R-GDP: Rituximab, Gemcitabine, Dexamethasone &Cisplatin

INDICATION

Relapsed or refractory Hodgkin and non-Hodgkin lymphoma.
Omit Rituximab for patients with Hodgkin Lymphoma or high grade T cell non-Hodgkin lymphoma.

TREATMENT INTENT

Curative or salvage therapy before autologous stem cell transplantation.

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis) and / or PET-CT, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests - FBC, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save.
4. Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for 7 days before harvest. See ‘Guidelines for the use of blood components in adult haematology' for details. Ensure irradiation card is attached to the patient's notes and copy given to the patient.
5. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
6. ECG +/- Echo - *if clinically indicated*.
7. Record performance status (ECOG).
8. Record height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
10. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
11. Consider dental assessment.
12. Treatment should be agreed in the relevant MDT.
13. Venous access should be assessed well in advance of collection. Every effort should be made not to use antecubital fossa veins in the run up to harvest.
14. If good antecubital fossa veins, insert Hickman line. Apheresis line to be inserted if poor antecubital veins.
15. Ensure the peripheral stem cell harvest / final donor clearance form (form FRM3721/1) is sent within 30 days of scheduled harvest date, via nhs.net mail to NHSBT STS, to confirm eligibility for PBSCH.

NB: Infective agent screen. Peripheral blood stem cells for autologous transplant are cryopreserved in liquid nitrogen. In order to eliminate the risk of transmitting infective agents during the storage of marrow, virology testing is mandatory within 30 days of the harvesting procedure and results must be known before priming.
Bottles and consent form provided by NBS Oxford. Please send to the Stem Cell Laboratory, Oxford. Address provided on consent form.

DRUG REGIMEN

Day 1*	**Pre-med** - Paracetamol 1g PO, Chlorphenamine 10 mg IV, Hydrocortisone 100mg IV 30 minutes before rituximab **RITUXIMAB** 375 mg/m^2 IV infusion in 500 mL sodium chloride 0.9% (rituximab does not necessarily have to be given first)
Days 1 & 8	**GEMCITABINE** 1000mg/m^2 IV infusion in 250 mL sodium chloride 0.9% over 30 minutes
Day 1	**PRE-HYDRATION** 1000mL sodium chloride 0.9% + 20mmol potassium chloride + 8mmol magnesium sulphate IV infusion over 2 hours 200mL mannitol 10% IV infusion over 30 minutes (immediately before cisplatin)
Day 1	**CISPLATIN** 75 mg/m^2 daily IV infusion in 1000mL sodium chloride 0.9% over 2 hours. Cisplatin must be started **after** the gemcitabine infusion
Day 1	**POST-HYDRATION** 1000mL sodium chloride 0.9% + 20mmol potassium chloride + 8mmol magnesium sulphate IV infusion over 2 hours NB. Furosemide 20-40mg may be added if weight gain >2kg during infusion
Day 1 - 4**	**DEXAMETHASONE** 40mg PO once daily

When used for priming:

Days 9 to 15 **Daily G-CSF** as per local policy. Continue until mobilisation completed. *G-CSF should be discontinued after completion of stem cell harvesting. (Pegfilgrastim must NOT be used). Aim to collect on days 15 and 16.

When not used for priming:

Days 9 to 15 **Daily G-CSF** as per local policy

* for cycle 1, rituximab can be administered on the day before the gemcitabine/cisplatin to ensure that enough time is available to use this as a day-unit protocol.
** for cycle 1, dexamethasone can be moved to the day before the gemcitabine/cisplatin with rituximab.

CYCLE FREQUENCY

Repeat every 21 days, maximum of three cycles.

RESTAGING

After 2 cycles with either CT or PET/CT.

HARVESTING (if used for priming)

- Stem cell collection performed days **15 & 16**
- Aim to collect minimum of 2.0 x 10^6 with target of 4.0 x 10^6 CD34-positive cells/kg

DOSE MODIFICATIONS

Haematological Toxicity

Day(s) of cycle	ANC (x 10^9/L)		Platelets (x 10^9/L)	Action this cycle
Day 1	≥ 1.0	AND	≥ 75	100% all drugs
	≥ 1 .0	AND	<75	Delay 1 week[+] If plat then ≥ 50, give 100%. Support with platelet transfusions as necessary.
	<1.0	AND	≥ 75	Delay 1 week[+] If ANC then ≥ 0.5, proceed with 100% and support with GCSF.[**]
	<1.0	AND	<75	Delay 1 week[+] If ANC then ≥ 0.5 and plat ≥ 50, give 100% dosing. Support with GCSF OR If ANC <0.5 and/or plat <50 defer and check counts every 3 days. Resume when ANC ≥0.5 and plat ≥50.[**]
Day 8	≥1.0	AND	≥75	Give 100% gemcitabine.
	0.5 -1.0	AND	≥75	Give 100% gemcitabine and support with GCSF**, or give 75% of the dose
	---		50-75	Give gemcitabine at 75% of the dose.
	<0.5	OR	<50	OMIT gemcitabine and start GCSF.**

[+] Discuss with consultant. If counts are presumed to be low due to marrow involvement, treat after 1 week delay (i.e. at 28 days) despite counts.
** GCSF should be given prophylactically for all future cycles

Renal & Hepatic Dysfunction

Cisplatin:

Renal impairment		Hepatic impairment
GFR (mL/min)	**Dose**	No dose reduction necessary.
>60	100%	
45-59	75%	
<45	consider carboplatin	
Consider carboplatin if GFR <45 ml/min. Conflicting information. Where GFR is less than 45 mL/min - clinical decision.		

Ototoxicity:
Grade 2 or above, discuss with consultant – dose may need to be reduced.

Gemcitabine:

Renal impairment	Hepatic impairment
CrCl <30 mL/min consider dose reduction - clinical decision.	Gemcitabine: limited information, consider dose reduction if bilirubin elevated. If bilirubin >27 micromol/L, then initiate treatment at 800 mg/m^2.

Reduce gemcitabine and cisplatin doses to 75% and 50% doses for all other grade 3 or 4 non-haematological toxicities respectively.

INVESTIGATIONS

- FBC, U&Es, Creatinine, LFTs
- Mg^{+2+}, Ca^{2+}, K^{+}

HARVESTING (if used for priming)

- Stem cell collection performed days **15 & 16.**
- Aim to collect minimum of 2.0 x 10^6 with target of 4.0 x 10^6 CD34-positive cells/kg.

CONCURRENT MEDICATION

Allopurinol	300 mg daily for 7 days starting 24-48 hours prior to chemotherapy (first course / cycle only)
PPI (omeprazole)	20mg once daily for the duration of treatment
Fluconazole	50 mg daily for the duration of treatment
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
Co-trimoxazole	480 mg daily on Mon/ Wed/ Fri for duration of treatment and for 3 months afterwards (Consider reducing the dose to 480 mg twice weekly during neutropenic periods)
G-CSF (priming/standard)	As per local policy

EMETIC RISK

Day 1 High
Day 8 low

Beware of delayed emesis with Cisplatin.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Diarrhoea, mucositis, steroid side effects, nausea or vomiting.
Cisplatin:
Nephrotoxicity - ensure adequate pre and post hydration is prescribed.
Ototoxicity - assess patient for tinnitus or hearing abnormalities.
Rituximab: severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation.

EXTRAVASATION RISK

Cisplatin: exfoliant
Gemcitabine: neutral
Rituximab: neutral

TREATMENT RELATED MORTALITY

Estimated 1-2%.

REFERENCES

1. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6.
2. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
3. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January2009).

NURSING CARE PLAN R-GDP

Indication: Relapsed or refractory Hodgkin and non-Hodgkin lymphoma.
Frequency: Repeat every 21 days (maximum 3 cycles, staging scan post cycle 2)**Alopecia:** yes
Emetic risk: high for day 1 and low for day 8

R=RITUXIMAB: Monoclonal antibody for CD 20.
Administered as IV infusion.
Classification of extravasation: neutral.
Emetic risk: low.
Side effects: risk of anaphylaxis, severe dyspnoea, bronchospasm and hypoxia

- Infusion reactions (Most common during first infusion - PREMED 30 MINS PRIOR TO INFUSION): fever, chills, rigors, urticaria, nausea, hypotension, dizziness, cough, chest tightness, back pain.
- Rituximab can cause hypotension. Consider withholding anti-hypertensives 12 hours prior to Rituximab (especially first dose).
- Risk of tumour-lysis syndrome, especially with bulky disease.
- Post infusion side effects: flu-like symptoms, fever, diarrhoea
- **For first Rituximab:**
  - Ensure patient is treated on a bed.
  - In DTU setting *(where the patient is visually in front of the nursing station with very close observation):* Record baseline vital observations and then if patient reacts. On the ward setting: record vital observations every 30 minutes for the first two hours and then hourly. To have close observation.
  - Have anaphylaxis box nearby.
  - Increment drug infusion rate as per protocol. *Note there are different rates for first and subsequent treatments and for different doses.*
  - Educate patients re possible reactions and the importance of reporting any symptoms immediately.
- **If patient reacts to Rituximab:**
  - Stop infusion.
  - Record observations.
  - Seek an immediate medical review.
  - Consider administration of Hydrocortisone, Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.
  - Restart infusion at same or previous rate after 30 minutes if symptoms resolved.

G=GEMCITABINE: Antimetabolite
Administered on **days 1 and 8** as 30 minute IV infusion.
Classification of extravasation: neutral.
Emetic risk: low.
Side effects: mild dyspnoea, mild rash, nausea and vomiting, flu like syndrome, bone marrow depression, altered liver function tests.

D=DEXAMETHASONE: steroid
Administered orally on days 1-4 with/after food.
Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression, visual changes.

P=CISPLATIN: platinum compound/alkylating agent
Administered as IV infusion over 2 hrs on Day 1.
Classification of extravasation: exfoliant.
Emetic risk: high – risk of delayed emesis
Side effects: hypersensitivity / anaphylaxis, nausea and vomiting, hyponatraemia, sepsis, arrhythmia, tinnitus, bone marrow depression, peripheral neuropathy, ototoxicity.

Drug Regimen

C1 days 1 and 2 only:
Day 1 - Rituximab only **administered at 1st infusion** rate (pre medications as per Aria).
Day 2 – Gemcitabine over 30 minutes.
Day 2 – Pre hydration n/saline + 20mmol KCL + 8mmol MgS04 infusion over 2 hours.
Day 2 – 200ml Mannitol 10% IV infusion over 30 minutes.
Day 2 – Cisplatin over 2 hours. **Cisplatin must be given after the gemcitabine infusion**
Day 2 – Post hydration n/saline + 20mmol KCL + 8mmol MgS04 infusion over 2 hours.
Furosemide 20-40mg may be given if weight gain >2kg during infusion

Subsequent Cycles day 1 only:
Day 1 - Rituximab administered at subsequent infusion rate or rapid rate if tolerated well on first cycle (pre medications as per Aria).
Day 1 – Gemcitabine over 30 minutes.
Day 1 – Pre hydration n/saline + 20mmol KCL + 8mmol MgS04 infusion over 2 hours.
Day 1 – 200ml Mannitol 10% IV infusion over 30 minutes.
Day 1 - Cisplatin over 2 hours. **Cisplatin must be given after the gemcitabine infusion.**
Day 1 – Post hydration n/saline + 20mmol KCL + 8mmol MgS04 infusion over 2 hours.
Furosemide 20-40mg may be given if weight gain >2kg during infusion

If patient has received Rituximab within the last 2 months, Cycle 1, day 1 can be treated as subsequent cycle if patient tolerated well.
The above regimen is specific to DTU due to time restraints. If being treated on the ward, all of the first cycle can be given on day 1.

Regime Specific Considerations

- When using cisplatin containing regimens, the patient's weight should be recorded pre-treatment, pre commencing cisplatin, post cisplatin and end of post hydration.
- GCSF on days 9-15. Ensure patient/carer are taught to self administer GCSF. Arrange a district nursing referral and prescription if this is not possible.
- Patients with a high white cell count/bulky disease are at increased risk of reacting to Rituximab and developing tumour lysis syndrome.
- Advise patients to maintain fluid intake of 2-3 litres a day for next few days.
- Bloods must be repeated prior to day 8.