TEMOZOLOMIDE IRINOTECAN – local funding required

INDICATION (ICD10) C71.6
1. Recurrent and progressive SHH+ medulloblastoma, second line after PCV (unlicensed)
PS 0, 1, 2

REGIMEN
Days 1 to 5 TEMOZOLOMIDE 150mg/m^2 orally once daily (1 hour before irinotecan)
Premedication: Atropine 250mcg subcutaneously 30 minutes prior to treatment
IRINOTECAN 50mg/m^2 in 250ml sodium chloride 0.9% (or licensed dose volume) IV infusion over 30 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES
Every 21 days for 6 cycles

ADMINISTRATION
Available as various strength capsules
Take on an empty stomach

ANTI-EMETICS
Moderate risk days 1 to 5

CONCURRENT MEDICATION REQUIRED

Irinotecan	Ensure premedication atropine given 30 minutes prior to treatment. Patients who experience delayed diarrhoea will require loperamide 2mg every 2 hours to continue for 12 hours after the last loose stool. This high dose should be discontinued after 48 hours Consider antibiotic if indicated

EXTRAVASATION AND TYPE OF LINE / FILTERS
Irinotecan - irritant

Peripheral line

INVESTIGATIONS
Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Serum creatinine every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Irinotecan	Acute cholinergic syndrome (including diarrhea and delayed diarrhoea, abdominal pain, hypotension, dizziness, malaise, increased salivation). Drink large volumes of fluid containing electrolytes and an appropriate antidiarrhoeal therapy - loperamide 4mg initially then 2mg every 2 hours, continuing for 12 hours after the last liquid stool (maximum of 48 hours in total).
Temozolomide	Myelosuppression, rare protracted aplastic picture can occur Hepatic toxicity – may still occur several weeks after end of treatment Renal impairment

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Irinotecan	Aprepitant and fosaprepitant increases exposure to irinotecan. Carbamazepine increases exposure to irinotecan, avoid. Enzalutamide, mitotane, phenobarbitone, phenytoin, primidone and rifampicin decreases exposure to irinotecan, avoid.

DOSE MODIFICATIONS

Dose level -1	Temozolomide dose 100mg/m^2/day	Reduction for prior toxicity
Dose level 0	Temozolomide dose 150mg/m^2/day	Cycle 1 dose

Haematological
Temozolomide
Neutrophils <1.5x10^9/l and platelets <100x10^9/l on day 21 then treatment should be delayed one week and then reduce by one dose level.

Non-haematological
Irinotecan
If patients suffer from severe diarrhoea, which required IV rehydration or neutropenic fever, consider reduction in subsequent cycles, discuss with SpR or Consultant.

Hepatic impairment
Irinotecan

Bilirubin 24-50micromol/L	give 50% dose
Bilirubin >51micromol/L	Clinical decision

Temozolomide
Stop temozolomide if there is a progressive rise in transaminases eg ALT >200 or rise in bilirubin.

Renal impairment
Temozolomide
Stop temozolomide if there is a significant rise in serum creatinine (more common in patients with pre-existing renal impairment).

REFERENCES

1. Grill, J., et al., Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study. Neuro Oncol, 2013 15(9): p1236-43.