BC Cancer Protocol Summary for Curative Therapy for Germ Cell Cancer using Bleomycin, Etoposide and CISplatin

Protocol Code	*GUBEP*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. Christian Kollmannsberger*

ELIGIBILITY:
The BEP protocol is the standard protocol for the adjuvant setting in stage I nonseminomas and for metastatic germ cell tumors. It may be used for patients with IGCCCG (International Germ Cell Consensus Classification) good (3 cycles) and intermediate (4 cycles) prognosis seminoma or nonseminoma as well as for poor risk (4 cycles) nonseminoma (irrespective of primary tumor location)

Adjuvant Criteria:
Clinical stage I nonseminoma with vascular invasion ("high risk") which has a 50% risk of relapse if surveillance is not an option

Retroperitoneal lymph node dissection pathology demonstrating involvement estimated to be associated with greater than 50% risk of subsequent relapse: 5 or more nodes involved, any involved node greater than or equal to 2 centimeters in diameter, or involved lymph node with extracapsular extension.

Low Risk Metastatic:
Testis/retroperitoneal primary AND no non-pulmonary visceral metastases AND AFP less than 1000 mcg/L or serum beta hCG less than 5000 unit/L or LDH less than 1.5 x N. Mediastinal seminomas which are a low risk form of mediastinal disease. Please note: most mediastinal germ cell cancers are non-seminomas and are considered high risk (4 cycles) disease.

Intermediate Risk Metastatic:
Testis/retroperitoneal primary AND no non-pulmonary visceral mets AND Intermediate Markers:

AFP greater than or equal to 1000 mcg/L but less than 10,000 mcg/L
Serum beta hCG greater than or equal to 5000 unit/L but less than 50,000 unit/L
LDH greater than or equal to 1.5 x N but less than 10 x N

High Risk Metastatic:
Mediastinal primary OR non-pulmonary visceral mets OR AFP greater than 10,000 mcg/L OR serum beta hCG greater than 50,000 unit/L OR LDH greater than 10 x N.

It is strongly recommended that all patients with metastatic germ cell tumours should be presented in GU tumour group conference and/or referred to a high volume center.

RELATIVE CONTRAINDICATIONS
Discussion with an expert center recommended:
- Inadequate renal function (calculated creatinine clearance less than 40 mL/min) (relative contraindication)
- Inadequate hematologic function
- Chronic pulmonary disease considered a risk factor for bleomycin toxicity
- Recent thoracic irradiation (bleomycin risk)

TESTS:

- Baseline: CBC and differential, platelets, bilirubin, ALT, alkaline phosphatase, LDH, creatinine, sodium, potassium, magnesium, calcium, AFP, beta hCG tumour marker, CEA, random glucose, pulmonary function tests (if indicated).
- Consider baseline audiogram for pretreatment hearing impairment.
- Consider pre-chemotherapy sperm count and banking if fertility is an issue.
- Before each cycle: CBC and differential, platelets, creatinine, LDH, AFP, beta hCG tumour marker, magnesium, sodium, potassium, random glucose.
- Repeat CBC on day 5 if ANC on day 1 less than 1.0 x 10^9/L (not required on day 5 of the first cycle)
- Repeat creatinine on day 5 if creatinine on day 1 greater than the upper limit of normal
- Creatinine within 24 hours prior to day 8 and day 15, if patient receiving bleomycin.

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy protocols (see SCNAUSEA).
- hydrocortisone and diphenhydrAMINE for history of hypersensitivity to etoposide

TREATMENT:

- **Cycle length 21 days regardless of ANC**
- **Duration by Risk Category:**
  1. Adjuvant: 2 cycles of GUBEP (total bleomycin 180 unit)
  2. Low Risk Metastatic: 3 cycles of GUBEP (total bleomycin 270 unit), may be substituted for 4 cycles of GUEP only if contraindications for bleomycin (Cave: BEP x 3 remains the preferred regimen for good risk disease)
  3. Intermediate Risk Metastatic: 4 cycles of GUBEP (total bleomycin 360 unit)
  4. *High Risk Metastatic*: 4 cycles of GUBEP (total bleomycin 360 unit)

Agent	Dose	BC Cancer Administration Guideline	Duration	Schedule
Pre-Hydration		IV 1000 mL NS with 20 mEq potassium chloride and 2 g magnesium sulfate over 60 minutes	days 1 to 5*	every 21 days
CISplatin	20 mg/m²/day	IV in 100 mL NS over 30 minutes	days 1 to 5*	every 21 days
etoposide	100 mg/m²/day	IV in 250 to 1000 mL NS over 45 min to 1 hour 30 min (use non-DEHP equipment with 0.2 micron in-line filter)	days 1 to 5*	every 21 days
hydrocortisone	100 mg	IV	bleomycin premedication	
bleomycin	30 Units	IV in 50 mL NS over at least 10 minutes	One day	every week to above maximum
Post-Hydration		IV 500 mL NS over 30 min to 1 hour	days 1 to 5*	every 21 days
Total hydration:		IV 2150 mL NS		

*NOTE: Treatment should be given on 5 consecutive days**.

**If treatment falls on a week with a statuary holiday, treatment can be scheduled over 4 days (ONLY for an exceptional situation if no option available to give over 5 days).

Agent	Dose	BC Cancer Administration Guideline	Duration	Schedule
Pre-Hydration		IV 1000 mL NS with 20 mEq potassium chloride and 2 g magnesium sulfate over 60 minutes	days 1 to 4	every 21 days
CISplatin	25 mg/m²/day	IV in 100 to 250 mL NS over 30 minutes	days 1 to 4	every 21 days
etoposide	125 mg/m²/day	IV in 500 to 1000 mL NS over 45 min to 1 hour 30 min (use non-DEHP equipment with 0.2 micron in-line filter)	days 1 to 4	every 21 days
hydrocortisone	100 mg	IV	bleomycin premedication	
bleomycin	30 Units	IV in 50 mL NS over at least 10 minutes	One day	every week to above maximum
Post-Hydration		IV 500 mL NS over 30 min to 1 hour	days 1 to 4	every 21 days
Total hydration:		IV 2150 mL NS		

DOSE MODIFICATIONS:

- No dose reduction or delay is permitted for counts.
- This program is given with curative intent and any delay or dose reduction may have serious implications and can result in inferior outcomes. In the event of elevated creatinine (e.g. greater than 200 micromol/L), neutropenic fever or low platelets, phone consultation with a contact physician is recommended.
- Prophylactic use of filgrastim is not recommended.
- Filgrastim is indicated in patients receiving their second or subsequent cycle of GUBEP who have had an episode of neutropenic fever or who have not recovered their neutrophil count by Day 5.

PRECAUTIONS:

1. **Bleomycin**: may cause severe and life threatening pulmonary toxicity. Limiting the total dose 270 units should decrease the risk but clinical assessment before each cycle must include a careful survey of respiratory symptoms, chest auscultation, and chest radiograph for pulmonary toxicity. Pulmonary function tests should be repeated in suspect cases. Febrile reaction can be prevented by hydrocortisone premedication. Oxygen may precipitate or aggravate bleomycin pulmonary toxicity. The FI O_2 must not exceed 30-40% unless absolutely necessary. The anesthesiologist must be aware of the bleomycin history before any surgery: an alert bracelet is recommended.
2. **Hypersensitivity:** Monitor infusion of etoposide for the first 15 minutes for signs of hypotension. Hypersensitivity reactions have also been reported for CISplatin. Refer to BC Cancer Hypersensitivity Guidelines.
3. **Extravasation**: Etoposide causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.

4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Avoid aminoglycoside antibiotics.
5. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.

Call Dr. Christian Kollmannsberger or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. International germ cell consensus collaborative group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 15:564-603, 1997
2. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 1989; 7:387-91.
3. Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 1987:316:1435-40.
4. de Wit R, Roberts JT, Wilkinson P, et al. Final analysis demonstrating the equivalence of 3 BEP vs 4 cycles and the 5 day schedule vs 3 days per cycle in good prognosis germ cell cancer. An EORTC/MRC phase III study. Proc Am Soc Clin Oncol 2000;19a:326a (abstract 1281).