**Cancer Chemotherapy and Pharmacology**

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1. A 12-year-old patient who weighs 43 kg has newly diagnosed acute promyelocytic leukemia (APL) with favorable cytogenetics of t(8,21). You are preparing to discuss the basis of therapy with the child and his 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 for the treatment. Its use for the treatment of APL was developed in the last 10 years.

B. The medication, ATRA, works as a differentiating agent and promotes the malignant leukemic cells to undergo differentiation to mature cells instead of uncontrolled production of blasts. The medication has been used for more than 30 years, with high cure rates, and the mechanism limits most long-term toxicities of chemotherapy.

C. The medication, ATRA, works as a differentiating agent and will be given as an intravenous medication with a 5-drug chemotherapy regimen to induce remission. The therapy will be about 48 months long.

D. The medication, ATRA, works as a differentiating agent and will be used in conjunction with arsenic trioxide, which is an anthracycline that works synergistically with ATRA to induce remission for patients with APL.

**Explanation**

Answer B is correct. Answer A is not correct because ATRA has been used successfully for treatment of APL since the 1980s. Answer C is not correct because ATRA is given orally, and therapy is generally, at most, 30 months. Answer D is not correct because arsenic trioxide is a partial differentiating agent, not an anthracycline. It is used in conjunction with ATRA as a resensitizing agent and has some overlapping mechanisms of action with ATRA.

2. What is the basis for using differentiating agents?

A. Differentiating agents kill cancer cells.

B. Differentiating agents cause apoptosis of cancer cells in the G2 stage of the cell cycle.

C. Differentiating agents modify cancer cells to stop maturing, and this sequence will cause cell death.

D. Differentiating agents have multiple mechanisms, including causing hyperproliferation of cancer cells and decreasing tumor suppression function to promote cell death.

E. Differentiating agents help cancer cells to become normal cells by stopping the proteins that prevent the maturation of the cancer cells to normal cells.

**Explanation**

Answer E is correct. Answer A is incorrect because differentiating agents do not kill cancer cells but promote their differentiation to mature cells. Answer B is incorrect because differentiating agents do not affect cell cycle stages like other chemotherapy but help cells follow the normal cell differentiation cycle. Answer C is incorrect because differentiating cells promote cell maturation and do not cause cell death directly. Answer D is incorrect because differentiating agents decrease hyperproliferation, not cause it, and increase tumor suppression functions.

3. Differentiating medications have a potentially strong future for pediatric cancers as our understanding of the tumor growth increases. Some of these medications are derived from common vitamins. There are two primary areas of use of differentiation medication for tumor differentiation that are currently standards of care in the pediatric cancer realm. What are they?

A. Vitamin A forms (all-trans-retinoic acid and cis-retinoic acid) for cancer therapy for acute promyelocytic leukemia and reducing risk of recurrence of neuroblastoma after intense chemotherapy and stem cell transplantation

B. Vitamin D form (1,25-dihydroxyvitamin D3) for cancer therapy for neuroblastoma and Wilms tumor

C. Vitamin D form (1,25-dihydroxyvitamin D3) and vitamin A form (all-trans-retinoic acid) for cancer therapy for Wilms tumor and neuroblastoma

D. Vitamin E for cancer treatment of rhabdomyosarcoma and acute myeloid leukemia

**Explanation**

Answer A is correct because these are currently part of multiple pediatric treatment regimens for neuroblastoma and acute promyelocytic leukemia. Answers B and C are incorrect because 1,25-dihydroxyvitamin D3 is being investigated for use in treatment of neuroblastoma but is not currently used for treatment. There is no evidence for use in Wilms tumor. Answer D is incorrect because there are no current investigations for the use of vitamin E for treatment of pediatric cancers.

4. NM is 4 years old and was diagnosed with stage 4 neuroblastoma (N-myc negative) with bone lesions in the left humerus and radius after presenting with a limp initially thought to be caused by a recent fall while playing on the playground. The patient progressed to refusing to bear weight on his left leg. After initial chemotherapy cycles, the patient had 95% tumor response.

In the future, to treat neuroblastoma by targeting certain potential pathways, which medication may be included in initial or subsequent therapies?

A. Pembrolizumab, which is a PD-L1 antibody

B. Sorafenib, which is an ALK inhibitor

C. Nifurtimox (difluoromethylornithine), which is a VEGF inhibitor

D. Crizotinib, which is an aurora kinase A inhibitor

E. Sirolimus, which is a PI3K inhibitor

**Explanation**

Answer A is correct; pembrolizumab is an immune checkpoint inhibitor therapy. Answer B is incorrect because sorafenib is a multi-kinase inhibitor that is being looked at for neuroblastoma treatment (targeted therapy). Answer C is incorrect because nifurtimox (difluoromethylornithine) is an irreversible inhibitor of ornithine decarboxylase that targets MYC and suppresses basal and TRKB-mediated Akt phosphorylation. These may contribute to cytotoxicity of neuroblastoma cells (targeted therapy). Answer D is incorrect because crizotinib is an ALK inhibitor that may work for ALK mutants that have been identified in patients with neuroblastoma (targeted therapy). Answer E is incorrect because sirolimus is an mTOR inhibitor being explored for use with other agents as a synergistic antitumor agent for neuroblastoma (targeted therapy).

5. NM is 4 years old and was diagnosed with stage 4 neuroblastoma (N-myc negative) with bone lesions in the left humerus and radius after presenting with a limp initially thought to be caused by a recent fall while playing on the playground. The patient progressed to refusing to bear weight on his left leg. After initial chemotherapy cycles, the patient had 95% tumor response. After tandem autologous transplants, the patient is now receiving immunotherapy.

For neuroblastoma, which of the following would this immunotherapy include?

A. Dinutuximab (anti-GD2 chimeric antibody) with granulocyte colony-stimulating factor (G-CSF), interleukin-2 (IL-2), and isotretinoin

B. Dinutuximab (anti-GD2 chimeric antibody) with granulocyte-macrophage-stimulating factor (GM-CSF) and IL-2, with added differentiation therapy with isotretinoin

C. Dinutuximab (anti-GD2 chimeric antibody) with GM-CSF and isotretinoin

D. Dinutuximab (anti-GD2 chimeric antibody) with IL-2 only

**Explanation**

Answer B is correct. Answer A is not correct because the immunotherapy drug for neuroblastoma is GM-CSF, not G-CSF, and isotretinoin is not immunotherapy. It is used as differentiation therapy. Answer C is not correct because immunotherapy for neuroblastoma also includes IL-2, and isotretinoin is a differentiating medication, not immunotherapy. Answer D is not correct because both GM-CSF and IL-2 are needed for immunotherapy in neuroblastoma.

6. NM is 4 years old and was diagnosed with stage 4 neuroblastoma (N-myc negative) with bone lesions in the left humerus and radius after presenting with a limp initially thought to be caused by a recent fall while playing on the playground. The patient progressed to refusing to bear weight on his left leg. After initial chemotherapy cycles, the patient had 95% tumor response. Because of progressive neuroblastoma found 6 months after immunotherapy is completed, our patient begins treatment in a phase 1 study of pembrolizumab. The patient presents to the clinic with severe dehydration and fatigue secondary to a 3-day history of severe abdominal cramping and increasing diarrhea with more than 10 stools per day for the last 2 days.

What is the next best step in management for this patient?

A. He should be admitted for IV fluids and observation, have pembrolizumab therapy held for 3 days, be held NPO, and start loperamide therapy.

B. He should be admitted for IV fluids and observation, have pembrolizumab therapy held for 3 days, and start corticosteroid therapy (prednisone 1 to 2 mg/kg/day with a 5-day taper).

C. He should be admitted for IV fluids and observation, have pembrolizumab therapy held until diarrhea resolves, and start corticosteroid therapy (prednisone 1 to 2 mg/kg/day or equivalent until symptoms resolve and then taper).

D. He should be given IV bolus for dehydration and sent home with continued pembrolizumab therapy and told to eat a bland diet.

**Explanation**

Answers A, B, and D are not correct because pembrolizumab should be held until diarrhea is almost resolved, and the patient should receive corticosteroid therapy (prednisone 1 to 2 mg/kg/day or equivalent with a taper). Loperamide use is not recommended.

7. Which is the best approach to the front-line treatment of children with newly diagnosed neuroblastoma and the *ALK* gene?

A. Crizotinib (an *ALK* inhibitor approved by the US Food and Drug Administration [FDA]) has shown significant promise in many phase 3 trials for neuroblastoma.

B. It is common for patients with neuroblastoma to have the *ALK* gene, and they do not respond to conventional chemotherapy alone and must receive crizotinib as part of their overall treatment plan.

C. Crizotinib should be used in the maintenance phase to maintain remission in a subset of children with *ALK-*positive neuroblastoma.

D. At this time, there is no recommendation regarding the best treatment for children with newly diagnosed neuroblastoma and the *ALK* gene; they should be treated similarly to non-*ALK-*positive patients or according to a clinical trial.

**Explanation**

Answer D is correct. Answer A is incorrect because, although FDA-approved for other uses, crizotinib is only in early clinical trials for patients with neuroblastoma with the ALK gene. Answers B and C are incorrect because the *ALK* gene is found in a subset of patients with neuroblastoma but is not necessarily common. Its place in therapy remains to be determined.

8. PP is 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. It is determined that he has recurrent medulloblastoma. The patient is planned to be started on an investigational 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 because he repeatedly pulled out his NG and NJ tubes during his previous treatment courses.

Which is the best treatment plan for this patient?

A. Because of the aggressive nature of medulloblastoma, the patient should be started immediately on the trial including bevacizumab and then undergo G-tube surgery around day 21 of the first cycle.

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 have the G-tube placed during his port placement surgery this week and start his chemotherapy including bevacizumab in about 1 week after his surgical sites have healed.

D. The patient should have the G-tube placed during his port placement surgery and have his investigational chemotherapy started this week, but 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.

9. PP is a boy who has recurrent medulloblastoma. He begins to complain of knee pain and refuses to walk at 3 1/2 years of age. He weighs 22 kg and is otherwise thought to have responded well to his clinical trial of bevacizumab, which finished 2 months ago, and his current scans show no further tumor progression. He has been healthy in last 2 weeks after finishing a course of amoxicillin for otitis media; he has been afebrile since day 2 of therapy, and his ear pain has resolved.

Which of the following should PP’s provider consider?

A. Possible neuropathy secondary to his overall medulloblastoma treatment including bevacizumab. Begin gabapentin 100 mg orally 3 times a day.

B. Possible tendinitis related to recent course of amoxicillin for otitis media and previous treatment with bevacizumab. Suggest use of acetaminophen for pain and return to clinic in 4 weeks.

C. Possible osteonecrosis of knee related to bevacizumab. Get an orthopedic consult for further radiographic recommendations.

D. Possible osteomyelitis of the knee due to bevacizumab. Admit the patient to the hospital for intravenous antibiotics and an orthopedic consult.

**Explanation**

Answer C is correct. Answer A is incorrect because peripheral neuropathy usually would occur during treatment and not present months later. Answer B is incorrect because tendinitis is not a known side effect of bevacizumab, and there is no drug interaction between amoxicillin and bevacizumab. Answer D is incorrect because although infection is a common adverse effect of bevacizumab, it would occur during treatment and not months later. The patient did not present with a fever, so osteonecrosis is more likely than osteomyelitis, and there is no need for hospital admission at this point.

10. EM is a 50.2-kg 17-year-old girl recently 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. It is decided that she will begin therapy on inotuzumab with the hopes of putting her in 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.

11. EM is a 50.2-kg 17-year-old girl recently 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. It is decided that she will begin therapy on inotuzumab with the hopes of putting her in complete remission so that she can receive chimeric antigen receptor T-cell therapy.

Which therapy modifications may need to occur?

A. The patient should have premedication with a corticosteroid, antihistamine, and antipyretic for future courses if she has an infusion-related reaction during any inotuzumab infusion.

B. If the patient develops a total bilirubin more than 1.5 times ULN and an AST/ALT more than 2.5 times normal, therapy should be interrupted until total bilirubin is less than 1.5 times ULN and AST/ALT is less than 2.5 times normal.

C. Therapy should be temporarily discontinued if the patient develops sinusoidal obstruction syndrome (SOS). Therapy may be restarted once SOS symptoms resolve for at least 14 days.

D. Inotuzumab does not need to be held for any hematologic toxicity at any time in therapy. Transfusions should be used to support blood counts.

**Explanation**

Answer B is correct. Answer A is incorrect because a patient should receive these premedications for all doses of inotuzumab. Answer C is incorrect because therapy should be permanently discontinued for a patient who develops SOS. Answer D is incorrect because inotuzumab should be held for future cycles if counts remain low until count recovery occurs as specified in the package insert. During a cycle that includes a day 8 and day 15 dose, treatment should be continued despite any hematologic abnormalities.