| Protocol title | Lung\_NSCLC\_Paclitaxel+Carboplatin+Pembrolizumab |
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| Administration | Intravenous |
| Schedule | 3 weekly |
| Antiemetic risk +  Antiallergic medications +  Premedication + Post chemotherapy medications | Intravenous- High antiemetic risk  Post-Chemotherapy medications: Tablet Paracetamol 500 mg BID PO for 5 days |
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| Chemotherapy dose and method of administration | Injection Paclitaxel 200 mg/m2 in 500 ml NS (glass bottle/non-PVC bag) IV over 3 hours using a non-PVC IV set (with in line 0.22-micron filter) on Day 1  Injection Carboplatin AUC 6 in 500 ml dextrose IV over 1 hour on Day 1.  Injection Pembrolizumab 200 mg in 100 ml NS IV over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter; on day 1 of 21-day cycle. Do not co-administer other drugs through the same infusion line on Day 1.  Administer Pembrolizumab prior to chemotherapy when given on the same day.  ***Dose levels for Paclitaxel***  Dose level 0: 200 mg/m2  Dose level -1: 150 mg /m2  Dose level -2: 100 mg /m2  ***Dose levels for Carboplatin***  Dose level 0- 6 AUC  Dose level 1- 5 AUC  Dose level 2- 4 AUC  ***Dose levels for Pembrolizumab***  Dose level 0- 200 mg  Dose level 1- NA  Dose level 2- NA |
| Number of days of chemotherapy in each cycle | 1 |
| Number of cycles | 4 cycles  Pembrolizumab: Up to 35 cycles |
| FN risk | 10-20% |
| Antithrombotic prophylaxis | Calculate Khorana score and consider prophylaxis accordingly. |
| Special instructions to Nurse- General | 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 instructions to Nurse- Protocol specific | Avoid extravasation.  **Paclitaxel:**   * Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. * Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP * Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL. * DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming. * Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder. * Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. * If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. * The reconstituted suspension should be milky and homogenous without visible particulates. * Discard the reconstituted suspension if precipitates are observed. Discard any unused portion. * Inject the appropriate amount of reconstituted Paclitaxel into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer Paclitaxel infusions. * The use of medical devices containing silicone oil as a lubricant (ie, syringes and intravenous bags) to reconstitute and administer Paclitaxel may result in the formation of proteinaceous strands. * Visually inspect the reconstituted Paclitaxel suspension in the intravenous bag prior to administration. Discard the reconstituted suspension if proteinaceous strands, particulate matter or discoloration are observed.   **Carboplatin:**   * Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Carboplatin. * Carboplatin should be administered 30 minutes after completion of Paclitaxel.   Preparation and Storage   * Carboplatin injection is a premixed 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. * Aqueous solutions are stable for 8 hours at room temperature (25°C). * 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 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 instructions to patients- General | * Encourage oral hydration * Post chemotherapy medications * In case of any emergency - Please visit the outpatient/ causality of hospital * Please respond to daily SMS sent for enquiring about your health * 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 * Any change in appointment or rescheduling can be discussed on this ……………………..number * Please avoid any social visits or public places without discussing with your oncologists * Prefer homemade food and or food prepared in hygienic conditions * In addition please check the patient information booklet available with the medicines for detailed instructions on do and don'ts |
| Instructions to patients- Protocol specific instructions | * Paclitaxel can cause myalgia & cause symptoms of peripheral neuropathy, report these symptoms to the physician if they occur. * Treatment with carboplatin is not recommended if you: are allergic to carboplatin or other platinum-containing products; have a weakened blood-forming system (bone marrow depression) or significant bleeding; are pregnant, intend to become pregnant, or are breastfeeding a baby * Report fever or other symptoms of an infection. |
| Stockists instructions | Injection Paclitaxel 30 mg (5 ml) multidose vial  Injection Paclitaxel 100 mg (16.7 ml) multidose vial  Injection Paclitaxel 300 mg (50 ml) multidose vial  Injection Carboplatin 50 mg vial  Injection Carboplatin 150 mg vial  Injection Carboplatin 450 mg vial  Injection Carboplatin 600 mg vial  Injection Pembrolizumab 50 mg lyophilized powder in single-dose vial for reconstitution  Injection Pembrolizumab 100 mg/4ml solution vial |
| Next visit instructions | CBC, LFT, RFT, SE, Mg, Ca, PO4, before every cycle |
| Drug interactions | Paclitaxel:   * The metabolism of Paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. * Caution should be exercised when Paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. * Caution should also be exercised when Paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. |
| New cycle planning  minimal requirements | Hemoglobin level >= 8 g/dl  Absolute Neutrophil Count>=1500/mm3  Platelet count >= 1,00,000/ mm3  Peripheral sensory neuropathy: grade 0 or grade 1  LFT: Serum total Bilirubin <=1.25\*ULN  Serum ALT & AST < 10\*ULN (for Paclitaxel)  All adverse events resolved to baseline or grade 1 (except fatigue or alopecia). |
| Dose modifications for adverse events | 1. Anemia    1. Grade 3/4 → reduce Paclitaxel and Carboplatin dose by 1 level 2. Neutrophil count decreased    1. Grade 3/4 → reduce Paclitaxel and Carboplatin dose by 1 level 3. Platelet count decreased    1. Grade 2 → reduce Paclitaxel and Carboplatin dose by 1 level    2. Grade 3/4 → reduce Paclitaxel and Carboplatin dose by 1 level 4. Blood bilirubin increased    1. Grade 2 → reduce Paclitaxel dose by 1 level    2. Grade 3 → reduce Paclitaxel dose by 1 level    3. Grade 4 → discontinue Paclitaxel 5. Peripheral sensory neuropathy    1. Grade 2 → reduce Paclitaxel dose by 1 level    2. Grade 3/4 → reduce Paclitaxel dose by 1 level 6. Colitis 7. Grade 4 → discontinue Pembrolizumab 8. Pneumonitis 9. Grade 3/4 → discontinue Pembrolizumab 10. Hyperthyroidism 11. Grade 4 → discontinue Pembrolizumab   9. Aspartate Transaminotransferase (AST) increased   1. Grade 3/4 -> Discontinue Pembrolizumab   10. Alanine Aminotransferase (ALT) increased   1. Grade 3/4 -> Discontinue Pembrolizumab   11. Stevens-Johnson syndrome   1. Grade 4 -> Discontinue   12. Toxic epidermal necrolysis   1. Grade 4 -> Discontinue |
| Special tests after a few cycles if any | DTPA GFR for elderly patients, 2D-ECHO, ECG,  ACTH, LH, FSH, TFT (TSH, T3,T4), Serum Cortisol, serum testosterone, NT pro BNP, Hba1c, lipid profile,  PFT-DLCO (if indicated) |
| Adverse events | Hypersensitivity  Extravasation  Neutropenia  Peripheral Neuropathy  Arthralgia/Myalgia  Hepatic Dysfunction  Renal Toxicity  Neurotoxicity  Ototoxicity  Immune mediated pneumonitis  Immune mediated colitis  Immune mediated hepatitis  Immune mediated endocrinopathies  Immune mediated nephritis  Immune mediated skin adverse reactions  Complications of allogeneic HSCT  Embryo-Fetal toxicity  Fatigue  Musculoskeletal pain  Decreased appetite  Diarrhea  Pruritus  Nausea/Vomiting  Rash  Pyrexia  Cough  Dyspnea  Constipation  Pain  Abdominal pain  Fatigue/Asthenia  Alopecia |
| Risk of death | 8.3% |
| Comment | - |
| References: | FDA drug label  N Engl J Med 2018; 379:2040-2051  DOI:10.1056/NEJMoa1810865 |