should the dosage of intrathecal chemotherapy that this patient receives be based?

A. Age

B. Body surface area

C. Weight

D. Body mass index

E. Head circumference

**Explanation**

The correct answer is A. Cerebrospinal fluid volume has been shown to correlate with patient age and not size and remains fairly constant above 3 years of age. Therefore, intrathecal dosing is age-based.

5. A 15-year-old girl is being treated for localized osteosarcoma of the left distal femur and received high-dose methotrexate. Her serum creatinine increased three times over baseline 24 hours after methotrexate administration, and her serum methotrexate level at 24 hours was 100 µmol/L.

What is the most effective way to rapidly decrease serum methotrexate level?

A. Double the leucovorin dosage for rescue.

B. Increase the frequency of leucovorin rescue from every 6 hours to every 3 hours.

C. Order hemodialysis.

D. Administer glucarpidase.

E. Increase IV hydration and give bicarbonate bolus infusion.

**Explanation**

The correct answer is D. Glucarpidase is a carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate concentrations (more than 1 µmol per liter) in patients with delayed methotrexate clearance due to impaired renal function and is administered as a single intravenous injection of 50 U/kg. It is a recombinant bacterial enzyme that hydrolyzes the carboxyl-terminal glutamate residue from folic acid and classic antifolates such as methotrexate. Glucarpidase converts methotrexate to its inactive metabolites 4-deoxy-4-amino-N10-methylpteroic acid and glutamate. It provides an alternative nonrenal pathway for methotrexate elimination in patients with renal dysfunction during high-dose methotrexate treatment. Leucovorin rescue should be continued even when glucarpidase is administered but should not be given within a 2-hour time period before and after glucarpidase because it is a competing substrate.

6. A 16-year-old girl with relapsed rhabdomyosarcoma received vincristine, irinotecan, and temozolomide. She developed grade 3 abdominal pain and diarrhea that resolved with loperamide therapy after a period of 1 week. When she is due for her next course of chemotherapy, she is started on cefixime to decrease the risk of gastrointestinal toxicity.

What is the rationale for using cefixime?

A. Cefixime decreases the conversion of irinotecan to its active metabolite, SN-38, which causes diarrhea.

B. Cefixime decreases the excretion of SN-38 in the bile, thus decreasing the incidence of diarrhea.

C. Cefixime decreases intestinal bacteria that are responsible for deconjugating SN-38 glucuronide.

D. Cefixime promotes healing of the small intestinal brush border that is damaged by SN-38.

E. Cefixime increases the transit of SN-38 through the gut, resulting in decreased diarrhea.

**Explanation**

The correct answer is C. Irinotecan is a prodrug that is converted by carboxylesterases in the liver and intestinal tract to the active metabolite SN-38. SN-38 is conjugated to SN-38 glucuronide (SN-38G) by hepatic uridine diphosphate glucuronosyltransferase 1A1 and excreted in the bile. Intestinal bacteria produce β-glucuronidase, which deconjugates SN-38G to SN-38, which may be responsible for the delayed diarrhea from irinotecan.

7. An 18-year-old man with localized osteosarcoma of the tibia is due to receive week 10 (cycle 2 day 29) of chemotherapy with high-dose methotrexate.

Which of the following is an absolute contraindication to proceeding with high-dose methotrexate therapy?

A. Serum AST and ALT that are 10 times upper limit of normal

B. Serum creatinine of 2.2 g/dL

C. Platelet count of 60,000/mm3

D. Grade 1 mucositis

E. History of transient hemiparesis associated with previous dose of high-dose methotrexate

**Explanation**

The correct answer is B. Methotrexate is excreted primarily through the kidneys. Delayed methotrexate excretion due to impaired renal function can result in severe methotrexate toxicity.

8. A 12-year-old patient with Ewing sarcoma of the chest wall is due to receive chemotherapy with vincristine, doxorubicin, and cyclophosphamide (VDC). The patient has been receiving local radiation therapy Monday through Friday and has 5 more treatment sessions to complete radiation. The patient’s peripheral blood counts are adequate to receive chemotherapy.

How should chemotherapy be administered?

A. Proceed with VDC chemotherapy unmodified.

B. Delay chemotherapy until radiation is completed and then proceed with VDC chemotherapy.

C. Administer VDC chemotherapy with dexrazoxane before doxorubicin infusion.

D. Omit doxorubicin and proceed with vincristine and cyclophosphamide.

E. Replace doxorubicin with dactinomycin.

**Explanation**

The correct answer is D. Doxorubicin should not be administered during radiation therapy or soon after radiation therapy because of the risk of radiation recall injury. Dactinomycin can also cause radiation recall injury.

9. A 12-year-old patient with localized osteosarcoma is being treated with cisplatin, doxorubicin, and high-dose methotrexate. The pain at his primary site rapidly resolves after initiation of chemotherapy. After tumor resection, pathology reveals the tumor was greater than 95% necrotic. You want to continue cisplatin, doxorubicin, and high-dose methotrexate.

Which of the following is the best answer regarding the evaluations that should be performed to monitor for toxicity in patients receiving cisplatin, doxorubicin, and high-dose methotrexate?

A. Complete blood count, creatinine, liver function tests

B. Complete blood count, serum electolytes (sodium, potassium, BUN, chloride), and EKG to monitor for prolonged QTc

C. Complete blood count, creatinine, serum magnesium, audiogram, and echocardiogram

D. Complete blood count, creatinine, serum magnesium, chest x-ray

E. Complete blood count, creatinine, serum magnesium, audiogram

**Explanation**

The correct answer is C, complete blood count, creatinine, serum magnesium, audiogram, and echocardiogram. Cisplatin is associated with high-frequency hearing loss, which can be symptomatic with tinnitus and requires periodic monitoring with audiogram. Cisplatin also causes decreases in glomerular filtration rate and cation wasting frequently resulting in hypomagnesemia. Although hypomagnesemia can predispose a patient to prolonged QTc, that is a secondary effect. Doxorubicin causes myelosuppression as well as a late effect of decreased left ventricular ejection fraction measured by echocardiogram. High-dose methotrexate is contraindicated in patients with significant acute or chronic kidney disease. Elevated serum creatinine should prompt further evaluation of renal function prior to administration of high-dose methotrexate.

10. A 13-year-old boy completed treatment for parameningeal alveolar rhabdomyosarcoma with vincristine, dactinomycin, and cyclophosphamide. He presented 3 years later with fatigue, pallor, and easy bruising. CBC reveals pancytopenia. You suspect acute myeloid leukemia secondary to cyclophosphamide.

What cytogenetic abnormality is most likely to be detected in the leukemic blasts?

A. 11q23 translocation

B. Monosomy 7

C. PAX3/FOXO1 fusion

D. Trisomy 8

E. Trisomy 21

**Explanation**

The correct answer is B. Secondary leukemia induced by alkylating agents such as cyclophosphamide commonly is associated with monosomy 7 and deletion of 5q. Topoisomerase 2 inhibition by etoposide can lead to double-strand DNA breaks that result in translocations involving 11q23.

11. A 9-year-old girl with standard-risk acute lymphoblastic leukemia is due to receive day 8 delayed intensification chemotherapy with vincristine and doxorubicin. The nurse places a peripheral IV catheter and administers doxorubicin as a short infusion over 15 minutes. During the infusion, the girl complains of severe pain at the catheter insertion site. The nurse notes significant swelling and redness distal to the catheter tip and stops the infusion immediately.

What is the appropriate management for this patient?

A. Remove the IV catheter and discharge the patient with instructions to take ibuprofen for pain and call if there are further skin changes.

B. Place ice immediately over the affected area and request a surgical consult for debridement.

C. Administer dexrazoxane IV once daily for 3 days.

D. Inject dimethylsulfoxide (DMSO) locally around the extravasation site.

**Explanation**

The correct answer is C. Severe skin necrosis is a serious complication of extravasation of certain chemotherapy agents such as anthracyclines, vinca alkaloids, and taxanes. The incidence of chemotherapy extravasation has decreased significantly after the routine use of central venous catheters for chemotherapy administration. Dexrazoxane has been approved for the treatment of extravasation injury due to anthracyclines and prevents significant skin necrosis necessitating surgical debridement in more than 90% of cases by acting as a free radical scavenger and speeding up removal of the extravasated drug from the tissues. It is usually administered at a dosage of 1,000 mg/m2 intravenously on days 1 and 2 and 500 mg/m2 on day 3. Using ice packs is generally discouraged because it decreases blood flow to the region; warm packs may be beneficial. Topical dimethyl sulfoxide (DMSO) is used in nonspecific treatment of chemotherapy extravasation burns.

12. A 9-year-old girl with Ewing sarcoma who is undernourished is hospitalized to receive a 5-day course of ifosfamide and etoposide and to begin hyperalimentation. She becomes agitated and confused on the second day of chemotherapy and also has some myoclonic jerks.

Which of the following is the most appropriate treatment for these new symptoms?

A. Vitamin B12

B. Methylene blue infusion

C. Activated charcoal

D. Flumazenil

E. Disulfiram

**Explanation**

The correct answer is B. The patient’s symptoms are likely caused by ifosfamide neurotoxicity. These encephalopathic symptoms are more likely to occur in patients with poor nutrition and decreased renal function and are related to the accumulation of chloroacetaldehyde, which disrupts the mitochondrial respiratory chain, leading to accumulation of NADH. Methylene blue can reverse these symptoms by disrupting the formation of chloroacetaldehyde.

13. A 16-year-old patient with history of high-risk B precursor acute lymphoblastic leukemia presents with headache, vomiting, and an upper motor neuron facial nerve palsy. His CBC count is normal, and CSF cytology reveals 300 WBCs/mm3, with 85% blasts that are Tdt positive. Bone marrow aspirate reveals a normocellular marrow with no morphological evidence of leukemia. However, an abnormal B cell population consistent with minimal residual disease of leukemia was detected by flow cytometry. After reinduction chemotherapy, the patient has persistent lymphoblasts in the CSF. The patient is referred to radiation oncology for craniospinal irradiation (CSI).

To ensure coverage of the thecal sac during CSI, the inferior border is best placed at approximately which of the following locations?

A. L3

B. L5

C. S3

D. Coccyx

**Explanation**

The Correct answer is C. For an individual patient, the thecal sac is best determined by the sagittal T2 MRI. At a population level, the mean position is at approximately S2. For coverage with a margin, the most appropriate level to cover is approximately S3. L3 is below the inferior extent of the spinal cord (not the thecal sac).

14. An 8-year-old boy with a newly diagnosed infratemporal parameningeal alveolar rhabdomyosarcoma is referred to radiation oncology for local tumor control. The radiation oncologist recommends proton beam radiation therapy over intensity-modulated radiation therapy with photons.

Which of the following statements is true regarding proton beam radiation therapy?

A. Proton radiation delivers much higher doses of radiation to the gross tumor volume.

B. Protons are more effective than photons in killing rhabdomyosarcoma cells.

C. Tissue surrounding the tumor receives less radiation, such that there are fewer acute and long-term effects.

D. The radiation dosage is reduced at the Bragg peak.

**Explanation**

The correct answer is C. Protons are charged particles that are used in external beam radiation to target tumor tissue by using a particle accelerator. Protons are heavier than photons and do not have significant scatter, thereby sparing surrounding normal tissue. The penetration range of protons is controlled by a given energy and is maximum at the Bragg peak. Different energies have different Bragg peaks, and the total radiation dosage with protons is called the spread-out Bragg peak. Proton beam radiation is used for children with brain tumors and many sarcomas to avoid acute and late toxicity caused by damage to surrounding tissue. The effective dosage delivered to the tumor is not different from that of intensity-modulated radiotherapy with photons.

15. A 9-year-old boy is being treated for standard-risk acute lymphoblastic leukemia. His treatment protocol calls for administration of intravenous methotrexate and intramuscular L-asparaginase during interim maintenance chemotherapy.

What is the most appropriate sequence of drug administration?

A. Administer L-asparaginase during the methotrexate infusion.

B. Administer L-asparaginase immediately after the methotrexate infusion.

C. Administer both drugs at the same time to maximize synergistic activity.

D. Administer methotrexate 24 hours after the asparaginase.

E. Administer the L-asparaginase 24 hours after the methotrexate.

**Explanation**

The correct answer is E, administer the L-asparaginase 24 hours after the methotrexate. L-asparaginase can prevent methotrexate toxicity, probably by interfering with the formation of methotrexate polyglutamates intracellularly. Therefore, L-asparaginase is administered 24 hours after methotrexate and is the rationale behind the Capizzi I regimen. The reverse sequence (L-asparaginase followed by methotrexate) or concomitant administration of both drugs can abrogate the anticancer effect of methotrexate.

16. A 14-year-old Hispanic girl weighing 52 kg with localized Ewing sarcoma develops 2+ glucosuria during her fifth course of etoposide and ifosfamide. Her serum glucose at the same time was 160 mg/dL.

What is the most likely cause of the glucosuria?

A. 10% dextrose that is being administered with her IV hydration

B. Dexamethasone that is being administered as an antiemetic

C. Secondary Fanconi syndrome

D. False positive on the urine dipstick

E. Hispanic ethnicity

**Explanation**

The correct answer is C, secondary Fanconi syndrome. The normal tubular maximum for glucose is 180 mg/dL. Ifosfamide can cause a proximal tubular defect that causes wasting of bicarbonate, certain electrolytes such as phosphorus and potassium, and glucose in the urine that usually gets worse with further ifosfamide exposure.

17. Purine analogs and pyrimidine analogs exert their cytotoxic action by being incorporated into DNA during which of the following phases of the cell cycle?

A. G0 phase

B. G1 phase

C. S phase

D. G2 phase

E. M phase

**Explanation**

The correct answer is C, the S phase. Antimetabolites interfere directly with DNA synthesis and are therefore cell cycle and S-phase specific. More prolonged drug exposure that results from administering these agents by continuous infusion or by chronic daily dosing increases the chance of exposing a higher proportion of the tumor cell population to drugs during active DNA replication.

18. A 2-year-old boy is being treated for stage III favorable histology Wilms’ tumor with adjuvant vincristine, dactinomycin, and doxorubicin. He is brought into the emergency department with seizures and lethargy. Serum electrolytes reveal serum sodium of 122 mEq/L.

What is the most likely cause of his hyponatremia?

A. Vincristine

B. Dactinomycin

C. Doxorubicin

D. Radiation damage to remaining kidney

E. Hyperperfusion injury to remaining kidney

**Explanation**

The correct answer is A. The most likely cause is syndrome of inappropriate ADH secretion, which is a known side effect of vincristine.

19. Which of the following inhibit topoisomerase I?

A. Etoposide

B. Doxorubicin

C. Topotecan

D. Methotrexate

E. Carmustine

**Explanation**

The correct answer is C. Currently the only two drugs that are used to treat cancer in children that are topoisomerase I inhibitors are topotecan and irinotecan. Doxorubicin and etoposide inhibit topoisomerase II. Methotrexate is an antifolate that inhibits dihydrofolate reductase. Carmustine is an alkylating agent that binds DNA.

20. A 16-year-old boy with T-cell leukemia is receiving multiagent chemotherapy. He develops progressive bilateral lower extremity weakness and a Guillain-Barre-like neuropathy. Which chemotherapy is associated with this neurotoxicity?

A. Nelarabine

B. Blinatumomab

C. Daunorubicin

D. Asparaginase

E. Cytarabine

**Explanation**

The correct answer is A. Neurotoxicity associated with nelarabine is ascending weakness that starts in lower extremities. It is frequently referred to as Guillain-Barre-like. It is the dose-limiting toxicity of nelarabine and is only very slowly reversible. Blinatumomab is anti CD19 and is not used to treat T-cell leukemia. Daunorubicin is not associated with neurotoxicity but is myelosuppressive and cardiotoxic. Asparaginase has central nervous system toxicity and can lead to sinus venous thrombosis. High-dose cytarabine causes cerebellar toxicity.

21. A 12-year-old patient has newly diagnosed acute promyelocytic leukemia (APL) PML-RARalpha gene fusion t(15;17)(q24.1;q21.2). Her white blood cell count is 30,000/mcL, and she has mild coagulopathy. You are preparing to discuss the therapy treatment plan with the child and her parents.

What is the best information to share with the family during your treatment discussion?

A. The medication, all-trans-retinoic acid (ATRA), works as a differentiating agent and will be used as a single agent for the treatment.

B. The medication, 13-cis-retinoid acid (isotretinoin), works as a differentiating agent and will be used in combination with chemotherapy for treatment.

C. All-trans-retinoid acid (ATRA) administered in combination with arsenic trioxide (ATO) can be administered in combination with chemotherapy with lower anthracycline exposure and equivalent event-free and overall survival compared with anthracycline-based chemotherapy alone.

D. Retinoic acid syndrome (APL differentiating syndrome) is associated with administration of anthracycline-based chemotherapy for APL.

E. All-trans-retinoic acid (ATRA) is associated with prolonged QTc interval, and therefore echocardiograms (EKGs/ECGs) must be performed prior to each dose.

**Explanation**

Answer C is correct. Answers A and B are not correct because the patient has high-risk APL based on white blood cell count and requires combination therapy; isotretinoin (13-cis retinoid acid) is used in neuroblastoma, not APL. Answer D is not correct because APL differentiation syndrome occurs following the initiation of treatment with ATRA and ATO and occurs in up to 20% of children. Answer E is incorrect because arsenic trioxide is associated with prolonged QTC, not ATRA.

22. A 4-year-old boy has high-risk neuroblastoma (N-myc amplified) with left adrenal primary bone and bone marrow metastases. He has completed induction chemotherapy, surgery, transplant, and radiation therapy. He is about to initiate consolidation immunotherapy with dinutuximab, GM-CSF, IL-2, and isotretinoin. What constellation of acute side effects are associated with administration of this immunotherapy?

A. There are minimal toxicities associated with consolidation immunotherapy for neuroblastoma.

B. Side effects include hypersensitivity reactions, capillary leak syndrome, and pain.

C. Side effects include prolonged severe myelosuppression and alopecia.

D. Frequent side effects include hearing loss, mucositis, and constipation.

**Explanation**

Answer B, hypersensitivity reactions, capillary leak syndrome, and pain, is correct. Answer A is not correct because dinutuximab, IL-2, and GM-CSF are associated with potentially life threatening side effects including hypersensitivity reactions, capillary leak syndrome, and pain requiring narcotics during infusion of dinutuximab because the target of dinutuximab (GD2) is present on peripheral nerves. Answer C and D are incorrect because these toxicities are associated with cytotoxic agents and are not typical for immunotherapy for neuroblastoma.

23. A 2-year-old, 12-kg boy who presents 6 months after finishing full treatment for medulloblastoma with increased nausea, vomiting, and inability to walk. Imaging and biopsy demonstrate that he has recurrent medulloblastoma. The patient is planned to be started on an regimen that includes bevacizumab, a vascular endothelial growth factor inhibitor. Because of poor oral intake since recurrence and more than 15% weight loss, the team has decided to place a percutaneous G-tube to improve this patient’s nutritional status.

Which is the best treatment plan for this patient?

A. Because of the aggressive nature of medulloblastoma, the patient should be started therapy immediately and undergo G-tube surgery within one week after administration of bevacizumab.

B. The patient should have the G-tube placed during his port placement surgery this week and then start chemotherapy including bevacizumab on postoperative day 1.

C. The patient should not have a G-tube placed or port placement surgery.

D. The patient should have the G-tube placed during his port placement surgery and have his chemotherapy started this week, however, the bevacizumab should not be started until cycle 2, which will be at least 28 days after the surgery.

**Explanation**

Answer D is correct. Answers A, B, and C are not correct because bevacizumab can cause major wound healing and surgical complications, so it should not be given until the wounds have fully healed from his G-tube and central venous line placement. These complications occurred for minor surgeries such as port placement. It is suggested to wait at least 28 days before bevacizumab treatment.

24. A 17-year-old girl is diagnosed with relapsed acute lymphoblastic leukemia who has 40% blasts, CNS1. Her leukemia shows standard cytogenetics 46 XX Del 13 Q12:34; cells positive for CD19, CD10 Tdt, CD38 cyCD79a, cyCD22 (CD20 and D34 negative). This is her third relapse, with the second relapse thought to be caused by lack of follow-up during maintenance therapy. She had an unrelated bone marrow transplant about 1.2 years ago after her second relapse. You plan to initiate therapy with inotuzumab with the hope of achieving a complete remission so that she can receive chimeric antigen receptor T-cell therapy.

Which of the following statements is most accurate?

A. Inotuzumab binds to CD19 as a targeted agent.

B. Inotuzumab works as an anti-angiogenic medication and as a partial differentiating agent.

C. Inotuzumab is a CD22-directed monoclonal antibody that releases calicheamicin when it binds to CD22 cells.

D. Inotuzumab is a CD20-directed monoclonal antibody that causes cell death through double strand cleavage.

E. Inotuzumab is a CD19- and CD22-directed murine antibody that causes cell death through apoptosis.

**Explanation**

Answer C is correct. Answers A, B, D, and E do not list the correct targets for inotuzumab.

25. A 6-year-old child is experiencing progression of his malignant rhabdoid tumor and new metastatic spread to his lungs after initial multiagent chemotherapy, surgery, and radiation. His tumor has a high mutational burden and is SMARCB1 deficient. He has recovered from the toxic effects of prior therapy. The family is interested in clinical trials of immune checkpoint therapy. In discussion with the family, which of the following is true?

A. Immune checkpoint therapies such as pembrolizumab, nivolumab, and alemtuzumab that inhibit programmed death receptor-1 (PD-1) have never been used in children.

B. Immunotherapy with PD-1 inhibitors (pembrolizumab, nivolumab, alemtuzumab) in combination with anti-CTLA-4 (ipilimumab) have fewer immune-related side effects compared with PD-1 inhibitors alone.

C. Immune-related side effects from PD-1 and anti-CTLA-4 inhibition can be serious and include autoimmune symptoms such as cardiomyositis, gastrointestinal perforation, hypo- or hyperthyroidism, uvitis, and hypophysitis.

D. Recurrent metastatic malignant rhabdoid tumor can be cured by surgery alone. A clinical trial of immune checkpoint inhibitors should not be considered.

**Explanation:**

Answer C is correct. Combination immune checkpoint therapy with PD-1 inhibition and anti-CTLA-4 have a high frequency of serious immune-related adverse events compared with anti PD-1 therapy alone. Answer A is incorrect because many clinical trials of PD-1 inhibitors have been conducted in children; however, other than for Hodgkin Lymphoma, the response rate in most common pediatric solid tumors has been low. High tumor molecular burden may be associated with better response to therapy; however, clinical trials are ongoing. Answer D is incorrect because metastatic malignant rhabdoid tumor cannot be cured by surgery alone.

26. The neonatal intensive care unit (NICU) consults you regarding a 7-day-old boy who was born with a rapidly enlarging mass on his tongue. Plastic surgery performed a biopsy of the mass on day of life 2. Bleeding post biopsy was controlled, but the child has remained in the NICU for observation. The mass continues to enlarge. The patient has a normal chest x-ray and normal platelet count. Molecular pathology calls you to report the mass has a NTRK-ETV6 fusion. What are your next steps?

1. The mass is a vascular malformation and can be observed.
2. The mass is a vascular malformation and should be treated with prednisone.
3. There is insufficient information to make a diagnosis, and additional biopsy should be done.
4. The mass is an infantile fibrosarcoma and should be observed because the child is too young to receive chemotherapy.
5. The mass is an infantile fibrosarcoma and should be treated immediately with an NTRK inhibitor such as larotrectinib.

**Explanation:**

Answer E is correct. NTRK-ETV6 is a fusion oncoprotein diagnostic for infantile fibrosarcoma. Larotrectinib is a NTRK inhibitor that is FDA approved for patients of any age with NTRK fusion positive tumors and is available in a liquid formulation. It is safe and effective in achieving rapid and durable complete remission. Entrectinib, an NTRK, ALK, and ROS inhibitor, is FDA approved for patients older than 12 years and is available only in capsule form. NTRK-ETV6 is not associated with vascular malformations.

27. A 13-year-old boy has been diagnosed with posttransplant lymphoproliferative disorder. Which of the follow is true about options for therapy.

1. Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF) and will rapidly deplete B-cells.
2. Dinutuximab is a monoclonal antibody that targets GD2 and will rapidly deplete B-cells.
3. Pembrolizumab is a monoclonal antibody that targets and rapidly depletes B-cells to abrogate immune checkpoints.
4. Rituximab is a chimeric monoclonal antibody that targets CD-56 and rapidly depletes malignant B-cells, resulting in prolonged lymphopenia and hypogammaglobulinemia.
5. Rituximab is a chimeric monoclonal antibody that targets CD-20 and rapidly depletes normal B-cells, resulting in prolonged lymphopenia and hypogammaglobulinemia.

**Explanation**

The correct answer is E. The antibodies bevacizumab, pembrolizumab, dinutuximab do not deplete B-cells. Rituximab target CD-20.

28. Which of the following statements is true about azacytidine?

A. Azacytidine inhibits dihydrofolate reductase and depletes folate within the cell.

B. Azacytidine activates enhancer of zeste homolog 2 (EZH2) mutations or aberrations of the switch/sucrose nonfermentable (SWI/SNF) complex (eg, mutations or deletions of the subunits INI1 or SMARCA4), which can lead to aberrant histone methylation.

C. Azacytidine is an oral histone deacetylase (HDAC) inhibitor targeting a broad range of HDACs including HDAC1, HDAC2, and HDAC3 (Class I) and HDAC6 (Class IIb)

D. Azacytidine is a nucleoside analogue of cytidine that incorporates into DNA and reversibly inhibits DNA methyltransferase, blocking DNA methylation.

E. Azacytidine induces antibody-mediated cytotoxicity (ADCC).

**Explanation**

The correct answer is D. Azacytidine is an antimetabolite that incorporates into DNA and inhibits DNA methyltransferase; it also incorporates into RNA and disrupts normal RNA function and impairs tRNA cytosine-5-methyltransferase activity. Methotrexate inhibits dihydrofolate reductase. HDAC inhibitors vorinostat and entinostat are not antimetabolites. Antibody-mediated cytotoxicity occurs with some antibody therapies.

29. Multitargeted kinase inhibitors that target vascular endothelial growth factor receptor inhibition (VEGFR) are associated with a toxicity profile, related to the mechanism of action, that can include which of the following?

1. Hypertension, poor wound healing, proteinuria
2. Thrombocytopenia, peripheral neuropathy, and alopecia
3. Cardiac myositis, pneumonitis, hypophysitis
4. Lymphopenia and hypogammaglobulinemia
5. Cheilitis, hypertriglyceridemia, hypercalcemia

**Explanation:**

The correct answer is A, hypertension, poor wound healing, and proteinuria. Class effect toxicity of inhibition of VEGF include increased blood pressure, proteinuria, and poor wound healing due to their effects on capillaries. Other toxicities of VEGF and multityrosine kinase inhibitors can be widening of the growth plate, cardiac dysfunction, palmar-plantar erythrodysesthesia, and gastrointestinal side effects including diarrhea. Answer B is incorrect because these are side effects of cytotoxic agents. The effects listed in answer C are those of immune checkpoint inhibition. Answer D lists side effects of rituximab related to depletion of normal B cells. Answer E lists side effects of isotretinoin (13-cis-retinoic acid).

30. The Goldie-Coldman hypothesis is the basis for the principles of therapy, including combination therapy, adjuvant therapy, and dose intensity. Which of the following statements about the Goldie-Coldman hypothesis is true?

A. The Goldie-Coldman Hypothesis is not relevant for molecularly targeted therapy.

B. The hypothesis states that development of resistance is related to cell cycle.

C. The hypothesis states that probability that a cancer develops a resistant clone is dependent on the mutation rate (genetic instability of the cancer) and size of the tumor.

D. The hypothesis states that resistance can be prevented with continuous administration of one drug.

E. The hypothesis relates the oxygen tension in a tumor to the radiation sensitivity of the tumor.

**Explanation:**

The correct answer is C. Curative therapy for cancer requires that the therapy prevents development of resistance using combination therapy; that therapy is provided when the tumor burden is low; and, for cytotoxic chemotherapy, that there is dose intensity to provide the highest dose in the shortest interval. For targeted therapy, the dose intensity relates to the drug’s ability to maintain target inhibition.

ONCOLOGIC EMERGENCY QUESTION

1. A 14-year-old boy of Middle Eastern descent presents with a history of fever, abdominal distension, and decreased urine output. His serum creatinine is 1.5 mg/dL, serum uric acid is 13 mg/dL, and serum LDH is 900 U/L. You suspect Burkitt lymphoma and would like to request computed tomography of his abdomen with intravenous contrast. However, his renal function precludes obtaining the study. You institute intravenous hydration and plan to administer rasburicase to rapidly bring down his serum uric acid.

Before administering rasburicase, which of the following is it imperative that you obtain?

A. Thiopurine s-methyltransferase status

B. Pyruvate kinase status

C. Uridine diphosphate glucuronosyltransferase 1 isoform A1 status

D. Glucose-6-phosphate dehydrogenase status

E. Adenosine deaminase status

**Explanation**

Rasburicase is contraindicated in patients with known G6PD deficiency because it can cause severe hemolytic anemia.

SUPPORTIVE CARE QUESTION

15. A 15-year-old boy with localized osteosarcoma of the right distal femur is being treated with cisplatin, doxorubicin, and high-dose methotrexate chemotherapy. His father reports that the night before he is admitted to the hospital for chemotherapy, his son complains of nausea and vomits several times on his way to the hospital for admission.

Which of the following pharmacotherapeutic agents is most likely to help his symptoms?

A. Ondansetron

B. Aprepitant

C. Dexamethasone

D. Lorazepam

E. Diphenhydramine

**Explanation**

The patient has anticipatory nausea and vomiting due to chemotherapy. There is modest evidence to suggest that benzodiazepines benefit both adult and pediatric patients with anticipatory nausea and vomiting due to chemotherapy. Lorazepam is preferred over alprazolam and diazepam and is recommended at a dosage of 0.04 to 0.08 mg/kg/dose (maximum dose 2 mg), given at bedtime the night before and on the morning of chemotherapy. The dosage may be titrated to minimize sedation and maximize efficacy.

CANCER PREDISPOSITION QUESTION

16. A 3-year-old girl presents with a cough and shortness of breath. On physical examination, she has tachypnea and labored respiration, with peripheral oxygen saturations of 94% on room air. A chest X ray reveals whiteout of the left lung field, with a mediastinal shift to the left. A CT scan of the chest shows a solid heterogenous mass occupying most of the left chest, with collapse of the left lung. A CT-guided biopsy reveals a small round blue cell and spindle cell neoplasm with focal areas of rhabdomyoblastic differentiation. The patient has a strong family history of thyroid disease and an older sister who had an ovarian Steroli-Leydig tumor.

You inform the patient’s parents that the patient and her sister have a cancer predisposition secondary to an inherited germline mutation in which of the following genes?

A. TP53

B. NF1

C. SMARCB1

D. DICER1

E. ALK

**Explanation**

Patients with DICER1 germline mutations are at increased risk for malignant and benign tumors that arise in the lungs, kidney, ovary, and thyroid gland. These tumors commonly arise in childhood and are rare in adults and include pleuropulmonary blastoma, cystic nephroma, Steroli-Leydig tumor of the ovary, and multinodular goiter. The DICER1 gene encodes micro-RNA that regulates protein expression.

CANCER PREDISPOSITION

17. A newborn infant has a birth weight of 4 kilograms and has a large protruding tongue, umbilical hernia, and right-sided hemihypertrophy.

While counseling the child’s parents, you inform them that their child is at risk of the following pediatric malignancies except which one?

A. Hepatoblastoma

B. Wilms tumor

C. Medulloblastoma

D. Rhabdomyosarcoma

E. Neuroblastoma

**Explanation**

The clinical features of the infant are diagnostic of Beckwith-Wiedemann syndrome, which is an overgrowth disorder caused by mutations in the short arm of chromosome 11 (11p15) that leads to overactivity of the IGF2 gene or no active copy of CDKN1C. Causes include paternal uniparental disomy, loss of heterozygosity, maternal gene rearrangement, and DNA methylation. Patients with Beckwith-Wiedemann syndrome are at increased risk of Wilms tumor and several other childhood cancers but not medulloblastoma.

ONCOLOGIC EMERGENCY QUESTION

20. A 14-year-old boy presents with cough, shortness of breath, and difficulty lying down. His face and neck swell when his arms are raised. Chest x-ray reveals a large mediastinal mass. A tissue diagnosis is desired. A biopsy is performed with local anesthesia because the anesthesiologist thinks that the patient has a very high general anesthesia risk.

Which of the following findings does *not* make general anesthesia unsafe?

A. Tumor diameter greater than 45% of transthoracic diameter

B. Tracheal cross-sectional area less than 50% of predicted

C. Peak expiratory flow rate less than 50% of predicted

D. A malignancy of hematopoietic origin

E. A large pericardial effusion

**Explanation**

There are no standard criteria to predict the severity of superior vena cava syndrome (SVCS). Several studies have evaluated anesthesia complication risks. Great vessel and tracheal compression with increasing respiratory symptoms and signs are predictive of anesthesia complications. SVCS results most often from an anterior mediastinal mass that can be caused by Hodgkin or non-Hodgkin lymphoma, T-cell lymphoblastic leukemia, sarcomas, and germ cell tumors. It is usually not caused by neuroblastoma, which can present as a posterior mediastinal mass.

CANCER PREDISPOSITION QUESTION

21. An 18-month-old boy is brought in by his parents with a history of vomiting and lethargy. The child is found to be irritable on clinical exam. A CT scan of the brain reveals hydrocephalus with a mass in the right lateral ventricle. The patient undergoes an emergency ventriculostomy, and the mass is biopsied endoscopically. The pathology is consistent with a choroid plexus carcinoma.

Germline testing on this patient is likely to reveal a mutation in which of the following genes?

A. RB1

B. BRCA

C. MSH2

D. TP53

E. NF1

**Explanation**

Li-Fraumeni syndrome (LFS) is characterized by an increased risk of several cancers, particularly in children and young adults. It is caused by a germline mutation in the TP53 gene and is inherited in an autosomal dominant pattern. Classic LFS is diagnosed when all of the following criteria are fulfilled: a sarcoma diagnosed before age 45 years, a first-degree relative with any cancer before age 45 years, and a second-degree relative being diagnosed with a sarcoma at any age or any cancer before age 45 years. Chompret criteria for the clinical diagnosis of LFS and indications to test for TP53 germline mutation include any of the following criteria: a tumor belonging to the LFS spectrum (soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumor, adrenocortical carcinoma, leukemia, or lung bronchoalveolar cancer) before age 46 years *and* at least one first-degree or second-degree relative with an LFS-related tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors; proband with multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 years; or patient with adrenocortical carcinoma or choroid plexus tumor irrespective of family history.