Systemic Anti Cancer Treatment Protocol

Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, Etoposide VDC/IE (non-compressed)

Sarcoma

PROTOCOL REF: MPHAVDCIENC
(Version No: 1.1)

Approved for use in:

Ewings sarcoma

Desmoplastic small round cell tumour

Alternative to VIDE protocol in metastatic disease

Dosage:

Schedule: this non- accelerated schedule is administered every 3 weeks **alternating VDC/VC and then IE** (see appendix 1)

VDC/IE induction-> Assessment/surgery/XRT as required -> **IE/VC consolidation**

	Induction chemotherapy					Consolidation chemotherapy									
Cycle	1	2	3	4	Surgery /XRT	5	6	7	8	9	10	11	12	13	14
Every 21 days	VDC	IE	VDC	IE		VDC	IE	VDC	IE	VDC	IE	VC	IE	VC	IE

VDC= Vincristine, Doxorubicin, Cyclophosphamide

IE = Ifosfamide, Etoposide

VC = Vincristine cyclophosphamide

VDC induction

Drug	Dosage	Route
Vincristine	1.5mg/m^2 (max 2mg)	IV
Doxorubicin	25mg/m^2 days 1, 2 and 3	IV
Cyclophosphamide + Mesna	1200mg/m^2+ 1200mg/m^2 day 1	IV
Mesna	See administration	

IE induction

Drug	Dosage	Route
Etoposide	150mg/m^2 days 1, 2 and 3	IV
Ifosfamide + Mesna	3g/m^2 +3g/m^2 days 1, 2 and 3	IV
Mesna	See administration	

Alternate VDC and IE every 21 days for 14 cycles in total – see schedule

Supportive treatments:

Anti-emetic risk – high

Dexamethasone tablets, 4mg twice daily for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Filgrastim to start on day 4 for 7 days, then repeat FBC, if neutrophils below 1.0 x 10^9/L then continue for further 7 days

Extravasation risk:

Vincristine – vesicant – follow trust /network policy, specific antidote may apply

Doxorubicin – vesicant – follow trust /network policy, specific antidote may apply

Cyclophosphamide – Non vesicant

Ifosfamide - irritant

Etoposide – irritant

Administration:

VDC

Day	Drug	Dosage	Route	Diluent and Rate
1	Ondansetron 30 minutes before chemotherapy	16mg	PO	
1	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
1	**Vincristine**	1.5mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9%
1	**Doxorubicin**	25mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing Sodium Chloride 0.9%
1	**Mesna**	500mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Cyclophophamide + Mesna**	1200mg/m^2+ 1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 3 hours
1	**Mesna**	1200mg/m^2	IV	In 1000mL sodium chloride 0.9% over 8 hours
2	Ondansetron 30 minutes before chemotherapy	16mg	PO	
2	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
2	**Doxorubicin**	25mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
3	Ondansetron 30 minutes before chemotherapy	16mg	PO	
3	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
3	**Doxorubicin**	25mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing sodium chloride 0.9%
4	Filgrastim	30MU or 48MU	SC	Subcutaneous injection daily and repeat FBC

Dexamethasone tablets, 4mg twice daily to continue for 3 days

IE

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 minutes before chemotherapy	125mg	PO	
1	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
1	Ondansetron 30 minutes before chemotherapy	16mg	PO	
1	**Etoposide**	150mg/m^2	IV	In 1000mL sodium chloride 0.9% over 2 hours
1	**Mesna**	500mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
1	**Ifosfamide + Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 8 hours
2	Aprepitant 30 minutes before chemotherapy	80mg	PO	
2	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
2	Ondansetron 30 minutes before chemotherapy	16mg	PO	
2	**Etoposide**	150mg/m^2	IV	In 1000mL sodium chloride 0.9% over 2 hours
2	**Mesna**	500mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes
2	**Ifosfamide + Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 8 hours
3	Aprepitant 30 minutes before chemotherapy	80mg	PO	
3	Dexamethasone 30 minutes before chemotherapy	8mg	PO	
3	Ondansetron 30 minutes before chemotherapy	16mg	PO	
3	**Etoposide**	150mg/m^2	IV	In 1000mL sodium chloride 0.9% over 2 hours
3	**Mesna**	500mg/m^2	IV	In 500mL sodium chloride 0.9% over 60 minutes

3	**Ifosfamide + Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
3	**Mesna**	1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 8 hours
4	Filgrastim	30MU or 48MU	SC	Subcutaneous injection daily and repeat FBC

Dexamethasone tablets, 4mg twice daily to continue for 3 days

Filgrastim dose:

For patients under 70kg: 30MU subcutaneous injection daily

For patients 70kg and above: 48MU subcutaneous injection daily

Notes:

Doxorubicin

Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2

Perform baseline MUGA if patient is considered at risk of significantly impaired cardiac contractility.

Substitute dactinomycin 1.5mg/m^2 if cardiac ejection fraction < 40%

Repeat MUGA during treatment if there is any suspicion of cardiac impairment – see toxicity management

Ifosfamide

Ensure adequate hydration and that fluids with mesna are prescribed and administered.

Record patients weight at the same time each day as well as a strict fluid balance chart.

If there is a postitive fluid balance of 2 litres or more, weight gain of > 2kg or symptoms of fluid overload give furosemide 20mg

Test urine for microscopic haematuria each cycle (see algorithm)

Observe for insidious signs of encephalopathy, initially somnolence and confusion

Main Toxicities:

Myelosuppression, alopecia, mucositis

Vincristine – neurotoxicity

Doxorubicin – cardiomyopathy, ovarian failure / infertility

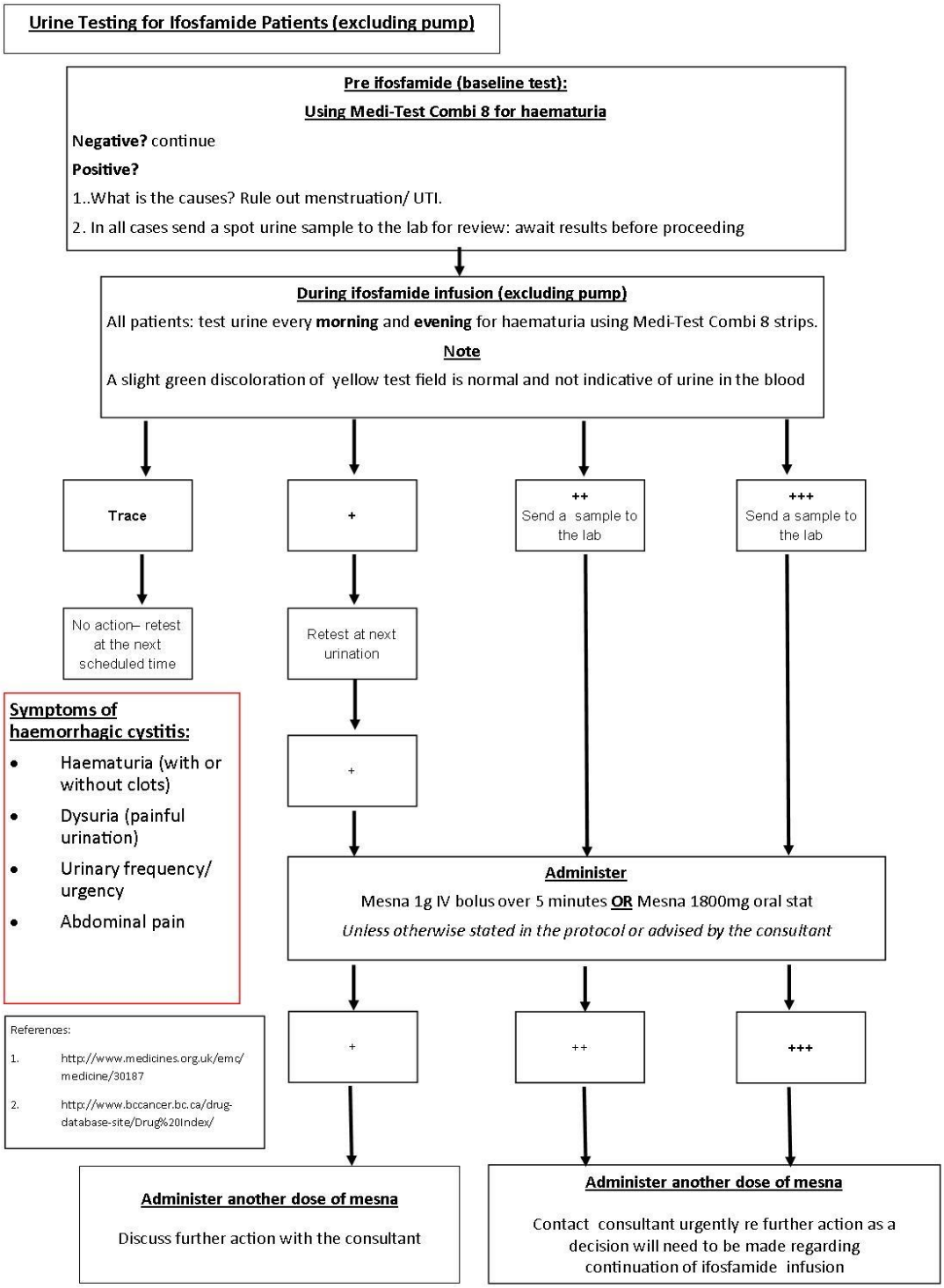
Cyclophosphamide – diarrhoea, haemorrhagic cystitis

Etoposide – nausea, vomiting, diarrhoea, allergic reactions, transient alterations in LFT

Ifosfamide – nephrotoxicity, central neurotoxicity, haemorrhagic cystitis leading to bladder fibrosis, ovarian failure

Investigations and treatment plan

	Pre	Cycle 1 VDC	Cycle 2 IE	Cycle 3 VDC	Cycle 4 IE	Ongoing / Comments
Medical Assessment	X		X	X	X	Every cycle
Nursing Assessment	X	X	X	X	X	Every cycle
MUGA/ECHO	X					If clinically indicated
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)	X	X	X	X	X	Every cycle
Ca^{2+}, Mg^{2+}, Cl^{-}, HCO_3	X	X	X	X	X	Every cycle
Urine PO_4 , creatinine, osmolarity (early morning)	X		X		X	Every ifosfamide cycle
Tp/Ccrea		X	X	X	X	Every ifosfamide cycle
CT scan	X			X		As clinically indicated
Informed Consent	X					
Blood pressure measurement	X					Repeat if clinically indicated
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle
Urine dipstick for protein / blood	X	X	X	X	X	Every cycle


Urine Testing for Ifosfamide Patients (excluding pump)
Pre ifosfamide (baseline test):
Using Medi-Test Combi 8 for haematuria
Negative? continue
Positive?
1..What is the causes? Rule out menstruation/ UTI.
2. In all cases send a spot urine sample to the lab for review: await results before proceeding
During ifosfamide infusion (excluding pump)
All patients: test urine every morning and evening for haematuria using Medi-Test Combi 8 strips.
Note
A slight green discoloration of yellow test field is normal and not indicative of urine in the blood
Trace
+
++
Send a sample to the lab
+++
Send a sample to the lab
No action– retest at the next scheduled time
Retest at next urination
+
Symptoms of haemorrhagic cystitis:
Haematuria (with or without clots)
Dysuria (painful urination)
Urinary frequency/ urgency
Abdominal pain
Administer
Mesna 1g IV bolus over 5 minutes OR Mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant
References:
1. http://www.medicines.org.uk/emc/medicine/30187
2. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/
+
++
+++
Administer another dose of mesna
Discuss further action with the consultant
Administer another dose of mesna
Contact consultant urgently re further action as a decision will need to be made regarding continuation of ifosfamide infusion

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

ANC ≥ 0.75 x 10^9/L	Platelets ≥ 75 x 10^9/L

Delay on day 1 if:-

ANC ≤ 0.74 x 10^9/L	Platelets ≤ 74 x 10^9/L

Obtain blood counts on day 7 and 14 of every cycle and on Monday, Wednesday and Friday after day 14 until the criteria for starting the next cycle are satisfied.

Toxicity	Action
If ANC and platelets have not recovered to required levels for treatment by day 22 from last chemotherapy	Consider dose reduction of doxorubicin, cyclophosphamide, ifosfamide and etoposide doses in subsequent cycles by 25%.
Further non recovery by day 22 despite dose reduction	Reduce doxorubicin, cyclophosphamide, ifosfamide and etoposide doses in subsequent cycles by a **further 25%.**
If in subsequent cycles ANC criteria is met by day 18	Increase dose by 25%
Febrile Neutropenia grade 3 or 4	VDC – reduce doxorubicin and cyclophosphamide by 25% IE – reduce etoposide by 25% VC – reduce cyclophosphamide by 25%

Note that dose and time intensity is an important strategy for induction. Ensure that filgrastim is prescribed and given. Filgrastim should be discontinued 24 hours prior to next cycle of chemotherapy.

If there is significant bone marrow toxicity reduce etoposide as shown rather than any of the other agents:

Non-haematological toxicity

Hepatic

Doxorubicin

Bilirubin (µmol/l)	Doxorubicin dose
20 - 50	50%
51 - 85	25%
>85	omit

Ifosfamide – note that ifosfamide is generally not recommended if bilirubin > ULN or ALP > 2.5 ULN – discuss with consultant if this is the case. See comments above about ifosfamide dose reductions
Vincristine – no adjustment required
Etoposide – conflicting information exists for reductions with etoposide, use table below but discuss with oncologist if in doubt

Bilirubin (µmol/L)	AST/ALT (units/l)	Etoposide Dose
26 to 51 or	60 to 180	50%
Above 51 or	Below 180	Clinical decision

Renal

Cyclophosphamide
Monitor serum creatinine before each cycle of chemotherapy. Calculate CrCl each time. Routine adjustment of cyclophosphamide is not needed as it is altered hepatically although most sources suggest

CrCl	Cyclophosphamide dose
≥10mL/min	100%
<10mL/min	75%

Ifosfamide and etoposide
Measure serum creatinine each cycle and calculate CrCl using Cockroft and Gault before each cycle of Ifosfamide.

GFR (mL/min)	Ifosfamide dose	Etoposide dose
≥ 60	100%	100%
40 to 59	70%	70%
< 40	Clinical decision	70%

Monitor renal function closely and if there is a significant rise in serum creatinine even if CrCl> 60 mL/min discuss with consultant as ifosfamide may cause delayed impairment.

Measure serum electrolytes and bicarbonate levels and calculate tubular function (Tp/Ccrea) before each cycle of ifosfamide

$$Tp/C_{creat} = \frac{PO_{4serum} - PO_{4urine} \times SrCr_{\mu mol/l}}{Creatinine_{Urine}}$$

Toxicity Grade*	GFR (ml/min/1.73 m2)	TpCreat (mmol/L)	HCO_3* (mmol/L)	Action (apply worst grade)
Grade 0/1	≥60	≥1.00	≥17.0	Continue Ifosfamide at 100% dose
Grade 2	40 to 59	0.80 to 0.99	14.0 to 16.9	Consider cyclophosphamide** 2100mg/m^2 d1 only
Grade 3 /4	≤40	≤0.80	≤14.0	Use cyclophosphamide** instead dose 2100mg/m^2 day 1 only

*Check low values of HCO_3 when patient is clinically stable to exclude e.g. infection as a cause before modifying Ifosfamide dose / treatment

****Always discuss / check with consultant to confirm before substituting Cyclophosphamide 1500mg/m^2 d1 for Ifosfamide.**

GI / mucositis

VDC

If grade 3 / 4 after VDC persisting beyond day 15 reduce doxorubicin dose by 25% in subsequent cycles.

IE

If grade 3 / 4 mucositis persists more than 21 days after start of chemotherapy reduce both ifosfamide and etoposide by 25% in subsequent cycles.

Cardiomyopathy

Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen.

If during treatment:

Cardiotoxicity	Action
Functional shortening (FS) < 28% or LVEF <40% or any decrease in absolute value ≥10 percentile points from previous	Delay chemotherapy cycle by 7 days and repeat echo
If FS has recovered to ≥ 29%	Proceed to next cycle at full dose
If FS remains < 29%	Omit doxorucicin and substitute with dactinomycin 1.25mg/m^2 on day 1 only.(max dose 2.5mg)

Neurotoxicity

Central

Observe closely for signs of encephalopathy. This may present

	insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours. If CTC grade 3 or 4 central neurotoxicity occurs (somnolence 30% of the time, disorientation / hallucination / coma or seizures on which consciousness is altered etc) **Stop Ifosfamide infusion** consider the use of methylene blue (methylonium) 50mg IV infusion as follows: 50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus Patients who have had an episode of ifosfamide enduced encephalopathy in a previous cycle should be treated as follows: Give one dose of 50mg (5ml ampoule of 1% solution) IV slow bolus 24 hours prior to ifosfamide. During ifosfamide infusion give 50mg (5ml ampoule of 1% solution) IV slow bolus every 6 hours during the infusion. If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m^2 on d1 only **Other** Vincristine and rarely etoposide may also cause neurotoxicity autonomic and/ or peripheral. Discuss with consultant if any persistent neuropathy greater than grade 1.

References:

Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2012;30(33):4148-54.

Euro Ewing 2012 Euro Ewing 2012 - International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours http://www.euroewing.eu/clinical-trials/ee2012-trial

Appendix 1: AEWS0031 trial protocol summary

Week	Regimen A_1, Surgery only	Regimen A_2, Radiation only	Regimen A_3, Surgery then Radiation	Regimen B_1, Surgery only	Regimen B_2, Radiation only	Regimen B_3, Surgery then Radiation
1	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)
2						
3				Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)
4	Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)			
5				Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)
6						
7	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)
8						
9				Cycle 5 (VDC)	Cycle 5 (VDC)	Cycle 5 (VDC)
10	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)			
11				Cycle 6 (IE)	Cycle 6 (IE)	Cycle 6 (IE)
12						
13	SURGERY	Cycle 5 (VDC) start RT	SURGERY	SURGERY	Cycle 7 (VDC) start RT	SURGERY
14						
15	Cycle 5 (VDC)		Cycle 5 (VDC) start RT	Cycle 7 (VDC)	Cycle 8 (IE)	Cycle 7 (VDC) start RT
16		Cycle 6 (IE)				
17				Cycle 8 (IE)	Cycle 9 (VC)	Cycle 8 (IE)
18	Cycle 6 (IE)		Cycle 6 (IE)			
19		Cycle 7 (VC)		Cycle 9 (VDC)	Cycle 10 (IE)	Cycle 9 (VC)
20						
21	Cycle 7 (VDC)		Cycle 7 (VC)	Cycle 10 (IE)	Cycle 11 (VC)	Cycle 10 (IE)
22		Cycle 8 (IE)				
23				Cycle 11 (VC)	Cycle 12 (IE)	Cycle 11 (VC)
24	Cycle 8 (IE)		Cycle 8 (IE)			
25		Cycle 9 (VDC)		Cycle 12 (IE)	Cycle 13 (VDC)	Cycle 12 (IE)
26						
27	Cycle 9 (VDC)		Cycle 9 (VDC)	Cycle 13 (VC)	Cycle 14 (IE)	Cycle 13 (VDC)
28		Cycle 10 (IE)				
29				Cycle 14 (IE)		Cycle 14 (IE)
30	Cycle 10 (IE)		Cycle 10 (IE)			
31		Cycle 11 (VDC)				
32						
33	Cycle 11 (VC)		Cycle 11 (VDC)			
34		Cycle 12 (IE)				
35						
36	Cycle 12 (IE)		Cycle 12 (IE)			
37		Cycle 13 (VC)				
38						
39	Cycle 13 (VC)		Cycle 13 (VC)			
40		Cycle 14 (IE)				
41						
42	Cycle 14 (IE)		Cycle 14 (IE)			
43						

IE = Ifosfamide – Etoposide - MESNA
VDC = Vincristine – Doxorubicin – Cyclophosphamide - MESNA
VC = Vincristine - Cyclophosphamide – MESNA