Appendix 3. EAU Guidelines on Testicular Cancer: Chemotherapy Protocols

1. Common Protocols and Indications

1.1 Adjuvant treatments

Carboplatin

Indication: adjuvant treatment for Seminoma stage I, single cycle. Dosing according to kidney function, using nuclear medicine glomerular filtration rate (GFR) measurement if available e.g. ^{99m}Tc-DTPA or ^{51}Cr-EDTA, NO dose capping! Check for thrombopenia!

Dosing according to Calverts formula (AUC 7): (Uncorrected GFR + 25).

Chemotherapy agent	Dosage	Duration of cycles
Carboplatin	AUC 7	Day 1

[1]

BEP – Bleomycin, Etoposide, Cisplatin

Alternative acronym: PEB

Indication: Non-Seminoma stage I, if given as adjuvant treatment: single cycle.

Prophylactic granulocyte colony stimulating factor (G-CSF) use can be considered (intermediate risk for febrile neutropenia)

Chemotherapy agent	Dosage	Duration of cycles
Bleomycin	30mg abs.	Days 1,8,15
Etoposide	100mg/m^2	Days 1-5
Cisplatin	20mg/m^2	Days 1-5

[2, 3]

1.2 First-line therapy for metastatic disease

BEP – Bleomycin, Etoposide, Cisplatin

Alternative acronym: PEB

Number of cycles: International Germ Cell Cancer Collaborative Group (IGCCCG) Good prognosis: 3, IGCCCG intermediate/poor prognosis: 4

Interval: 21 days.

Prophylactic G-CSF use can be considered (intermediate risk for febrile neutropenia)

Chemotherapy agent	Dosage	Duration of cycles
Bleomycin	30mg abs.	Days 1,8,15
Etoposide	100mg/m^2	Days 1-5
Cisplatin	20mg/m^2	Days 1-5

[4]

* A 3-day protocol can be used but caution due to toxicity.

EP –Etoposide, Cisplatin

Alternative acronym: PE

Number of cycles: IGCCCG Good prognosis: 4

Interval: 21 days.

Prophylactic G-CSF use can be considered (intermediate risk for febrile neutropenia)

Chemotherapy agent	Dosage	Duration of cycles
Etoposide Cisplatin	100mg/m^2 20mg/m^2	Days 1-5 Days 1-5

[5]

VIP – Etoposide (=VP 16), Ifosfamide, Cisplatin

Alternative acronym: PEI

Number of cycles: IGCCCG Intermediate/poor prognosis: 4

Interval: 21 days

Caution: Primary G-CSF prophylaxis recommended

Chemotherapy agent	Dosage	Duration of cycles
Etoposide/VP-16 Ifosfamide Cisplatin	75-100mg/m^2 * 1.2g/m^2 20mg/m^2	Days 1-5 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage	
G-CSF prophylaxis		Pegylated G-CSF 6 mg OR Daily GCSF approximately 5µg/kg

*75mg/m^2 is used both in first and salvage settings, however there is no agreement on the dose and a consensus statements suggest 100mg/m^2 for salvage lines [6, 7].

1.3 Salvage therapies – conventional dosing

TIP – Paclitaxel, Ifosfamide, Cisplatin

Number of cycles: 4

Interval: 21 days

Caution: Primary G-CSF prophylaxis recommended

Chemotherapy agent	Dosage	Duration of cycles
Paclitaxel Ifosfamide Cisplatin	250mg/m^2 over 24h 1.5g/m^2 25mg/m^2	Day 1 Days 2-5 Days 2-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
G-CSF prophylaxis		Pegylated G-CSF 6 mg OR

		Daily GCSF approximately 5µg/kg

[8]

VIP – Etoposide (=VP 16), Ifosfamide, Cisplatin

Alternative acronym: PEI

Number of cycles: 4

Interval: 21 days

Caution: Primary G-CSF prophylaxis recommended

Chemotherapy agent	Dosage	Duration of cycles
Etoposide/VP-16 Ifosfamide Cisplatin	75-100mg/m^2 * 1.2g/m^2 20mg/m^2	Days 1-5 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage	
G-CSF prophylaxis		Pegylated G-CSF 6 mg OR Daily GCSF approximately 5µg/kg

*75mg/m^2 is used both in first and salvage settings, however there is no agreement on the dose and a consensus statement suggest 100mg/m^2 for salvage lines [7, 9]

VeIP – Vinblastine, Ifosfamide, Cisplatin

Number of cycles:4

Interva : 21 days

Caution: Primary G-CSF prophylaxis recommended

Chemotherapy agent	Dosage	Duration of cycles
Vinblastine Ifosfamide Cisplatin	0.11 mg/kg 1.2g/m^2 20mg/m^2	Days 1 & 2 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
G-CSF prophylaxis		Pegylated GCSF 6 mg OR Daily GCSF approximately 5µg/kg

[10]

GIP – Gemcitabine, Ifosfamide, Cisplatin

Number of cycle: 4

Interval: 21 days

Caution: Primary G-CSF prophylaxis recommended

Chemotherapy agent	Dosage	Duration of cycles

Gemcitabine Ifosfamide Cisplatin	1000mg/m^2 1.2g/m^2 20mg/m^2	Days 1+5 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
G-CSF prophylaxis		

[11]

Comment on limitation: Eligibility criteria for this study included favourable prognostic factors to conventional-dose salvage chemotherapy including a testis primary tumour and a previous CR to first-line chemotherapy for metastatic disease.

1.4 Upfront dose-dense chemotherapy for IGCCCG poor prognosis non-seminoma patients

For poor prognosis non-seminoma patients with insufficient (unfavourable) tumour marker decline after cycle one of standard treatment, an upfront dose-dense regimen can be considered [5].

➔ Calculation of tumor marker decline (gustaveroussy.fr)

The first cycle BEP is given as standard. Patients with unfavourable marker decline on day 18-21 after cycle one proceed to the dose-dense protocol. Patients with favourable marker decline will receive a total of 4 cycles of BEP.

T-BEP-Oxaliplatin followed by Cisplatin, Bleomycin, Ifosfamide

Number of cycles: 2 each
Interval: 21 days
Caution: High potential for neurotoxicity

T-BEP-Oxaliplatin

Chemotherapy agent	Dosage	Duration of cycles
Paclitaxel Bleomycin Etoposide Cisplatin Oxaliplatin	175mg/m^2 over 3h 30mg abs. 100mg/m^2 20mg/m^2 130mg/m^2 over 3h	Day 1 Days 1,8,15 Days 1-5 Days 1-5 Day 10
G-CSF prophylaxis		263ug/d day daily except on treatment days

Cisplatin, Bleomycin, Ifosfamide

Chemotherapy agent	Dosage	Duration of cycles
Cisplatin Bleomycin Ifosfamide	100mg/m^2 over 2h 25 Units/day via 24h infusion 2g/m^2 over 3h	Days 1 Days 10-14 Days 10,12,14
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	0,3,7,11h after Ifosfamide on Ifosfamide days

G-CSF prophylaxis		263ug/d daily except on treatment days

[5]

High-dose VIP – Etoposide (=VP 16), Ifosfamide, Cisplatin

Cycle 1: standard dosing

Chemotherapy agent	Dosage	Duration of cycles
Etoposide Ifosfamide Cisplatin	75mg/m^2 1.2g/m^2 20mg/m^2	Days 1-5 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
G-CSF stimulation		Starting on Day 6 until adequate collection of stem cells
Stem cell harvest For one high dose cycle usually a minimum of 2x10^6 CD34+ cells/kg bodyweight should be collected		From Day 15 onwards

Cycle 2-4: high dose

Interval: 21 days, subsequent cycle of high dose given when haematological toxicity ≤ grade 1

Chemotherapy agent	Dosage	Duration of cycles
Etoposide Ifosfamide Cisplatin	300mg/m^2 2.4g/m^2 20mg/m^2	Days 1-5 Days 1-5 Days 1-5
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
Autologous stem cells	≥ 2x10^6 CD34+ cell/kg bodyweight	Day 7
G-CSF stimulation		Starting on day of stem cell transfusion

[12]

1.5 Salvage therapies – high dose therapy

For stem cell mobilisation and harvest prior to high dose, often a mobilisation chemotherapy with agents active in germ cell tumours is applied.

Mobilisation chemotherapy examples:

TI –Paclitaxel, Ifosfamide

Number of cycles: 2 when given as TI-CE
Interval: 14 days

Chemotherapy agent	Dosage	Duration of cycles
Paclitaxel Ifosfamide	200mg/m^2 2.0g/m^2	Days 1 Days 2-4
Mesna for bladder protection	Total daily mesna dosage is at least 60% of the Ifosfamide dosage, ideally 100%	
G-CSF stimulation		e.g. G-CSF 10 µg/kg subcutaneously daily beginning 6 to 24 hours after completion of Ifosfamide on day 3 until adequate CD34+ cell collection or day 15, whichever occurs first
Stem cell harvest For <u>one high dose cycle</u> usually a minimum of 2x10^6 CD34+ cells/kg bodyweight should be collected		From Day 11 onwards daily until reaching the collection goal of ≥ 8 x 10^6 CD34+ cells/kg or day 15, whichever occurs first. Minimum requirement of > 6 x 10^6 CD34+ cells/kg in total to proceed to stem cell reinfusion

[13]

<u>CE – Carboplatin, Etoposide High dose</u>

Number of cycles: 3
Interval: 21-28 days

Chemotherapy agent	Dosage	Duration of cycles
Carboplatin Etoposide	AUC 8 400mg/m^2	Days 1-3 Days 1-3
Autologous stem cells	≥ 2x10^6 CD34+ cell/kg bodyweight	Day 5
G-CSF stimulation		Starting on day of stem cell reinfusion
Alternative schedule		
Carboplatin Etoposide	500mg/m^2 500mg/m^2	Days 1-3 Days 1-3
Autologous stem cells	≥ 2x10^6 CD34+ cell/kg bodyweight	Day 5
G-CSF stimulation		Starting on day of stem cell reinfusion

[13, 14]

1.6 Palliative chemotherapy options/salvage for cisplatin-refractory patients (selected regimens)

GOP – Gemcitabine, Oxaliplatin, Paclitaxel

Number of cycles: 4-6 (if tolerated even more cycles)

Interval: 21 days

Chemotherapy agent	Dosage	Duration of cycles
Gemcitabine	800mg/m^2	Days 1,8
Oxaliplatin	130mg/m^2	Day 1
Paclitaxel	80mg/m^2	Days 1,8

[15]

GO – Gemcitabine, Oxaliplatin

Number of cycles: 6

Interval: 21 days

Chemotherapy agent	Dosage	Duration of cycles
Gemcitabine	1,000mg/m^2	Days 1,8
Oxaliplatin	130mg/m^2	Day 1

[16-18]

Oral Etoposide

Option for palliation, possibly also as maintenance/bridging

Chemotherapy agent	Dosage	Duration of cycles
Oral VP-16	50mg/m^2	21 days on, 7 days off 4 weekly cycles Alternative: 10-14 days on, 5 days off

[19]

2. Supportive therapy

Hydration:

For kidney protection hydration is required with all cisplatin-based chemotherapy regimens., e.g. with 1l of NaCl 0.9% over 1h before start of cisplatin infusion.

Antiemetics:

All multi-agent chemotherapy options used for treatment of testicular cancer must be seen as having high emetogenic potential. Antiemetic medication should therefore include steroids, 5-HT3 and NK1 receptor antagonists. Intense upfront antiemetic treatment is very important to prevent anticipatory nausea and emesis in subsequent cycles.

Option for further reading on antiemetics: https://www.annalsofoncology.org/article/S0923-7534(19)31641-2/fulltext .

G-CSF prophylaxis:
Primary prophylaxis should be used with VIP in general and with the salvage regimens TIP and GIP, as well as for the dose-dense and high-dose protocols [20].

For EP and BEP primary G-CSF prophylaxis is not generally recommended as both regimens have an intermediate risk of febrile neutropenia (10-20%). Risk of febrile neutropenia is usually highest in the first cycle of treatment. G-CSF use can therefore be considered and should be based on individual risk assessment and comorbidities of a patient. If a patient experiences febrile neutropenia during chemo, secondary G-CSF prophylaxis for subsequent cycles should be considered because dose delays and/or reductions must be avoided [5].

Management of hematotoxicity during chemotherapy:
Patients must be monitored for cytopenia during chemotherapy cycles. Treatment by well-trained GU oncologists is therefore required [20-22].

The incidence of febrile neutropenia is 5% to 7% of good-risk patients receiving EP×4 or BEP×3 [23] and 10% to 20% of intermediate- and poor-risk patients receiving BEP×4 [12, 24] .

Especially the salvage regimens can lead to threatening cytopenia, sometimes requiring transfusions of blood or platelets. Nadir of thrombocytes is often to be expected around day 15 of a cycle.

In general, treatments should be given without dose reductions and dose delays whenever possible [25]. Persistence of mild cytopenia on day 1 of a planned subsequent cycle should never result in delay of the cycle.

Cytopenia on day fifteen of BEP are common; however, Bleomycin on day fifteen should be given irrespective of neutropenia or thrombocytopenia.

Delaying a chemotherapy cycle is justified only in the presence of severe active infection/in a critically ill patient.

Bleomycin toxicity
The incidence of bleomycin-induced lung damage is associated with cumulative bleomycin dose. High-grade toxicity increases from 0%-2% for BEPx3 to 6%-18% after BEP x4, the later associated with an 1%-3% mortality [24, 26-31]. Baseline pulmonary function tests (PFTs) can be considered at baseline prior to any bleomycin-containing regimen. For patients receiving 3 BEPs, repeat PFTs ought to be considered at the end of chemotherapy. For patients receiving 4 BEPs, repeat PFTs ought to be considered after 2 or 3 cycles. In the dose-dense GETUG 13 regimen, PFTs are recommended to be repeated prior to C4 and C5. Repeat PFTs ought to be also considered at any timepoint if clinical/radiological suspicion of lung bleomycin toxicity.
Bleomycin ought to be omitted if impaired PFTs, e.g., if DLCO/Va (Kco)< 60% or if drop of vital capacity of > 10% compared to baseline [32].

An alternative non bleomycin regime should be considered in patients with impaired renal function, advanced age, significant lung disease or active smoking history [7, 30, 33]. Specific care ought to be

applied regarding pulmonary toxicity of bleomycin to patients with mediastinal tumours who will undergo mediastinal surgery [34].

Renal toxicity

Given the curative intent, although renal function ought to be taken in consideration and monitored carefully, the risk-benefit ratio in patients whose renal function is compromised owing to compression by retroperitoneal metastatic disease is in favour of administering cisplatin (at least in the first cycles) in patients even if GFR not strictly >60 ml/min, considering dose reduction, fractionation, and intravenous hydration. For patients who worsen their renal function on cisplatin while showing disease response, a switch to carboplatin ought to be considered, despite the inferior overall outcomes of carboplatin compared to cisplatin [35-39].

Ototoxicity

The cisplatin dose ought not be reduced or delayed for ototoxicity such as tinnitus, unless permanent and significantly impacting the patient's quality of life or accompanied by documented hearing loss on an audiogram. Again, the risk-benefit ratio is in favour of treating those patients [25].

Venous access devices:

Due to the high risk of thromboembolic events, the panel agrees that central venous access devices should be avoided whenever possible [40].

Thromboprophylaxis:

Retrospective studies have identified multiple risk factors for the development of thromboembolic events including increasing stage, size of retroperitoneal lymph nodes at different cut-offs, Khorana score > 3 and indwelling vascular access device (only modifiable risk factor) [40-42]. Given the apparent high VTE incidence and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men and those panel members that restricted thromboprophylaxis to men with certain risk factors.

Primary antimicrobial prophylaxis

No consensus exists regarding primary antimicrobial prophylaxis. Some centres/countries consider it as per local standard of care.

ARDS and tumour lysis syndrome

If high-volume disease in the lung (especially if cannon-ball metastases), the following is suggested:

- Consider starting treatment in an intensive care unit setting.
- Avoid bleomycin at least for C1.
- Start C1 as reduced regimen to avoid massive tumour lysis and ARDS (e.g., EP day 1 -2 or 1-3), then monitor and complete cycle after 7-10 days if good tolerance [43].
- Monitor daily for tumour lysis syndrome and treat appropriately early if suspicion.

If risk of bleeding (choriocarcinoma, brain metastases, important vascular or bronchial invasion by a tumour mass), the following is suggested:

- Start C1 as reduced regimen to avoid haemorrhage secondary to massive tumour lysis (e.g., EP Day 1 -2 or 1-3), especially if intracranial choriocarcinoma metastases. Monitor and complete cycle after 7-10 days if good tolerance.
- Avoid thromboprophylaxis especially if choriocarcinoma brain metastases.
- Monitor thrombocytopenia.
- Maintain a higher platelet transfusion threshold (e.g., 50,000 platelets) [43].

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