The Clatterbridge Cancer Centre NHS Foundation Trust

Immune-Related Adverse Event Guideline: Hepatoxicity

Hepatic transaminases (ALT/AST) and bilirubin must be evaluated before each dose of immunotherapy, as early laboratory changes may indicate emerging immune-related hepatitis. Elevations in LFTs may develop in the absence of clinical symptoms. This guidance should be used in context of baseline LFTs and presence of known liver metastases. No dose adjustment is required for mild hepatic impairment but data is limited for use of these drugs in moderate/severe hepatic impairment and patients should be closely monitored for elevation in LFTs from baseline.
Prior to commencement of immunotherapy all patients should have LFTs checked

Mild (Grade 1)

AST or ALT < 3 x ULN but increasing from baseline

Investigations:
- Weekly LFT (including ALT) check between cycles of immunotherapy and ensure remain stable prior to next cycle. Inform oncology team
- Consider culprit concomitant medications

Actions:
- Continue immunotherapy treatment

Biochemical Abnormality WORSENS or RELAPSE see moderate/ severe strand (LFT dependant)

Moderate (Grade 2)

AST or ALT >3 to ≤5 x ULN

Clinical Assessment

As per mild (grade 1) +

Investigations:
- Regular LFTs, direct and indirect bilirubin and clotting profile
- MRI/USS of liver to exclude PD & thromboembolism and evaluate if evidence of inflammation
- Hepatitis viral panel (hepatitis A, B, C, E)
- CMV, EBV and HIV and auto-antibodies

Treatment:
- Commence prednisolone 60mg/day+ gastric protection

Actions:
- Withhold dose until the adverse reaction resolves to Grade 0-1 (or returns to baseline).
- Review medications (e.g. statins, antibiotics)
- **Re-check LFTs and INR every 3 days and review patient by phone twice weekly. If improving check LFTs weekly.**

Symptoms: Resolve or Improve to Mild See steroid tapering guidance

Biochemical Abnormality PERSISTS (≥3 days), WORSEN or RELAPSE see severe strand

Severe or Life-Threatening (Grade 3/4)

AST or ALT >5 x ULN (Grade 4 >20 x ULN)

Clinical Admission
As per moderate (Grade 2) +
Consider admission of patient

Investigations:
- Daily LFTs, clotting profile and lactate. If deteriorating, consider venous gas.
- MRI of liver to exclude PD & thromboembolism and evaluate if evidence of inflammation or sclerosing cholangitis
- Exclude other causes (e.g. Heart failure/ PD)

Treatment:
- IV methylprednisolone 2mg/kg/day
- Increasing to 4mg/kg/day could be considered if clinical improvement is unsatisfactory.
- IV hydration (patients need to be well hydrated to promote hepatic perfusion with fluid balance)
- Vitamin K 10mg IV daily x 3 days if INR deranged
- **Grade 4 (loss of synthetic function or hyperbilirubinemia) commence** N-acetylcystine (NAC as per paracetamol overdose protocol in BNF)

If albumin low, discuss with hepatologist and consider administration of human albumin solution (HAS)

Actions:
- Referral to hepatologists for further advice
- Consider antibiotic prophylaxis with patients on high dose, prolonged steroids
- Establish escalation plan and ceiling of care

Symptoms: Resolve or Improve to Mild See steroid tapering guidance

Assess response to treatment, if no improvement within 72 hours, consider additional immunosuppression. Consider CCC Subsequent Management guidelines

Abbreviations
LFTs = liver function tests

INR = international normalised ratio
ULN = upper limit of normal
PD = progressive disease

Interrupt SACT immunotherapy until discussed with Acute Oncology Team. Please contact on-call oncology/haematology team for advice. Ensure that the patient has monitoring/follow up planned with their oncology/immuno-oncology team.