| Protocol title | GI\_Colorectal\_FOLFIRI+Bevacizumab |
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| Administration | Intravenous |
| Schedule | 4 weekly |
| Antiemetic risk  Antiallergic medications  Premedications | Day 1 and 15- Moderate emetic risk  Day 2 and 16- Low emetic risk  Pre-Irinotecan medication: Injection Atropine 250 mcg  Subcutaneous |
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| Chemotherapy dose and method of administration | Injection Irinotecan 180 mg/m2 in 500 ml 0.9% NaCl IV over 90 minutes on Day 1 and 15  Injection Bevacizumab 5 mg/kg in 100 ml 0.9% NaCl IV over 90 minutes on Day 1 and 15  (if tolerated well can be administered in 60 minutes in subsequent cycles. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 min.)  Injection Leucovorin 200 mg/m2 in 250 ml 0.9% NaCl IV over 2 hours on Day 1, 2, 15 and 16  Injection 5-Fluorouracil 400 mg/m2 IV push over 2 – 4 mins on after Leucovorin on Day 1, 2, 15 and 16  followed by  Injection 5-Fluorouracil 600 mg/m2 in 500 ml 0.9% NaCl IV over 22 hours on Day 1, 2, 15 and 16  ***Dose levels for Irinotecan***  Dose level 0- 180 mg/m2  Dose level 1- 150 mg/m2  Dose level 2- 120 mg/m2  ***Dose levels for Leucovorin***  Dose level 0- 200 mg/m2  Dose level 1- NA  Dose level 2- NA  ***Dose levels for 5-FU bolus***  Dose level 0- 400 mg/m2  Dose level 1- 320 mg/m2  Dose level 2- 240 mg/m2  ***Dose levels for 5-FU infusion***  Dose level 0- 600 mg/m2  Dose level 1- 500 mg/m2  Dose level 2- 400 mg/m2  ***Dose levels for Bevacizumab***  Dose level 0- 5 mg/kg  Dose level 1- NA  Dose level 2- NA |
| Number of days of chemotherapy in each cycle | 4 |
| Number of cycles | 6  Bevacizumab until disease progression or development of intolerable side effects |
| FN risk | 10-20% |
| Antithrombotic prophylaxis | Calculate Khorana score and give prophylaxis accordingly. |
| Special instruction 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 instruction to Nurse- Protocol specific | 1.Do not administer in the same intravenous line concomitantly with other medicinal products.  2. Discard solution if the solution is discolored or contains particulate matter.  3. Irinotecan solution should be used immediately after reconstitution as it contains no antibacterial preservative.  Irinotecan can lead to life-threatening diarrhea and cholinergic symptoms. Diarrhea can appear either as acute reaction or also some days after Irinotecan administration.  In case of Diarrhea: Capsule Loperamide 4 mg, thereafter 2 mg every 2 hours  Do not administer Bevacizumab for 28 days following major surgery  and until the surgical wound is fully healed.  DO NOT ADMINISTER OR MIX BEVACIZUMAB WITH DEXTROSE  SOLUTION |
| Special instruction to Patients- General | 1. Encourage oral hydration 2. In case of any emergency - Please visit the outpatient/ causality of …. hospital 3. Please respond to daily SMS sent for enquiring about your health 4. 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 5. Any change in appointment or rescheduling can be discussed on this ……………………..number 6. Please avoid any social visits or public places without discussing with your oncologists 7. Prefer homemade food and or food prepared in hygienic conditions 8. 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 | Patients must be made aware of the risk of delayed diarrhoea occurring 24 hours after the administration of Irinotecan and at any time before the next cycle.  Fluorouracil may damage spermatozoa.-advised to use effective contraception  In case of Diarrhea: Capsule Loperamide 4 mg, thereafter 2 mg every 2 hours  Advise patients:  • To undergo routine blood pressure monitoring and to contact their health  care provider if blood pressure is elevated.  • To immediately contact their health care provider for unusual bleeding,  high fever, rigors, sudden onset of worsening neurological function, or  persistent or severe abdominal pain, severe constipation, or vomiting.  • Of increased risk of wound healing complications during and following  Bevacizumab.  • Of increased risk of an arterial thromboembolic event.  • Of the potential risk to the fetus during and following Bevacizumab and  the need to continue adequate contraception for at least 6 months  following the last dose of Bevacizumab.  • Of the increased risk for ovarian failure following Bevacizumab treatment. |
| Stockists instructions | Injection Irinotecan 40 mg (2 mg/mL) in a single-dose vial  Injection Irinotecan 100 mg (5 mg/mL) in a single-dose vial  Injection Irinotecan 300 mg (15 mg/mL) in a single-dose vial  Injection Leucovorin 50 mg vial  Injection Leucovorin 100 mg vial  Injection Leucovorin 200 mg vial  Injection Leucovorin 350 mg vial  Injection 5-Fluorouracil 2.5 g in a 50 mL vial  Injection Bevacizumab: 100 mg/4 mL (25 mg/mL) in a single-dose vial  Injection Bevacizumab: 400 mg/16 mL (25 mg/mL) in a single-dose vial |
| Next visit instructions | CBC,RFT/SE,LFT after each cycle |
| Drug interactions | **5-FU**- 1.Anti coagulants- INR found to be deranged when 5 –FU given with coumarin.  **Irinotecan**- CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine increase metabolism of irinotecan  With enzyme inhibitors– ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole – ass with increased toxicity  **Bevacizumab:** None |
| New cycle planning minimal requirements | Hemoglobin level >= 8 g/dl  Absolute Neutrophil Count>=1000/mm3  Platelet count >=75,000/ mm3  GFR >= 40 ml/min  All adverse events resolved to baseline or grade 1 (Except alopecia  and fatigue) |
| Dose modifications for adverse events | 1. Neutrophil count decreased 2. Grade 3 → discontinue 5-FU bolus, reduce 5-FU and Irinotecan dose by 1 level 3. Alanine aminotransferase increased 4. Grade 4 → reduce Irinotecan by dose level 1 5. Aspartate aminotransferase increased 6. Grade 4 → reduce Irinotecan by dose level 1 7. Creatinine increased 8. Grade 3 → reduce Irinotecan by dose level 1 9. Grade 4 → reduce Irinotecan by dose level 1, discontinue 5-FU bolus 10. Heart failure 11. Grade 2/3/4 → discontinue 5-FU 12. Confusion 13. Grade 4 → discontinue 5-FU 14. Hepatic failure 15. Grade 3/4 → discontinue 5-FU 16. Hypertension   a. Grade 4 → discontinue Bevacizumab   1. Proteinuria   a. Grade 4 → discontinue Bevacizumab   1. Intracranial hemorrhage   a. Grade 2/3/4 → discontinue Bevacizumab   1. Bronchopulmonary hemorrhage   a. Grade 2/3/4 → discontinue Bevacizumab   1. Thromboembolic event   a. Grade 4 → discontinue Bevacizumab   1. Arterial thromboembolism   a. Grade 1/2/3/4 → discontinue Bevacizumab |
| Special tests after a few cycles if any | - |
| Adverse events | Diarrhea  Sweating  Abdominal cramping  Myelosuppression  Alopecia  Dizziness  Anaphylaxis  Nausea/Vomiting  Palmar plantar erythrodysesthesia syndrome  Arthralgia/Myalgia  Myelosuppression  Neuropathy  Alopecia  Epistaxis  Arthralgia/Myalgia  Hypersensitivity reactions  Sensory motor peripheral neuropathy  Leukopenia  Anemia  Fatigue  Alopecia  Nausea  Stomatitis  Bradycardia  Hypotension  Interstitial pneumonitis |
| Risk of death | 0.9% |
| Comment | - |
| Reference | FDA drug label  Hurwitz H. et al., N Engl J Med 350: 2335ff, 2004 |