| **Protocol title** | Bladder\_Cisplatin+5-Fluorouracil |
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| **Administration** | Intravenous |
| **Schedule** | Four weekly |
| Antiemetic risk + Anti-allergic medications + Premedications + Post chemotherapy medications | Intravenous- High emetic risk  Premedication: 500 ml 0.9% NaCl + 10 mEq KCl + 8 mEq  MgSO4 i.v. over 60 min.  200 ml Mannite 20% over 30 min  Postmedication: 500 ml 0.9% NaCl i.v. + 10 mEq KCl |
| **Chemotherapy dose and method of administration** | Injection Cisplatin 100 mg/m2 in 500mL Normal Saline over 2 hours Day1. Maintain adequate hydration and urinary output for 24 hours after cisplatin for injection administration. Administer pre-treatment and posttreatment antiemetics as appropriate  Injection 5-Flurouracil 1000 mg/ m2 in 1000mL Normal Saline over 24 hours: Day 1 to Day 5. Administer either as an intravenous bolus or as an intravenous infusion. Do not inject the entire contents of the vial directly into patients.    Dose levels  CISPLATIN  Dose level 0 100 mg/m2  Dose level -1 75 mg/m2  Dose level -2 50 mg/m2  5- FLUOROURACIL  Dose level 0 1000 mg/m2  Dose level -1 750 mg/m2  Dose level -2 500 mg/m2 |
| Number of days of chemotherapy in each cycle | 5 |
| Number of cycles | 6 |
| FN risk | >20% |
| **Antithrombotic prophylaxis** | To follow the Khorana score |
| **Special instruction to Nurse** | 1. Orders related checks    1. To check whether the orders for chemotherapy are signed manually or by using electronic approval by licensed independent practitioners who are determined to be qualified by the health care setting.    2. Verbal orders are not allowed from medical practitioners except to hold or stop chemotherapy administration.    3. **Check Consent**    4. To check new orders or changes to orders, including changes to regimens, for example, dose adjustments communicated directly to patients, are documented in the medical record.    5. Check patient’s name and a second patient identifier like a phone number    6. The date of order is written (Orders are valid for only 3 working days)    7. Regimen or protocol name and number, Cycle number and day, when applicable    8. All medications within the order set are listed by using full generic names    9. Drug dose is written following standards for abbreviations, trailing zeros, and leading zeros.    10. Route of administration 2. Before preparation, a second person—a practitioner or other personnel approved by the health care setting to prepare or administer chemotherapy— independently verifies    1. Two patient identifiers.    2. Drug name.    3. Drug dose.    4. Route of administration.    5. Rate of administration    6. The calculation for dosing, including the variables used in this calculation.    7. Treatment cycle and day of the cycle 3. Upon preparation, a second person approved by the health care setting to prepare parenteral chemotherapy verifies:    1. The drug vial(s).    2. Concentration.    3. Drug volume or weight.    4. Diluent type and volume    5. Administration fluid type, volume, and tubing. 4. Chemotherapy drugs are labeled immediately upon preparation, and labels include the following 10 elements at a minimum:    1. Patient’s name.    2. A second patient identifier.    3. Full generic drug name.    4. Drug dose.    5. Drug administration route.    6. The total volume required to administer the drug.    7. Date the medication is to be administered.    8. Expiration dates and/or times.    9. Sequencing of drug administration, when applicable, and the total number of products to be given when medication is provided in divided doses—each product should be labeled with the total number of products to be administered and the sequence of the individual product within that total grouping, for example, one of five, two of two, etc.    10. A warning or precautionary label or sticker, as applicable, to storage and handling; may be included within the label or on an auxiliary label. 5. Administration    1. Before initiation of each chemotherapy administration cycle, the practitioner who is administering the chemotherapy confirms the treatment with the patient, including, at a minimum, the name of the drug, infusion time, route of administration, and infusion-related symptoms to report—for example, but not limited to, hypersensitivity symptoms or pain during infusion.    2. At least two individuals, in the presence of the patient, verify the patient identification by using at least two identifiers.    3. Check vitals before starting. They need to be within the institutes/centers approved normal limits    4. Use a new IV cannula or Chemo port and needs to be inserted at a sight with limited movements and not over a joint    5. Check for backflow prior to giving chemotherapy    6. In case of extravasation→ Follow the institutes/centers approved extravasation algorithm    7. In case of hypersensitivity→ Follow the institutes/centers approved extravasation algorithm    8. In case of breathlessness or chest pain or syncope or bradycardia → Follow an emergency cardiac algorithm |
| **Special Instruction to nurse- Protocol Specific** | 1. Administer pre-treatment hydration and pre- and post-treatment antiemetics. 2. Administer by slow intravenous infusion. 3. Do not use needles or intravenous sets containing aluminum parts that can come in contact with cisplatin for injection during preparation or administration. Aluminum reacts with cisplatin for injection, causing precipitate formation and a loss of potency 4. Do not administer in the same intravenous line concomitantly with other medicinal products. 5. For bolus administration, store undiluted fluorouracil in the syringe for up to 4 hours at room temperature (25°C). Administer fluorouracil as an intravenous bolus through an established intravenous line. 6. Store diluted solutions of fluorouracil for up to 4 hours at room temperature (25°C) prior to administration to the patient. For intravenous infusion regimens, administer through a central venous line using an infusion pump. |
| **Special instruction to patients** | 1. Encourage oral hydration 2. Post chemotherapy medications 3. In case of any emergency - Please visit the outpatient/ causality of …. hospital 4. Please respond to daily SMS sent for enquiring about your health 5. In case of fever or more than 2 loose motions/vomiting or giddiness or weakness or any other troublesome symptom. Please visit the outpatient/ causality of …. hospital 6. Any change in appointment or rescheduling can be discussed on this ……………………..number 7. Please avoid any social visits or public places without discussing with your oncologists 8. Prefer homemade food and or food prepared in hygienic conditions 9. In addition please check the patient information booklet available with the medicines for detailed instructions on do and don'ts |
| **Special instruction to patients-protocol specific** | 1. Contact your healthcare provider for new onset fever, symptoms of infection, or bleeding 2. Report any symptoms of hearing loss or vestibular dysfunction 3. Cisplatin for injection can cause alopecia 4. Notify your healthcare provider if you have a known DPD deficiency, if you are at an increased risk of severe and life-threatening mucositis, diarrhea, neutropenia and neurotoxicity 5. Go to an emergency room for new onset of chest pain, shortness of breath, dizziness, or lightheadedness 6. Go to an emergency room for new onset of confusion, disorientation, or otherwise altered mental status; difficulty with balance or coordination; or visual disturbances 7. Contact your healthcare provider for severe diarrhea or for painful mouth sores with decreased oral intake of food or fluids 8. Contact your healthcare provider for tingling or burning, redness, flaking, swelling, blisters, or sores on the palms of their hands or soles of their feet 9. Patients to monitor their temperature on a daily basis and to immediately contact their healthcare provider for fever or other signs of infection 10. Notify your healthcare provider of all drugs you are taking, including warfarin or other coumarin-derivative anticoagulants |
| **Stockist instructions** | Injection Cisplatin: Single-dose vials containing 50 mg lyophilized powder  Injection 5-fluorouracil: 2.5 g in a 50 mL vial |
| **Next visit instructions** | Hemoglobin level >= 8 g/dl  Absolute Neutrophil Count>=1500/mm3  Platelet count >=1,00,000/ mm3  GFR >= 60 ml/min  All adverse events resolved to baseline or grade 1 (except fatigue or alopecia) |
| **Drug interactions** | 1. Aminoglycosides, amphotericin B, other nephrotoxic agents—Increased renal toxicity with concurrent use of cisplatin and aminoglycosides, amphotericin B, and/or other nephrotoxic agents. 2. Aminoglycosides, furosemide—Risk of ototoxicity is increased when cisplatin is combined with aminoglycosides and loop diuretics such as furosemide. 3. Phenytoin—Cisplatin decreases pharmacologic effect of phenytoin. For this reason, phenytoin dose may need to be increased with concurrent use with cisplatin. 4. Amifostine, mesna—The nephrotoxic effect of cisplatin is inactivated by amifostine and mesna. 5. Etoposide, methotrexate, ifosfamide, bleomycin—Cisplatin reduces the renal clearance of etoposide, methotrexate, ifosfamide, and bleomycin, resulting in the increased accumulation of each of these drugs. 6. Etoposide—Cisplatin may enhance the antitumor activity of etoposide. 7. Radiation therapy—Cisplatin acts as a radiosensitizing agent. 8. Paclitaxel—Cisplatin should be administered after paclitaxel when cisplatin and paclitaxel are used in combination. This sequence prevents delayed paclitaxel excretion and increased toxicity. 9. Anticoagulants and CYP2C9 Substrates 10. Leucovorin—Leucovorin enhances the antitumor activity and toxicity of 5-FU. Stabilizes the TS-FdUMP-reduced folate ternary complex resulting in maximal inhibition of TS. 11. Methotrexate, trimetrexate—Antifolate analogs increase the formation of 5-FU nucleotide metabolites when given 24 hours before 5-FU. 12. Thymidine—Rescues against the TS- and DNA-mediated toxic effects of 5-FU. 13. Vistonuridine (uridine triacetate)—Rescues against the toxic effects of 5-FU. |
| **Dose modifications for adverse events** | 1. Platelet count decreased 2. Grade 4 → discontinue 5FU 3. Neutrophil count decreased 4. Grade 4 → Discontinue 5-FU 5. Peripheral Sensory Neuropathy 6. Grade 3/4 → discontinue Cisplatin   3. Diarrhea   1. Grade 3/4 -> Reduce 5-Fluorouracil dose by 1 level   4. Palmar-plantar erythrodysesthesia (hand-foot syndrome)   1. Grade 2/3 -> Reduce 5-Fluorouracil dose by 1 level   5. Mucositis   1. Grade 3/4 -> Reduce 5-Fluorouracil dose by 1 level   6. Cardiac Toxicity   1. Any Grade -> Discontinue 5-Fluorouracil   7. Encephalopathy   1. Any Grade -> Discontinue 5-Fluorouracil   8. Confusion   1. Any Grade -> Discontinue 5-Fluorouracil   09. Ataxia   1. Any Grade -> Discontinue 5-Fluorouracil   10. Myocardial Infraction   1. Any Grade -> Discontinue 5-Fluorouracil   11. Ventricular arrhythmia   1. Any Grade -> Discontinue 5-Fluorouracil   12. Heart Failure   1. Any Grade -> Discontinue 5-Fluorouracil |
| **Special tests after a few cycles if any** | DPD Levels |
| **Adverse events** | Hypersensitivity reactions  Ototoxicity  Ocular toxicity  Secondary leukemia  Embryo-fetal toxicity  Nephrotoxicity  Peripheral neuropathy  Nausea and vomiting  Myelosuppression  Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase Activity  Cardiotoxicity  Hyperammonemic Encephalopathy  Neurologic Toxicity  Diarrhea  Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)  Mucositis  Increased Risk of Elevated INR with Warfarin |
| **Risk of death** | <1% |
| **Comment** | - |
| **Reference** | FDA label |