Chemotherapy Protocol

COLORECTAL CANCER

Bevacizumab and Trifluridine - Tipiracil (LONSURF)

Regimen

- Colorectal Cancer- Bevacizumab and Trifluridine - Tipiracil (LONSURF)

Indication

- Trifluridine - Tipiracil (LONSURF) is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti- EGFR agents.

Toxicity

Drug	Adverse Effect
Trifluridine-Tipiracil	Diarrhoea, nausea, neutropenia, thrombocytopenia, proteinuria, fatigue, decreased appetite
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

- FBC, LFTs and U&Es prior to day one of treatment
- Blood pressure and dipstick urinalysis for proteinuria prior to treatment

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. (See below for information on bevacizumab and transfusions).

Prior to prescribing on day one of cycle one the following criteria must be met:

Criteria	Eligible Level
Neutrophils	Equal to or more than 1.5 x 10^9 /L
Platelets	Equal to or more than 75 x 10^9 /L

Dose Interruption and Resumption Criteria:

Parameter	Interruption Criteria	Resumption Criteria**
Neutrophils	<0.5 x 10^9 /L	≥1.5 x 10^9 /L
Platelets	<50 x 10^9 /L	≥75 x 10^9 /L

**The resumption criteria are applied to the start of the next cycle regardless of whether the interruption criteria were met.

Following Dose Modifications/ Recommendations apply to Trifluridine - Tipiracil only:

Adverse Reaction	Recommendations
• Febrile neutropenia • CTCAE Grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 × 10^9/L) that results in more than 1 week's delay in start of next cycle. • CTCAE* non-haematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrheal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily (or 15 mg/m^2/dose twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

A maximum of three dose reductions are permitted, at 5mg/m^2 increments, from 35mg/m^2 to 30mg/m^2, 25mg/m^2 to a minimum dose of 20 mg/m^2 of trifluridine twice a day.

Dose escalation is not permitted after it has been reduced.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

No dose adjustment needed for bevacizumab based on hepatic impairment.

Trifluridine - Tipiracil is not recommended when bilirubin > 1.5 x ULN.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose
Bevacizumab	N/A	The safety and efficacy have not been studied in patients with renal impairment. But no needed for dose adjustment is expected.
Trifluridine - Tipiracil	>30	Give 100% of Dose
	15-29	A starting dose of 20 mg/m^2 twice daily is recommended. One dose reduction to a minimum dose of 15 mg/m^2 twice daily is permitted based on individual safety and tolerability. Dose escalation is not permitted after it has been reduced.
	<15	Administration is not recommended in patients with end stage renal disease

Other toxicities

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Bevacizumab

Bevacizumab doses should be omitted and not reduced for adverse reactions. If more than two doses are missed due to adverse events treatment should be stopped. It should be noted that the half-life of bevacizumab is approximately twenty days. Discontinuation of treatment in response to adverse effects is not expected to influence the short-term clinical evolution of the event, symptomatic treatment is often necessary.

Bevacizumab should be stopped if the individual develops:

- Gastrointestinal perforation
- Arterial thromboembolic events
- NCI-CTC grade 3 and above haemorrhagic events (requiring a blood transfusion or a major non-elective intervention)
- NCI-CTC grade 3 and above congestive heart failure or left ventricular function.
- NCI-CTC grade 4 fistula

If an NCI-CTC symptomatic grade 4 venous thromboembolic event occurs bevacizumab should be stopped. However, if this is a pulmonary embolism bevacizumab may be restarted once a full recovery has been made and the individual is anti-coagulated with a subcutaneous low molecular weight heparin. An oral anticoagulant must not be used.

Hypertension is a common consequence of bevacizumab therapy. For an NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider antihypertensive therapy. For an NCI-CTC grade 3 and above hypertension that is persistent consider stopping treatment. Bevacizumab may be continued for an NCI-CTC grade 1 proteinuria or the first occurrence of a grade 2 proteinuria. For the second occurrence of a NCI-CTC grade 2 proteinuria or any NCI-CTC grade 3 proteinuria give the bevacizumab as

scheduled. A 24-hour urine collection or UPCR should be conducted at most three days before the next dose. If there is less than 2g protein per 24 hours or a UPCR 0-1 administer the bevacizumab and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the bevacizumab. Repeat the 24-hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the bevacizumab and continue 24-hour urine collection until the protein is 1g per 24 hours or less.

Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be held for at least 28-60 days before elective surgery.

Regimen

28 day cycle until disease progression or intolerance

Drug	Dose	Days	Administration
Bevacizumab	5mg/kg	1 and 15	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Trifluridine - Tipiracil (LONSURF)	35mg/m2 twice a day	1, 2, 3, 4, 5, 8, 9, 10, 11, 12	Oral

Dose Information

- Bevacizumab will be dose banded in accordance with the national dose bands (25mg/ml NS)
- For LONSURF, the dose is calculated based on the trifluridine dose.
  - The maximum dose is 80mg of trifluridine.
  - The minimum dose is 20mg/m2 of trifluridine.
  - Doses will be rounded to the nearest 5mg (up if halfway).
  - Available as Trifluridine - Tipiracil 20mg/8.19mg and 15mg/6.14mg Tablets.

Administration Information

- The dosage schedule for LONSURF is easier to remember if it is started on a Monday and taken through to the Friday with the weekend off.
- If a dose of LONSURF is missed or withheld the patient must not make up the doses
- The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

Extravasation

- Bevacizumab – neutral

Additional Therapy

- Anti-emetics are not routinely required but you may consider adding:
  - metoclopramide 10mg three times a day oral when required.
- Antidiarrheal agents such as loperamide or codeine.
- Gastric protection with a proton pump inhibitor or a H2 anta

Additional Information

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that the LONSURF is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

References

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3. UHS (2020) *Chemotherapy Protocol COLORECTAL CANCER BEVACIZUMAB- CAPECITABINE.* Available at https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Colorectal/Bevacizumab-Capecitabine.pdf [Accessed 4 Nov. 2024].
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5. Aaron Teoh for The Clatterbridge Centre NHS Foundation Trust (2024). LONSURF + Bevacizumab (trifluridine and tipiracil) Metastatic Colorectal Cancer. Available at: https://www.clatterbridgecc.nhs.uk/application/files/1917/2906/8111/Lonsurf_trifluridine_and_tipiracil__plus__Bevacizumab_v1.0.pdf [Accessed 4 Nov. 2024].
6. Nice.org.uk. (2024). *Overview | Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/ta1008 [Accessed 4 Nov. 2024].

REGIMEN SUMMARY

Bevacizumab and Trifluridine - Tipiracil

Day 1

1. Bevacizumab 5mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes
   Administration Instructions
   The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

Take Home Medicines

2. Trifluridine – Tipiracil 35mg/m2 twice a day oral
   Administration Instructions
   Take on days 1, 2, 3, 4, 5, 8, 9, 10, 11, 12
   The dose is based on the dose of trifluridine.

Day 15

3. Bevacizumab 5mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes
   Administration Instructions
   The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Nov 2024	None	Beth Douse Pharmacist	Dr Ann O'Callaghan Consultant Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.