Chemotherapy Protocol

GYNAECOLOGICAL CANCERS

NIRAPARIB

Regimen

- Ovarian Cancer – Niraparib

Indication

- Niraparib is recommended as maintenance treatment in patients with relapsed, platinum-sensitive and high grade serous ovarian, fallopian tube or primary peritoneal carcinoma who are in response following platinum-based SECOND line chemotherapy and who HAVE a germline BRCA mutation OR are in response following platinum-based SECOND OR LATER line chemotherapy and who DO NOT HAVE a germline BRCA mutation where the following criteria are met:

  - The prescribing clinician is fully aware of the likely toxicities of niraparib, the associated monitoring required and the reasons why 48% of patients in the ENGOT-OV16/NOVA trial had dose interruptions in the 1st cycle and 47% commenced their 2nd cycle at a reduced niraparib dosage

  - they have a germline BRCA mutation and have had 2 courses of platinum-based chemotherapy or they do not have a germline BRCA mutation and have had 2 or more courses of platinum-based chemotherapy

  - The patient relapsed following **1st** line chemotherapy (ie the penultimate line of treatment) **and had platinum-sensitive disease at this relapse**, platinum sensitivity defined by a complete or partial remission which lasted for more than 6 months following completion of **1st** line platinum-based chemotherapy (whether given pre- and/or post-operatively or if the patient did not have surgery)

  - For those with a BRCA mutation, then the patient must be in a complete or partial response following completion of **2nd** line platinum-based chemotherapy (ie the most recent chemotherapy) and that the serum CA125 is either normal or has demonstrated a >90% decrease from before the initiation of 2nd line chemotherapy **and** is stable

  - For those patients who do not have a BRCA germ line mutation they must be in a complete or partial response following completion of the most recent line platinum-based chemotherapy **which must be at least second line treatment** and that the serum CA125 is either normal or has demonstrated a >90% decrease from before the initiation of this most recent line of chemotherapy and is stable)

  - The patient is less than 12 weeks since completing chemotherapy

  - The patient has not previously received any PARP inhibitor

- formal medical review as to whether maintenance treatment with niraparib should continue or not and at what dose will be scheduled to occur at least by the start of the second cycle of treatment

- Niraparib will be used as monotherapy

- No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve)

- WHO Performance status 0, 1 (those with a PS of 2 or more are not eligible for treatment

Toxicity

Drug	Adverse Effect
Niraparib	Nausea, thrombocytopenia, neutropenia, AML/myelodysplastic syndrome, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, insomnia, headache, decreased appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- BRCA testing prior to starting therapy

- FBC, U&Es, creatinine, LFTs prior to starting day 1 cycle one. FBC should then be conducted weekly for the first month of treatment. Thereafter FBC, U&Es and LFT's then monthly for the following eleven months and then 2-3 monthly thereafter if levels have been stable.

- CA125 where appropriate

- Prior to the initial dose of niraparib, blood pressure shall be measured for baseline monitoring. Continue to measure monthly for the first twelve months and periodically thereafter, as deemed appropriate. Hypertension can be medically managed with antihypertensive medications or adjustment of niraparib dose.

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 cancer treatments 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.

It is worthy of note that 48% of patients in the ENGOT-OV16/NOVA trial had dose interruptions in the 1st cycle and 47% commenced their 2nd cycle at a reduced niraparib dosage

Haematological

Eligible levels for cycle one should be;

Test	Level
Neutrophils	Greater than or equal to $1x10^9$/L
Platelets	Greater than or equal to $100x10^9$/L

Dose Modifications for Haematologic Adverse Reactions	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with thrombocytopenia platelet transfusion should be considered according to clinical circumstance. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelets, consider interrupting these substances and/or transfusion. • Resume niraparib at a reduced dose.
Platelet count less than $100x10^9$/L	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to $100x10^9$/L or more. • Resume niraparib at same or reduced dose based on clinical evaluation. • If platelet count is less than $75x10^9$/L at any time, resume at a reduced dose.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to $100x10^9$/L or more
	• Resume niraparib at a reduced dose. • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100mg.
Neutrophil less than $1x10^9$/L or Haemoglobin less than 8g/dL (80g/L)	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to $1.5x10^9$/L or haemoglobin returns to 9g/Dl (90g/L). • Resume niraparib at a reduced dose. • Discontinue niraparib if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue niraparib

Hepatic Impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment, use with caution in these patients

Renal Impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis, use with caution in these patients

Other

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.

In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that niraparib be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that niraparib be discontinued.

Dose reductions may be implemented based on adverse reactions. The recommended dose reductions are first from 300mg to 200mg. If further dose reduction is needed, a second dose reduction from 200mg to 100 mg may be implemented.

Dose Modifications for Non-Haematologic Adverse Reactions	
Non-haematologic NCI-CTC grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite supportive treatment	First occurrence: • Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • Resume niraparib at a reduced dose (200 mg/day).
	Second occurrence: • Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • Resume niraparib at a reduced dose (100 mg/day).
NCI-CTC grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100mg/day	Discontinue treatment.

Hypertension

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose if necessary. In the clinical programme, blood pressure measurements were obtained on day 1 of each 28-day cycle. In most cases, hypertension was controlled adequately using standard antihypertensive treatment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Regimen

28 day cycle until disease progression or unacceptable toxicity occurs or the patient chooses to stop treatment (12 cycles will be set in Aria)

Consider a starting dose of 200mg once a day in those whose weight is less than 70kg.

Drug	Dose	Days	Administration
Niraparib	300mg once a day	Continuous	Oral

Dose Information

- Niraparib is available as 100mg hard capsules

Administration Information

- The capsules should be swallowed whole with water
- Bedtime administration may help to minimise nausea
- If a dose is missed, the next dose should be taken at its scheduled time.

Additional Therapy

- No routine supportive medication is required

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to niraparib.
- It must be made clear to all staff, including those in the community, that niraparib should only be prescribed under the supervision of an oncologist.
- Niraparib interacts with many other agents. Always check for drug interactions.

Coding

- Procurement – X71.5
- Delivery – X73.1

References
1. National Institute for Health and Clinical Excellence (2018). Niraparib for the maintenance treatment of relapsed platinium sensitive ovarian, fallopian tube and peritoneal cancer . Technology appraisal guidance TA528. DOH:London

REGIMEN SUMMARY

Niraparib

Cycle 1 onwards

Take Home Medicines

1. Niraparib 300mg once a day
   Administration Instructions
   Oral chemotherapy.
   Swallow whole with water

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	June 2019	LFT and U&Es removed from the monitoring for the first four weeks of treatment	Dr Deborah Wright Pharmacist	Dr C Green Consultant Medical Oncologist
1	Sept 2018	None	Dr Deborah Wright Pharmacist	Dr C Green Consultant Medical 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. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.