| **Protocol title** | **Carboplatin+5-Flurouracil+Pembrolizumab** |
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| **Administration** | Intravenous |
| **Schedule** | Three weekly |
| Antiemetic risk + Anti-allergic medications + Premedications + Post chemotherapy medications | Intravenous-Highly antiemetic |
| **Chemotherapy dose and method of administration** | Inj Pembrolizumab (2mg/Kg / 200mg flat dose )should be dissolved in 100 mL Non DHEP 0.9% NaCl and administered intravenously over 30 minutes through intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Flush the intravenous line at end of infusion.  Injection Carboplatin AUC5 in 500mL 5% Dextrose over 1 hour Day1  Injection 5-Flurouracil 1000mg/ m2 in 500mL Normal Saline over 24 hours: Day 1 to Day 4  -----------------------------------------  ***CARBOPLATIN Dose levels***  Dose level 0 AUC5  Dose level -1 AUC4  Dose level -2 AUC3  ***5- FLUOROURACIL Dose levels***  Dose level 0 1000mg/m2  Dose level -1 800mg/m2  Dose level -2 640mg/m2 |
| Number of days of chemotherapy in each cycle | 5 |
| Number of cycles | Until disease progression or development of intolerable side effects |
| FN risk | >20% |
| **Antithrombotic prophylaxis** | Calculate Khorana score and consider accordingly |
| **Special instruction to Nurse** | Pembrolizumab  Mix the diluted injection in infusion bag by gentle inversion, do not shake.  Monitor for infusion reactions.  Flush the intravenous line at end of infusion.   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. Carboplatin Injection is a premixed aqueous solution of 10 mg/mL Carboplatin. Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP. 2. When prepared as directed, Carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). 3. Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin aqueous solutions be discarded 8 hours after dilution   **Pembrolizumab:**  Instructions for Preparation   * Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed. * Dilute Pembrolizumab (Pembrolizumab) solution prior to intravenous administration. Withdraw the required volume from the vial(s) of Pembrolizumab and transfer into an intravenous (IV) bag containing **0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection**, USP. Mix diluted solution by gentle inversion. Do not shake. * The final concentration of the diluted solution should be between **1 mg/mL to 10 mg/mL.** * The product does not contain a preservative. Store the diluted solution from the Pembrolizumab 100 mg/4 mL vial either: * At room temperature for **no more than 6 hours** from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion. * Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than **96 hours** from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake. * Discard after 6 hours at room temperature or after 96 hours under refrigeration. * **Do not freeze**. |
| **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** | * If you are pregnant or think you might be pregnant, or if you are breastfeeding, let your doctor know right away. Carboplatin may harm your developing fetus or breastfeeding baby. If you are a woman of childbearing age, you should use birth control to avoid getting pregnant while you are taking carboplatin. * You should avoid contact with adults and children who have infections, and tell your doctor right away if you show signs of infection such as cough, fever, and/or chills. * Also, while you are being treated with carboplatin or after you stop treatment, first check with your doctor before getting any immunizations (vaccinations) |
| **Stockist instructions** | Injection carboplatin 50mg/5mL  Injection carboplatin 150mg/15mL  Injection carboplatin 450mg/45mL  Injection carboplatin 600mg/60mL  Injection 5-fluorouracil: 2.5 g in a 50 mL vial  Injection Pembrolizumab: 100 mg/4 mL (25 mg/mL) |
| **Next visit instructions** | Check CBC, LFT, RFT, Na, K,,RBS ,Urine Routine prior to each cycle  Assess T3, T4 and TSH, Lipid profile every 2 cycles or clinically indicated  Hemoglobin >=9.0 g/dL  Absolute neutrophil count >= 1500/mm3  Platelet count >= 100,000/mm3  AST/ALT <= 2x ULN alkaline phosphatase levels <=5x ULN  All adverse events resolved to baseline or grade 1 (except fatigue  or alopecia) |
| **Drug interactions** | Pembrolizumab   1. Corticosteroids : May diminish therapeutic efficacy (Risk D) carefully consider need of steroids ≥ 10 mg predinoslone equivalent 2. Axitinib: May enhance hepatotoxic effect of pembrolizumab (Risk C) monitor LFTs   Thalidomide analogues: Pembrolizumab May enhance the adverse effect of thalidomide (Risk X) Avoid combination  Carboplatin   * Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely. * Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.   5FU   1. Anticoagulants and CYP2C9 Substrates 2. 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. 3. Methotrexate, trimetrexate—Antifolate analogs increase the formation of 5-FU nucleotide metabolites when given 24 hours before 5-FU. 4. Thymidine—Rescues against the TS- and DNA-mediated toxic effects of 5-FU. 5. Vistonuridine (uridine triacetate)—Rescues against the toxic effects of 5-FU. |
| **Dose modifications for adverse events** | Neutrophil count decreased  Grade 4: Reduce carboplatin and fluorouracil by 1 dose level  Platelet count decreased  Grade 2: Reduce carboplatin and fluorouracil by 1 dose level  Grade 3: Reduce carboplatin and fluorouracil by 1 dose level  Febrile neutropenia  Grade 3: Reduce carboplatin and fluorouracil by 1 dose level  Grade 4: Discontinue carboplatin and fluorouracil  Mucositis/Diarrhea  Grade 2/4: Reduce 5-FU by 1 Dose Level    Chronic kidney disease  Grade 2: Reduce carboplatin by 1 dose level  Grade 3: Reduce carboplatin by 1 dose levels  Grade 4: Discontinue carboplatin  Aspartate aminotransferase increased  Grade 3: Discontinue fluorouracil  Palmar-plantar erythrodysesthesia  Grade 3/4 – Reduce 5-FU by 1 Dose level  **Pembrolizumab**  Aspartate aminotransferase increased  Grade 3: Discontinue pembrolizumab  Alanine aminotransferase increased  Grade 3: Discontinue pembrolizumab  Creatinine increased  Grade 3: Discontinue pembrolizumab  Diarrhea/Colitis  Grade 4- Permanently discontinue  Pneumonitis  Grade 3 or 4 - Permanently discontinue  Hypophysitis  Grade 3: Discontinue the drug  Hyperthyroidism:  Grade 3: Discontinue the drug  Rash acneiform  Grade 3: Withhold till recovery  Grade 4: Discontinue the drug  Confusion/Hallucinations  Grade 3 / 4: Permanently discontinue.  Pneumonitis  Grade 2/4: Permanently discontinue  Infusion site extravasation  Grade 3 / 4: Permanently discontinue |
| **Special tests after a few cycles if any** | Assess T3, T4 and TSH, Lipid profile every 2 cycles or clinically indicated |
| **Adverse events** | Neutropenia  Thrombocytopenia  Leukopenia  Anemia  Nausea-vomiting  Asthenia  Infections  Infusion reactions  Hypomagnesemia  Alopecia  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  Infusion Reactions  Cardiopulmonary Arrest  Pulmonary Toxicity  Dermatologic Toxicity  Hypomagnesemia and Accompanying Electrolyte Abnormalities  Increased tumor progression, increased mortality, or lack of benefit observed in patients with Ras-mutant mCRC  Embryo-Fetal Toxicity  Rash  Pruritus  Nail changes  Headache  Diarrhea |
| **Risk of death** | - |
| **Reference** | FDA label |