Pharmacist role in pediatric : What we need to concern?

Bussaba Trakarnsanga, B.Pharm, BCOP
Pharmacy department,
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Age grouping

Guidance for Industry – General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological products, Draft Guidance, US FDA, 10 November 1998.

Premature Newborns	< 38 weeks gestational age
Term Newborns	> 38 weeks gestational age
Neonate	0 – 30 days of age
Infant	1 month – 2 years
Young Child	2 – 6 years
Child	6 – 12 years
Adolescent	12 – 18 years

Pediatrics VS Adults

Orkin S.H. et al. Oncology of infancy and childhood 1st ed. Chapter 6 Chemotherapy in the pediatric patient. Saunders Elsevier

Gastric emptying time variations – drug absorption
Gastric pH – drug absorption
Drug vs milk interaction – drug absorption
Extracellular fluid volume – drug peak concentration
Incomplete organ function – drug elimination

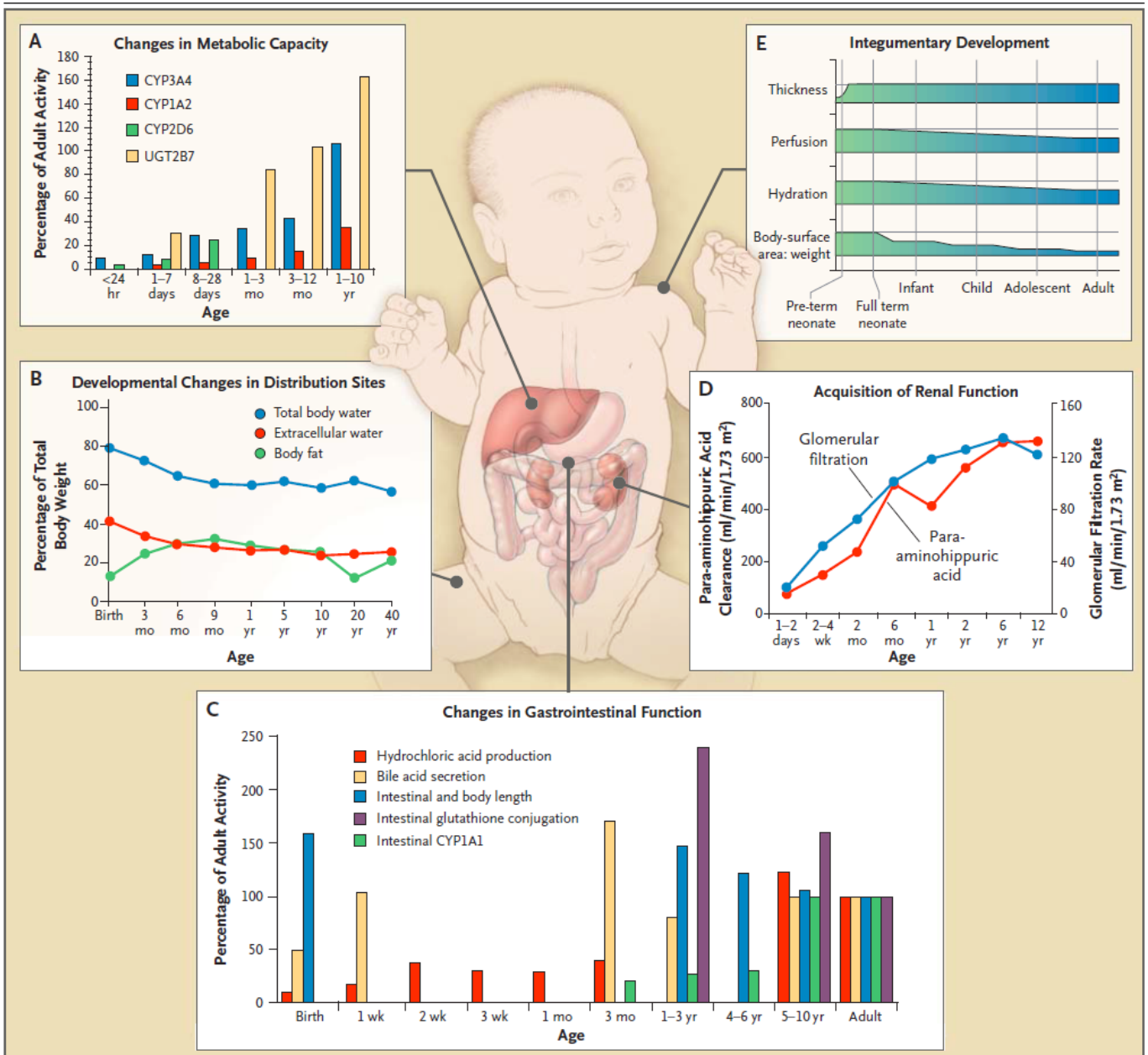

Figure 1. Developmental Changes in Physiologic Factors That Influence Drug Disposition in Infants, Children, and Adolescents.

N Engl J Med 2003;349:1157-67

Patient characteristics affecting anticancer drug pharmacokinetics in children

Orkin S.H. et al. Oncology of infancy and childhood 1st ed. Chapter 6 Chemotherapy in the pediatric patient. Saunders Elsevier

Parameter	Anticancer Drug
Renal function	Bleomycin, Carboplatin, Cisplatin, Cyclophosphamide, Etoposide, Methotrexate, Topotecan
Hepatic function	Doxorubicin, Epirubicin, Vinblastine, Vincristine
Serum albumin	Etoposide
Third space	Methotrexate
Obestity	Cyclophosphamide, Doxorubicin, 6-Mercaptopurine, Methotrexate
Cancer cachexia	5-Fluorouracil, Methotrexate

Oncology Pharmacist role ?

CouncilonCredentialinginPharmacy,AlbaneseNP,RouseMJ.Scopeofcontemporarypharmacypractice:roles,responsibilities,andfunctionsofpharmacistsandpharmacytechnicians.JAmPharmAssoc(2003).2010;50:e35-e69.

- Selection
- Prescribing, Dosing, Transcribing
- Procurement
- Storage
- Preparation
- Administration
- Monitoring, Evaluation, Counseling

Prescribing, Dosing, Transcribing

Jacobson JO, et al. American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards. OncolNursForum. 2009 Nov;36(6):651-8.

Prescribing – THAI POG

Check timing of treatment and dosage schedule

แนวทางการรักษาโรคมะเร็งในเด็ก

พ.ศ. 2561

National protocol for the treatment of childhood cancers 2018

ชมรมโรคมะเร็งเด็กแห่งประเทศไทย

(The Thai Pediatric Oncology Group: ThaiPOG)

สมาคมโลหิตวิทยาแห่งประเทศไทย

(The Thai Society of Hematology)

สำนักงานหลักประกันสุขภาพแห่งชาติ (สปสช.)

(National Health Security Office: NHSO)

ThaiPOG Thai Pediatric Oncology Group ชมรมโรคมะเร็งเด็ก

Page 2 of 7

Patient's name _____ Age _____ Sex _____

Hospital _____ HN _____ BW _____ Ht _____ BSA _____

Phase I: SR-INDUCTION (5 weeks) Date start: _____

Week / Day	1 / 1	2 / 8	3 / 15	4 / 22	5 / 29	6 / 36
Date due						
Date given						
Medication:						
VCR _____ mg IV	V	V	V	V		
PRED _____ mg po BID						
L-ASP _____ IU IM	A/A	A/A/A/A				
IT-MTX _____ mg	T	T	(T*)		T	
Investigation:						
CBC/diff	+	+	+	+	+	
CSF cell count/ cytospin	+	+	(+)		+	
BUN, Cr, TB,DB, AST, ALT	+				+	
BM Aspiration					+	
Biopsy and MRD (optional)					+	
ECHOor MUGA and EKG (optional)					+	

Begin Consolidation on Day 36 or when CBC parameter was met (whichever occurs later). Patient with M2 and M3 marrow on day 29 should begin Consolidation therapy irrespective of hematologic values as soon as Day 29 marrow results are known except patient have active infection or life threatening organ dysfunctions.

Drug	*Dosage*		*Days*
Vincristine (VCR)	1.5 mg/m^2/dose IV push over 1 min (Max 2 mg)		Day 1, 8, 15, 22
Prednisolone (PRED)	30 mg/m^2/dose PO BID (No max dose)		Day 1-28
L-Asparaginase (L-ASP)	10,000 IU/m^2/dose IM		Day 4, 6, 8, 10, 12,14
Intrathecal Methotrexate (IT MTX)	Age (yrs)	Dose	Day 1,8, 29 *Day 15 only for traumatic tap.
	1-1.99	8 mg	
	2-2.99	10 mg	
	3-8.99	12 mg	
	≥9 (but <30 kg)	12 mg	
	≥9	15 mg	

Note:

- Methylprednisolone IV can be use in patient who can't tolerate PO prednisolone at the dose of 24 mg/m^2/dose IV Q 12 H
- Trimetroprim-Sulfamethoxazole 150/750 mg/m^2/day (Max 320 mg) po bid 3 consective days/week as soon as possible
- Consider hydration post L-asparaginase (optional)

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Guideline for administration of HDMTX 12 gm/m^2(Osteosarcoma)

- Hold Bactrim, NSAID, penicillin, PPI or aspirin containing medication on the day of IV MTX infusion and for at least 72 hours after start MTX infusion

- **Hours -6 to 0 :** 5% D/N/_____ ..... ml
  + 7.5% $NaHCO_3$ ..... ml (40–60 mEq/L)
  + KCl ..... ml (10 mEq/L)
  IV drip .....ml/hr (200 ml/m^2/hr)

  Titrate $NaHCO_3$ to keep urine pH ≥7, start HDMTX when urine Sp gr<1.010

- **Hours 0-4 :** MTX ..... mg (12 gm/m^2, max 20 gm)
  in5% D/N/_____ ..... ml (500 ml/m^2)
  + 7.5% $NaHCO_3$ ..... ml (40 mEq/L)
  IV drip .....ml/hr (125 ml/m^2/hr) (Total drip in 4 hr)

- **Hours 4-72 :** 5% D/N/_____ ..... ml
  + 7.5% $NaHCO_3$ ..... ml (40 mEq/L)
  + KCl ..... ml (10 mEq/L)
  IV drip .....ml/hr (125 ml/m^2/hr)

  $NaHCO_3$ can be titrated to keep urine pH ≥7 for the whole period until MTX is cleared

- **Hours 24:** Start Leucovorin 15 mg/m^2 PO/IV q 6 hr **(at least 8 doses)**. Continue LCV until serum **MTX is < 0.1 µM** or until delayed excretion criteria is reached.

- **Consider 5%D/N/5 in children less than 30 kg (BSA 1 m^2), and 5%D/N/2 in children over 30 kg (BSA >1 m^2)**

**** Maximum dose of leucovorin = 1,500 mg/dose***

Review medical history for potential interactions and allergies

Check appropriateness of pharmacological treatment order

Prescribing, Dosing, Transcribing

Jacobson JO, et al. American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards. OncolNursForum. 2009 Nov;36(6):651-8.

Dosing - BSA

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Ann Med Health Sci Res. 2014 Nov-Dec; 4(6): 889–898. PMCID: PMC4250987
doi: 10.4103/2141-9248.144907 PMID: 25506482

Evaluation of Five Formulae for Estimating Body Surface Area of Nigerian Children

AE Orimadegun and AO Omisanjo[1]

Results:

The study participants comprised of 1229 males and 1246 females with mean (standard deviation) ages of 6.3 (3.0) years and 6.6 (3.1) years respectively (P = 0.01). Reference values for BSA estimates by gender were proposed each age group. Furthermore, BSA estimates from Boyd's and Mosteller's formulae were most similar to the mean-BSA with mathematically perfect correlations. The degree of deviation of BSA estimates from DuBois was largest with a remarkable increase at ages <6 years.

Conclusion:

Formulae by Boyd and Mosteller are the best BSA estimate for Nigerian children among the existing formulae.

Table 2.

Autors	BSA (KVL) formula
Boyd[7]	$BSA\ (m^2) = Wt(kg)^{0.4838} * Ht(cm)^{0.3} * 0.017827$
Gehan and George	$BSA\ (m^2) = Wt(kg)^{0.51456} * Ht(cm)^{0.42246} * 0.02350$
Mosteller	$BSA\ (m^2) = [\ Ht(cm) * Wt(kg) / 3600\ ]^{½}$ vai $BSA\ (m^2) = [\ Ht(in) * Wt(lbs) / 3131\ ]^{½}$
Haycock	$BSA\ (m^2) = Wt(kg)^{0.5378} * Ht(cm)^{0.3964} * 0.024265$
Du Bois and Du Bois	$BSA\ (m^2) = Wt(kg)^{0.425} * Ht(cm)^{0.725} * 0.007184$

British Journal of Cancer (2001) **85**(1), 23–28

doi: 10.1054/ bjoc.2001.1859, available online at http://www.idealibrary.com on IDEAL®

http://www.bjcancer.com

Body surface area estimation in children using weight alone: application in paediatric oncology

I Sharkey[1], AV Boddy[2], H Wallace[3], J Mycroft[4], R Hollis[5] and S Picton[5]
on behalf of the Chemotherapy Standardisation group of the United Kingdom Children's Cancer Study Group

Infants and young children, BSA can greatly overestimates the dose needed to achieve a desired AUC, whereas BW may be a more accurate predictor of drug exposure.

Appendix Guidelines for dose adjustments in children less than 10 kg or less than 12 months of age

Caution

- For children less than 10 kg body-weight, dosing by body surface area represents a change in usual clinical practice: This will result in an **increase** in calculated dose.
- The implications of this change, in clinical practice, are not known in terms of drug toxicity.
- Recommendations:

Starting doses: For infants **less than 6 months** of age:
50% of calculated dose by body surface area.
For infants **6 months to 1 year** of age:
75% of calculated dose by body surface area.
For infants **over 1 year** of age:
100% of calculated dose by body surface area.

- These doses may be adjusted according to clinical circumstances.
- Individual investigators (and protocols) should have **clear** recommendations for dosing in infants, and should monitor both disease response and toxicity closely in order to identify any clinical problems related to change in chemotherapy doses.

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Treatment protocol for Ewing sarcoma [ThaiPOG-EWS-13SR]

Protocol name ThaiPOG-EWS-13SR
Protocol for Localized and metastasis EWS
Reference Womer RB, West DC, Krailo MD, et al. J Clin Oncol 2012;30:4148-54.
Open Date January 2014 (revised October 2015)

Patient eligibility ☐ localized EWS ☐ metastatic EWS

Patient's name..... Sex..... HN.....
Age (yy/mm)..... BW..... kg. Ht.....cm BSA.....m^2

Regimen	Given Dose	Drug	Desired dose	Day
VDC regimen	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Doxorubicin (Doxo)	37.5 mg/m^2/day IV slowly push	1,2
	_____mg	Cyclophosphamine (CTX)*	1,200 mg/m^2 IV drip in 1 hr	1
	_____mg	Mesna	300 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of CTX	1
VC regimen	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Cyclophosphamine (CTX)*	1,200 mg/m^2 IV drip in 1 hr	1
	_____mg	Mesna	300 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of CTX	1
IE regimen	_____mg	Ifosfamide*	1,800 mg/m^2/day IV drip in 1 hr	1-5
	_____mg	Etoposide	100 mg/m^2/day IV drip in 1-2 hr	1-5
	_____mg	Mesna	450 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of ifosfamide	1-5

* see hydration guideline for cyclophosphamine and ifosfamide.

☐ *Give chemotherapy q 2 weeks when ANC > 750 and platelet > 75,000, and after 24 hours of the last G-CSF dose*
☐ *Blood for LFT, BUN, Cr or before each course*
☐ *If BW < 12 kg, calculate chemotherapeutic agent dose per kg [(desired dose/ 30) xBW]*
☐ *Start G-CSF 5 µg/kg daily at 24-36 hours after completion of each cycle of chemotherapy, and continue G-CSF until ANC >750 for 2 consecutive days.*
☐ *Total cumulative dose of Doxorubicin is 375 mg/m^2, consult cardiologist at END of protocol for evaluation cardiac function*
☐ *Give appropriate anti-emetics drugs.*

Radiation: start at week 14

"Rule of 30"

Adjust a dose from mg/m^2 to mg/kg

Pt with BSA of 1 m^2 weighs approximately 30 kg

The rule of 30 is applied for children <12 kg preventing for overestimated BSA-based dosing problem

Prescribing, Dosing, Transcribing

Dosing – Renal function assessment

Adult → Cockcroft-Gault equation
Pt<18 years old → Schwartz method

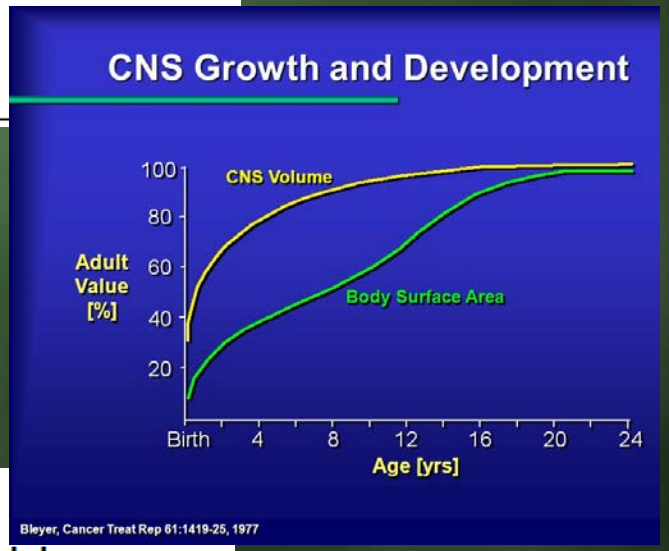
$$CrCl\ (ml/min/1.73m^2) = (k) \times (height\ in\ cm) / Scr$$

k = 0.33 for low birth weight infants during the first year of life
0.45 for infants during the first year of life
0.413 for children and adolescent girls
0.70 for adolescent boys

Most common chemotherapeutics to cause renal dysfunction in pediatric patients : Cisplatin, Carboplatin, Methotrexate

Drug	Dosage		Days
Vincristine (VCR)	1.5 mg/m^2/dose IV push over 1 min (Max 2 mg)		Day 1, 8, 15, 22
Prednisolone (PRED)	30 mg/m^2/dose PO BID (No max dose)		Day 1-28
L-Asparaginase (L-ASP)	10,000 IU/m^2/dose IM		Day 4, 6, 8, 10, 12,14
Intrathecal Methotrexate (IT MTX)	Age (yrs)	Dose	Day 1,8, 29 *Day 15 only for traumatic tap.
	1-1.99	8 mg	
	2-2.99	10 mg	
	3-8.99	12 mg	
	≥9 (but <30 kg)	12 mg	
	≥9	15 mg	

Dosing – intrathecal



Cancer Treat Rep. 1977 Nov;61(8):1419-25.

Clinical pharmacology of intrathecal methotrexate. II. An improved dosage regimen derived from age-related pharmacokinetics.

Bleyer AW.

Abstract

Cerebrospinal fluid (CSF)-antifolate concentration was analyzed in 100 specimens from 47 patients treated with intrathecal methotrexate (MTX) (12 mg/m2 of body surface area [BSA]). The drug concentrations varied 100-fold, with high levels associated with neurotoxicity and low levels with a poor response to therapy. CSF-MTX concentration was correlated directly with patient age, suggesting that a constant dose, regardless of age or BSA, should provide more consistent CSF-drug concentrations. In a subsequent study 25 patients treated with a conventional-dose schedule of 12 mg/m2 of BSA were compared with a matched group of 24 patients administered a constant dose of 12 mg. There was significantly less variability of drug levels in the CSF with the constant-dose method than with the dosage derived from BSA. It is recommended that patients between 3 and 40 years of age receive the same intrathecal dose rather than varying doses adjusted for patient BSA.

Dosing – carboplatin

Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin Oncol.1996;14:2590-2611

Calvert AH. Et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol.1989;7:1748-1756

Carboplatin have large interpatient PK variability

Carboplatin excrete almost entirely unchanged in the urine, GFR alone can predict drug exposure more accurately than body size can.

Pediatr Blood Cancer 2010;55:47–54

Comparison of Two Methods for Carboplatin Dosing in Children With Retinoblastoma

Steven Allen, BS,[1] Matthew W. Wilson, MD,[2,3] Amy Watkins, MS,[4] Catherine Billups, MS,[4] Ibrahim Qaddoumi, MD,[1,5] Barrett H. Haik, MD,[2,3] and Carlos Rodriguez-Galindo, MD[1,5]*

Background. Carboplatin is the most effective drug in retinoblastoma but systemic clearance is variable in young patients. While most regimens use a flat dose, individualized targeting may provide a more adjusted systemic exposure. ***Patients and Methods.*** We compared carboplatin doses between two groups of children with retinoblastoma that were treated using a flat dose of 560 mg/m^2 or a targeted AUC of 6.5 using a modified Calvert formula. ***Results.*** Ninety-eight patients with retinoblastoma received a total of 576 cycles of carboplatin (median 8 cycles). Fifty patients (51%) received a fixed dose per m^2, 32 (33%) received a dose based on AUC, 1 patient received fixed dose per kilogram, and in 15 patients a combination AUC and fixed doses was used. The median cumulative carboplatin dose (mg/m^2) for patients who received eight cycles using fixed per m^2 dosing was 2151.8 (range, 1414.2–2852.0), compared to 1104.1 for nine patients who received eight cycles using Calvert dosing (range, 779.0–1992.7) ($P < 0.001$). For cycles given using AUC, the median percentage of the hypothetical fixed per m^2 dose was 70% (range, 48–134%). Younger patients had larger differences. Patients receiving carboplatin based on fixed per m^2 dosing were 3.0 times more likely to have a platelet transfusion (95% confidence interval, 1.3–7.3). ***Conclusions.*** Carboplatin administration needs to consider the changes in renal function occurring during the first months of life. The use of a targeted AUC provides the most accurate method; however, mg per kg of body weight dosing is a very reliable alternative method. Pediatr Blood Cancer 2010;55:47–54.

Key words: carboplatin; glomerular filtration rate; retinoblastoma

ThaiPOG Thai Pediatric Oncology Group
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Treatment protocol for retinoblastoma [ThaiPOG-RB-1301]

Protocol name ThaiPOG-RB-1301

Protocol for Retinoblastoma ICRB group B, C orPost enucleation with high risk features

Reference Orkin SH,et al. Oncology of Infancy and Childhood, 1st ed, 2009. P 576-601.
Lanzkowsky P. Manual of Ped Hematology and Oncology, 5th ed, 2011. P.759-775.

Open Date January 2014 (revised October 2015)

Patient's name..... Sex..... HN.....

Age (yy/mm)..... BW..... kg. Ht.....cm BSA.....m^2

Inclusion criteria

☐ Retinoblastoma ICRB group B ☐ Retinoblastoma ICRB group C

☐ Retinoblastoma post enucleation with high risk features

☐ Anterior chamber seeding ☐ Optic nerve tumor, but not to surgical margin

☐ Choroidal involvement ☐ Scleral and extrascleral extension

Given dose	Drug	Dosage	Day
_____mg	Vincristine	0.05 mg/kg or 1.5 mg/m^2/day IV slowly push(max 2 mg)	1
_____mg	Carboplatin	18.7 mg/kg or 560 mg/m^2/day IV drip in 15-30 min	1
_____mg	Etoposide	5 mg/kg or 150 mg/m^2/day IV drip in 60 min	1, 2

In patient BW <12 kg, use doses per kg

- Give chemotherapy every 28 days for total 6 courses
- G-CSF 5 mcg/kg SC daily should be considered if experienced significant neutropenia in previous course (to be started 24-36 hours from last dose of chemotherapy, until ANC > 1,000/mm^3 x 2 days)
- Criteria for starting chemotherapy:
  - Absolute neutrophil count >1,000/mm^3
  - Platelet count >100,000/mm^3
  - ALT <10 × the upper limit of normal
  - Normal glomerular filtration rate
- Record BP q 15 min during etoposide infusion
- Fundoscopic examination by ophthalmologist before each cycle
- Hearing exam before starting chemotherapy, at cycle 3 or 4 and end of treatment (Optional)
- Consider enucleation or EBRT if patient does not fully respond to chemotherapy

6-MP

Guideline for dose-modification of oral MTX and 6-MP in maintenance phase

Keep ANC between 500 -1,500

Leukopenia-targeted dosing

- For low blood count:
  - ANC <500 or Platelet<50,000: Hold 6-MP and MTX until recovery
    - For first episode of ANC <500 or Platelet<50,000; resume medication at same dose when ANC >500 and Platelet>50,000
    - For second episode of ANC <500 or Platelet<50,000;
      - Resume med at 50% dose when ANC >750 and Platelet>75,000 (consider changing bactrim to dapsone)
      - Increase 6-MP and MTX to 75% and 100% at 4 week interval providedANC >750 and Platelet>75,000
  - Prolonged cytopenia defined as ANC <500 and/or Platelet <50,000 more than 4 weeks
    - Consider BM evaluation to rule out relapse
    - TPMT status evaluation in severe and unexpected myelosupression
      - Prolonged cytopenia after rule out relapse
      - Don't tolerate 50% dose of 6-MP and MTX
- For persistent ANC ≥1,500
  - ANC ≥1,500 for 2 consecutive months; alternate increase dose of MTX or 6-MP by 25%
  - If both MTX and MP are increased once without fall in ANC consider non-compliance
    - Check TPMT status
      - Heterozygous or homozygous deficiency: consider increase MTX by 25% in 4 weeks interval
      - Homozygous wild type (no mutation): consider increase 6-MP alternate with MTX by 25% in 4 weeks interval
- 6-MP dosing base on TPMT status
  - Homozygous wild type (no mutation): full dose
  - Heterozygous: start 50-75% of actual dose
  - Homozygous deficiency: start 10-20% of actual dose

Circadian rhythm-based dosing

Lancet. 1985 Dec 7;2(8467):1264-6.

Maintenance chemotherapy for childhood acute lymphoblastic leukaemia: better in the evening.

Rivard GE, Infante-Rivard C, Hoyoux C, Champagne J.

Abstract

The course of 118 children with acute lymphoblastic leukaemia who had achieved complete remission with a standard induction protocol and had also received meningeal prophylaxis with intrathecal methotrexate (MTX) and cranial irradiation was reviewed. Maintenance chemotherapy consisted of daily 6-mercaptopurine (6-MP), weekly MTX, and monthly vincristine and prednisone. 82 children took 6-MP and MTX in the morning and 36 in the evening. Disease-free survival as determined by Kaplan-Meier analysis was better for children on evening chemotherapy. Regression analysis (Cox proportional hazards model, with evening vs morning schedule as exposure variable, and age at diagnosis, leucocytosis at diagnosis, and sex as covariates) showed that, for those surviving free of disease for longer than 78 weeks, the risk of relapsing was 4.6 times greater for the morning schedule than for the evening one.

PMID: 2866334 DOI: 10.1016/s0140-6736(85)91551-x

Drug summary from THAI-POG

L-asparaginase

- Allergy:
  - Local allergic reactions (inflammation at injection site, swelling, transient flushing or rash, drug fever <38°C): continue asparaginase administration.
  - Systemic allergic reactions: discontinue asparaginase administration.
  - Anaphylaxis (symptomatic bronchospasm with or without urticaria, allergy related angioedema, hypotension, parenteral intervention indicated): discontinue future asparaginase therapy. Suplement L-ASP with Erwinia ASP or escalate treatment to higher risk regimen without asparaginase and consider HSCT with matched sibling.

ERWINASE® - Erwinia asparaginase leaflet

Shorter half-life than E.coli ASP

Dose : Substitution for native E. coli asparaginase: 25,000 IU/m² IM/IV for each scheduled dose

Reconstitution : add 1 ml or 0.9% NS/10,000 U vial
(IM volumn<2 ml each site)

Stability : 8 hr

Drug summary from THAI-POG

MTX

Hold bactrim, NSAID, penicillins, PPI or aspirin containing medication on the day of IV MTX infusion and for at least 72 hours after start MTX infusion.

- Doses of leucovorin >25 mg PO should be given IV due to saturation of absorption. Leucovorin contain calcium and should not be given at the rate faster than 160 mg per minute.
- During MTX administration maintain urine pH 7-8 at all times.

$NaHCO_3$ can be titrated to keep urine pH ≥7 for the whole period until MTX is cleared

- **Hours 42:** Start Leucovorin 15 mg/m^2 PO/IV q 6 hr **(at least 6 doses).** Continue LCV until serum **MTX is <0.1 µM** or until delayed excretion criteria is reached.
- **Consider 5%D/N/5 in children less than 30 kg (BSA 1 m^2), and 5%D/N/2 in children over 30 kg (BSA >1 m^2)**

Methotrexate / Penicillins

Risk Rating

C: Monitor therapy

Summary

Penicillins may increase the serum concentration of Methotrexate.

Severity Moderate

Reliability Fair

The mechanism of this interaction is uncertain. There is some in vitro evidence that penicillins could compete with methotrexate for excretion sites in the renal tubules.[9] This could in turn reduce methotrexate elimination and increase the likelihood of significant toxicity. The significance of this interaction is expected to increase with increasing doses of penicillin or methotrexate.

Methotrexate / Trimethoprim

Risk Rating

D: Consider therapy modification

Summary

Trimethoprim may enhance the adverse/toxic effect of Methotrexate.

Severity Major

Reliability Good

The mechanism of the interaction is unclear. TMP-SMX may increase the concentration of free (unbound) methotrexate by approximately 30% and reduce its excretion by approximately one-half.[16] However, one study failed to demonstrate any pharmacokinetic interaction.[17] Both TMP-SMX and methotrexate can contribute to folate deficiency (via suppression of dihydrofolate reductase) which might affect bone marrow activity. Whether the presumed interaction is due to a single component of TMP-SMX or the combination is unclear.

Methotrexate / Proton Pump Inhibitors

Dependencies

- **Dose**: The clinical significance of this interaction may be lower with the typically lower antirheumatic methotrexate doses.

Risk Rating

C: Monitor therapy

Summary

Proton Pump Inhibitors may increase the serum concentration of Methotrexate.

Severity Moderate

The mechanism for this possible interaction is uncertain, but possible mechanisms have been proposed. Methotrexate is actively secreted in the distal renal tubules with hydrogen ions produced via the hydrogen/potassium ATPase pump. Proton pump inhibitors, by inhibiting renal elimination of the hydrogen ion, may inhibit methotrexate elimination. Other data from in vitro and animal studies support at least some role for PPI-mediated inhibition of the breast cancer resistance protein (BCRP, ABCG2) and/or MRP2 transporters.[9,16]

Lexicomp – interact

Doxorubicin

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Treatment protocol for Ewing sarcoma [ThaiPOG-EWS-13SR]

Protocol name ThaiPOG-EWS-13SR
Protocol for Localized and metastasis EWS
Reference Womer RB, West DC, Krailo MD, et al. J Clin Oncol 2012;30:4148-54.
Open Date January 2014 (revised October 2015)

Patient eligibility ☐ localized EWS ☐ metastatic EWS

Patient's name..... Sex..... HN.....
Age (yy/mm)..... BW..... kg. Ht.....cm BSA.....m^2

Regimen	Given Dose	Drug	Desired dose	Day
VDC regimen	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Doxorubicin (Doxo)	37.5 mg/m^2/day IV slowly push	1,2
	_____mg	Cyclophosphamine (CTX)*	1,200 mg/m^2 IV drip in 1 hr	1
	_____mg	Mesna	300 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of CTX	1
VC regimen	_____mg	Vincristine (VCR)	2 mg/m^2 IV push (max dose 2 mg)	1
	_____mg	Cyclophosphamine (CTX)*	1,200 mg/m^2 IV drip in 1 hr	1
	_____mg	Mesna	300 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of CTX	1
IE regimen	_____mg	Ifosfamide*	1,800 mg/m^2/day IV drip in 1 hr	1-5
	_____mg	Etoposide	100 mg/m^2/day IV drip in 1-2 hr	1-5
	_____mg	Mesna	450 mg/m^2/dose IV drip in 15 min at hr 0, 3, 6, 9 of ifosfamide	1-5

* see hydration guideline for cyclophosphamine and ifosfamide.

☐ *Give chemotherapy q 2 weeks when ANC > 750 and platelet > 75,000, and after 24 hours of the last G-CSF dose*
☐ *Blood for LFT, BUN, Cr or before each course*
☐ *If BW < 12 kg, calculate chemotherapeutic agent dose per kg [(desired dose/ 30) xBW]*
☐ *Start G-CSF 5 µg/kg daily at 24-36 hours after completion of each cycle of chemotherapy, and continue G-CSF until ANC >750 for 2 consecutive days.*
☐ *Total cumulative dose of Doxorubicin is 375 mg/m^2, consult cardiologist at END of protocol for evaluation cardiac function*
☐ *Give appropriate anti-emetics drugs.*

Radiation: start at week 14

Total cumulative dose of doxorubicin is 375 mg/m^2

Preparation

Strict volumn? - 24-hour maintenance water

Holliday-Segar method

BW (kg)	Volumn per day
0-10	100 ml/kg
11-20	1000 ml + 50 ml/kg for each 1 kg>10 kg
>20	1500 ml + 20 ml/kg for each 1 kg>20 kg (max 2400 ml/day)
>30	1600 ml/m^2/day

Rate 125 ml/m^2/hr

Diluent - hypernatremia prophylaxis

Age < 2 months D5N/5

Age 2-12 months D5N/4

Age >12 months D5N/3

Age >5 years D5N/2

Administration

Cannot swallow

- cutting, crushing tablets or capsules
- rounding each dose to the nearest tablet or capsule
- alternating dose to attain the weekly cumulative dose
- compounding an extemporaneous solution from oral tablet or capsule (safe handling of hazardous drugs)

REVIEWS OF THERAPEUTICS

Extemporaneous Compounding of Oral Liquid Dosage Formulations and Alternative Drug Delivery Methods for Anticancer Drugs

Masha S. H. Lam, Pharm.D.

Key Words: extemporaneous, compounding, stability, bioavailability, chemotherapy, oral anticancer drugs.
(Pharmacotherapy 2011;31(2):164–192)

Administration

Drug-milk interaction

J Oncol Pharm Practice (2007) 13: 237–240

CASE REPORT

Interaction between mercaptopurine and milk

Mário L de Lemos, PharmD MSc (Oncol)

Linda Hamata, BSc (Pharm)

Sarah Jennings, BSc (Biomed), BSc (Pharm)

Tanya Leduc, BSP

Mercaptopurine is a purine analog used for acute lymphoblatic leukemia and chronic myelogenous leukemias. Since it is inactivated by xanthine oxidase (XO), concurrent intake of substances containing XO may potentially reduce bioavailability of mercaptopurine. Cow's milk is known to contain a high level of XO. In vitro and in vivo data suggest that concurrent intake of cow's milk may reduce the bioavailability of mercaptopurine. This interaction may be clinically significant. Therefore most patients should try to separate the timing of taking mercaptopurine and drinking milk. *J Oncol Pharm Practice (2007) 13: 237–240.*

Key words: mercaptopurine; milk; drug interaction; xanthine oxidase

Administration

Drug-milk interaction

THE LANCET, NOVEMBER 1, 1980

CAN FOOD INFLUENCE THE ABSORPTION OF METHOTREXATE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKÆMIA?

C. R. PINKERTON
J. F. T. GLASGOW
S. G. WELSHMAN
J. M. BRIDGES

Royal Belfast Hospital for Sick Children, Departments of Hæmatology and Child Health, Queen's University, and Department of Clinical Chemistry, Belfast City Hospital, Belfast

Summary Serum levels of methotrexate (MTX) were measured in 10 children with acute lymphoblastic leukæmia over a 4 hour period after oral administration. The drug was given to each child on three occasions: first, with no food, then with a milky meal, and finally with a citrus meal. Peak serum MTX levels were significantly reduced by the milky meal and both meals delayed drug absorption in most children. The area under the absorption curve was also significantly reduced by the milky meal. Thus, for maximum serum levels, MTX should not be given with food, and if patients are to be grouped on the basis of their MTX absorption profile this should be determined under standard conditions in relation to meals.

Supportive Treatment in pediatric "Nausea/Vomiting"

Antiemetic protection

Antiemetic should be given as needed. The routine use of steroids should be avoided.

POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO

COLLABORATING FOR KIDS WITH CANCER SINCE 1983

Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

POGO 2017

Received: 12 December 2016 | Revised: 18 February 2017 | Accepted: 23 February 2017

DOI: 10.1002/pbc.26542

CLINICAL PRACTICE GUIDELINE

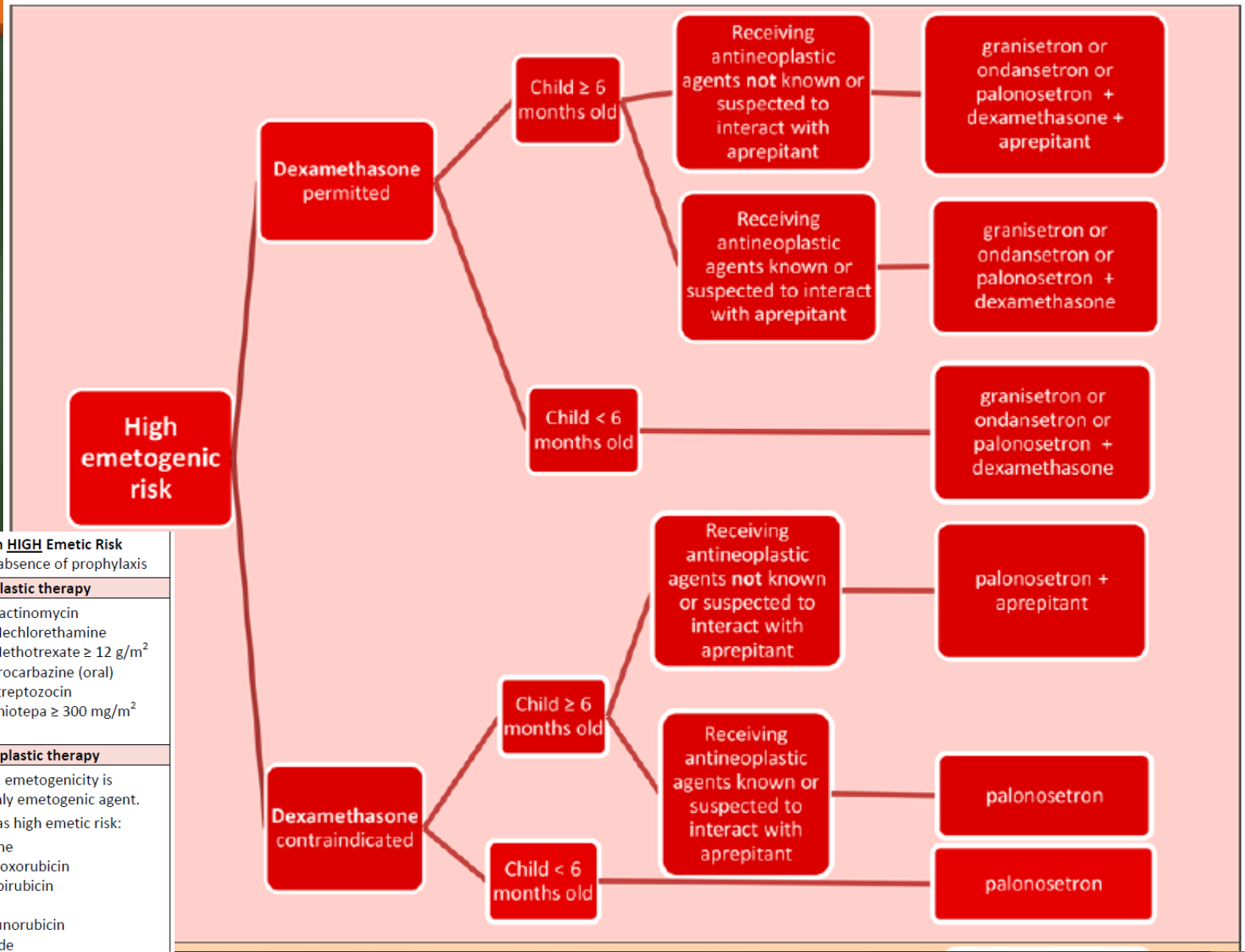
WILEY Pediatric Blood & Cancer

Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update

Priya Patel[1,2] | Paula D. Robinson[3] | Jennifer Thackray[4] | Jacqueline Flank[1] | Mark T. Holdsworth[5] | Paul Gibson[6] | Andrea Orsey[7,8] | Carol Portwine[9] | Jason Freedman[10,11] | Jennifer R. Madden[12] | Robert Phillips[13,14] | Lillian Sung[15,16] | L. Lee Dupuis[1,2,16]

Major updates from 2013 guideline

- Recommend aprepitant for children ≥ 6 months receiving HEC
- Inclusion of palonosetron as alternate 5HT-3 antagonist
- Deletion of nabilone/metochlorpramide /chlorpromazine for prevention of CINV



Antineoplastic Agents with HIGH Emetic Risk
> 90% frequency of emesis in absence of prophylaxis

Single agent antineoplastic therapy

Altretamine	Dactinomycin
Carboplatin	Mechlorethamine
Carmustine > 250 mg/m^2	Methotrexate ≥ 12 g/m^2
Cisplatin	Procarbazine (oral)
Cyclophosphamide ≥1 g/m^2	Streptozocin
Cytarabine 3 g/m^2/dose	Thiotepa ≥ 300 mg/m^2
Dacarbazine	

Multiple agent antineoplastic therapy

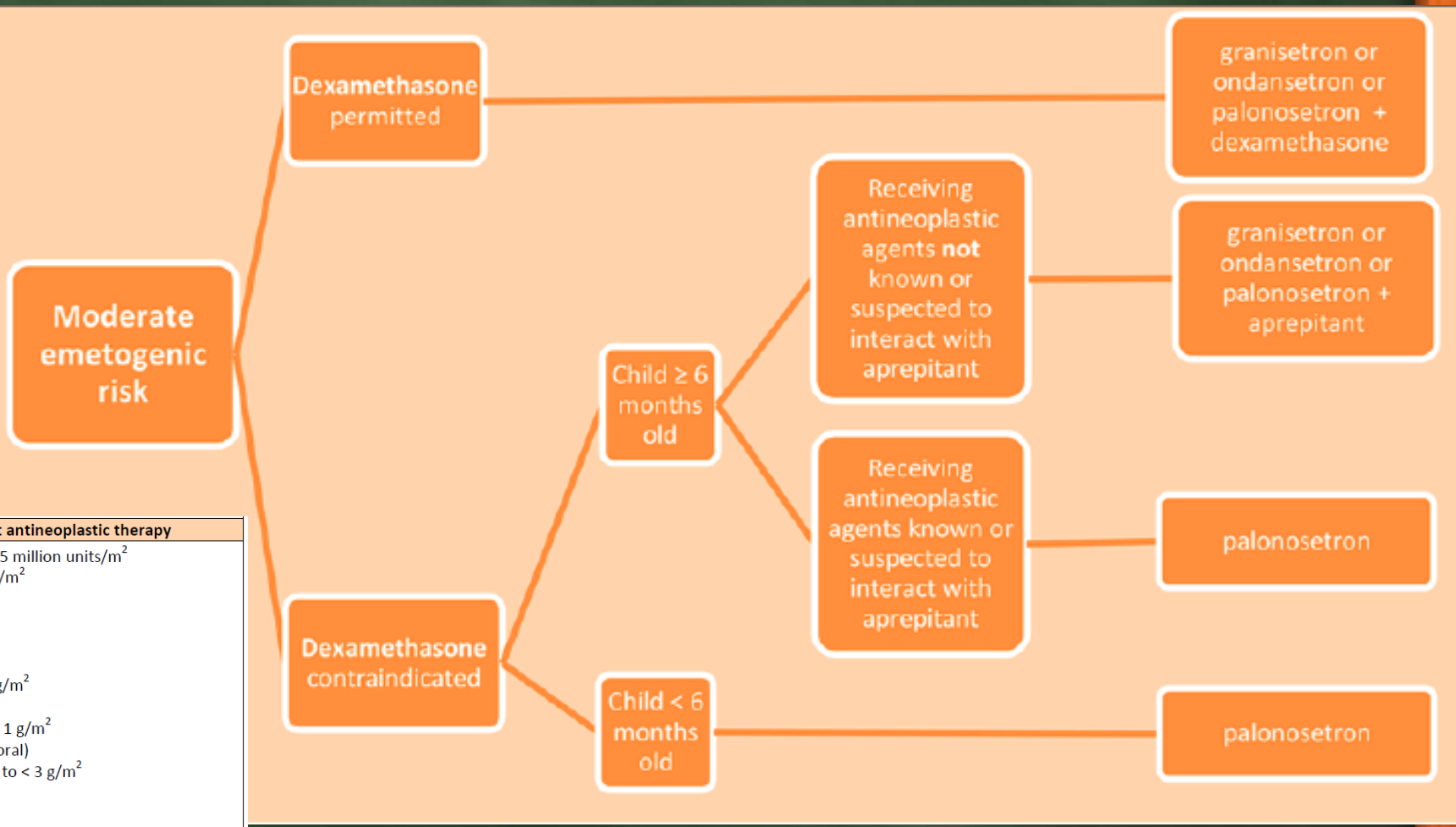
With the exceptions listed below, emetogenicity is classified based on the most highly emetogenic agent.

The following are also classified as high emetic risk:

Cyclophosphamide + anthracycline
Cyclophosphamide + doxorubicin
Cyclophosphamide + epirubicin
Cyclophosphamide + etoposide
Cytarabine 150-200 mg/m^2 + daunorubicin
Cytarabine 300 mg/m^2 + etoposide
Cytarabine 300 mg/m^2 + teniposide
Doxorubicin + ifosfamide
Doxorubicin + methotrexate 5 g/m^2
Etoposide + ifosfamide

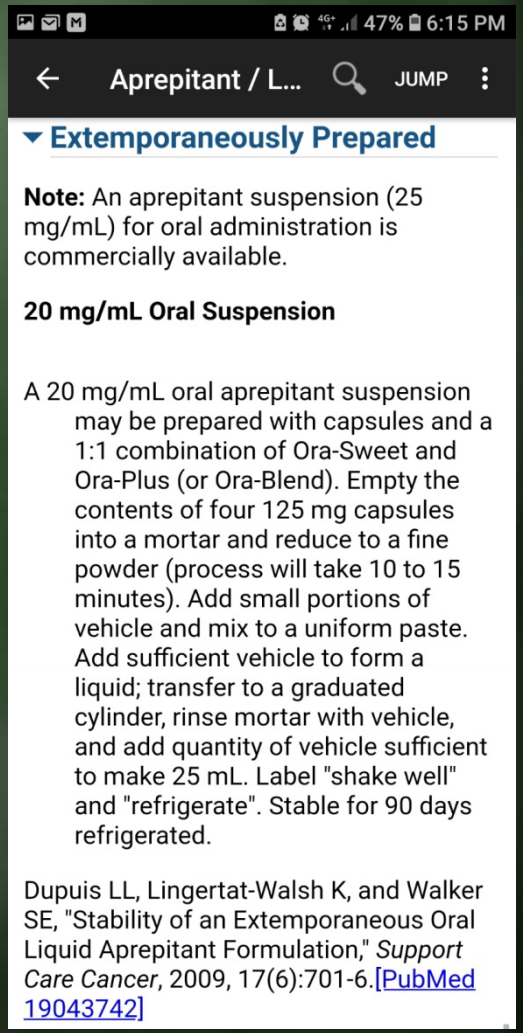
Multi-day antineoplastic therapy

Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.



Single agent antineoplastic therapy
Aldesleukin > 12 to 15 million units/m^2
Amifostine > 300 mg/m^2
Arsenic trioxide
Azacitidine
Bendamustine
Busulfan
Carmustine ≤ 250 mg/m^2
Clofarabine
Cyclophosphamide < 1 g/m^2
Cyclophosphamide (oral)
Cytarabine > 200 mg to < 3 g/m^2
Daunorubicin
Doxorubicin
Epirubicin
Etoposide (oral)
Idarubicin
Ifosfamide
Imatinib (oral)
Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)
Irinotecan
Lomustine
Melphalan > 50 mg/m^2
Methotrexate ≥ 250 mg to < 12 g/m^2
Oxaliplatin > 75 mg/m^2
Temozolomide (oral)
Vinorelbine (oral)

Drug	Dose
Ondansetron	0.15 mg/kg/dose (max 8 mg/dose) IV/PO q 8 (HEC) – 12 (MEC) h
Palonosetron	Age 1 month–17 years : 0.02 mg/kg (max 1.5 mg/dose) Age ≥17 years : 0.25 mg IV
Dexametha-sone	HEC: 6 mg/m^2/dose IV/PO q6h MEC: BSA ≤ 0.6m^2 : 2 mg/dose IV/PO q12h BSA > 0.6m^2 : 4 mg/dose IV/PO q12h (reduce half dose if given concurretly with aprepitant)
Aprepitant	≥6 months : (d1) 3 mg/kg – (d2) 2 mg/kg – (d3) 2 mg/kg Adult dose : (d1) 125- (d2) 80- (d3) 80 mg



Novel agents for CINV

- Fosaprepitant (IVEMEND®)

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2019) **61**, 235–239 doi: 10.1111/ped.13780

Original Article

Evaluation of aprepitant and fosaprepitant in pediatric patients

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Abstract ***Background*:** Single-dose i.v. fosaprepitant has been approved as an alternative to 3 day oral aprepitant, a neurokinin-1 receptor antagonist, and improves prevention of chemotherapy-induced nausea and vomiting (CINV). Because fosaprepitant has shown similar efficacy to aprepitant in adult patients only, this study compared the efficacy and safety of aprepitant and fosaprepitant in pediatric patients.

***Methods*:** Children younger than 18 years who received aprepitant or fosaprepitant to manage CINV between January 2015 and March 2018 at the National Cancer Center Hospital (Tokyo) were recruited to this study. The primary endpoint was complete response (CR; no vomiting/rescue medication) between 0 and 120 h after the start of chemotherapy. Secondary endpoints were safety based on the frequency of severe adverse events, and evaluation of patient characteristics as risk factors (effect of age and sex).

***Results*:** A total of 125 chemotherapy cycles were evaluated. In the aprepitant group, CR was observed in 36 of 80 treatment cycles (45.0%), whereas in the fosaprepitant group, it was observed in 19 of 45 cycles (42.2%; $P = 0.852$). No treatment-related severe adverse events were observed in either group. The number of non-CR was greater than that of CR in patients aged 6–14 years. The difference in CR rate between male and female patients was not statistically significant (47.1% vs 40.0%, respectively; $P = 0.471$).

***Conclusions*:** Aprepitant and fosaprepitant were safely used and may be equally useful for pediatric patients receiving highly emetogenic chemotherapy. CR rate may be associated with patient age.

Key words aprepitant, chemotherapy-induced nausea and vomiting, fosaprepitant, pediatric, supportive care.

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RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Intravenous fosaprepitant for the prevention of chemotherapy-induced vomiting in children: A double-blind, placebo-controlled, phase III randomized trial

Venkatraman Radhakrishnan[1] | Archit Joshi[1] | Swaminathan Rajaraman[2] | Prasanth Ganesan[1] | Manikandan Dhanushkodi[1] | Tenali G. Sagar[1]

Abstract

Background: Fosaprepitant is a neurokinin-1 receptor antagonist, approved for the prevention of chemotherapy-induced nausea and vomiting. The data on the use of fosaprepitant in children are limited and therefore we conducted a phase III randomized controlled trial.

Procedure: Children aged 1-12 years scheduled to receive moderately or highly emetogenic chemotherapy were randomly assigned to arm-A (fosaprepitant) or arm-B (placebo). Children recruited to arm-A received intravenous ondansetron plus dexamethasone followed by fosaprepitant infusion. Children recruited to arm-B received the same drugs as those given to children in arm-A, except that fosaprepitant was substituted with a placebo. Ondansetron and dexamethasone were continued for 48 hours after completion of chemotherapy. The primary end point of the study was to determine the proportion of patients who achieved a complete response (CR), defined as no vomiting, no retching, and no use of rescue medication, during the 24-120 hours (delayed phase) after administration of the last dose of chemotherapy. Secondary end points were the proportion of patients who achieved a CR during the acute phase (0-24 hours) and overall after administration of the last dose of chemotherapy.

Results: One-hundred-sixty-three patients were analyzed (81 in the fosaprepitant arm and 82 in the placebo arm). CR rates were significantly higher in the fosaprepitant arm compared to those in the placebo arm during the acute phase (86% vs 60%, $P < 0.001$), delayed phase (79% vs 51%, $P < 0.001$), and overall phase (70% vs 41%, $P < 0.001$). Three (4%) patients in the fosaprepitant arm and sixteen (20%) in the placebo arm required rescue anti-emetics ($P = 0.0017$).

Conclusion: Addition of fosaprepitant to ondansetron and dexamethasone improved chemotherapy-induced vomiting control in children treated with moderately or highly emetogenic chemotherapy.

KEYWORDS

chemotherapy, fosaprepitant, pediatric cancer, vomiting

Novel agents for CINV

- Netupitant/Palonosetron (AKYNZEO®)

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PK/PD Study of Netupitant and Palonosetron in Pediatric Patients for Prevention of Chemotherapy-induced Nausea and Vomiting (CINV)

Study Description

Go to ▾

Brief Summary:

This study is Phase 2 pharmacokinetic (PK) and pharmacodynamic (PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in pediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy. Two different netupitant dosages will be tested in patients aged from 3 months to < 18 years: 1.33 mg/kg up to a maximum of 100 mg, and 4 mg/kg up to a maximum of 300 mg. All netupitant doses in all age classes will be concomitantly administered with palonosetron 20 µg/kg (up to a maximum dose of 1.5 mg) which is the IV palonosetron dose approved by USA FDA for the pediatric population. The primary objective is to investigate the PK/PD relationship between netupitant exposure (AUC, Cmax) and antiemetic efficacy (CR in delayed phase) after a single oral netupitant administration, concomitantly with oral palonosetron in pediatric cancer patients receiving Moderately Emetogenic Chemotherapy (MEC) or Highly Emetogenic Chemotherapy (HEC) cycles. Efficacy parameter to be used in the correlation is the proportion of patients with Complete Response (CR i.e., no emetic episodes and no rescue medication) during (> 24-120 h after the start of chemotherapy on Day 1).

The secondary objectives are to assess the safety and tolerability after single oral administration of netupitant given concomitantly with a single oral administration of palonosetron; to evaluate the pharmacokinetic (AUC, Cmax, tmax and t1/2) of oral palonosetron at the fixed dose of 20 µg/kg in pediatric patients with the concomitant administration of netupitant. A total of 92 pediatric cancer patients receiving either HEC or MEC will be enrolled in the study.

TABLE 4 Aprepitant and palonosetron for the prevention of acute CINV in children: examples of evidence gaps

Aprepitant
Aprepitant dosing and safety in children <6 months old
Aprepitant dosing in children receiving multiple-day chemotherapy
Fosaprepitant dosing in children of all ages
Evaluation of the extent of aprepitant pharmacokinetic drug interactions with commonly used pediatric chemotherapy agents
Evaluation of the efficacy and safety of adjunctive antiemetics such as chlorpromazine nabilone and metoclopramide in children
Evaluation of the efficacy of a 5-HT_3 antagonist plus aprepitant in children receiving MEC who cannot receive dexamethasone
Palonosetron
Palonosetron dosing in children receiving MEC or multiple-day chemotherapy
Oral palonosetron dosing
Effectiveness of palonosetron IV doses lower than 0.02 mg/kg/dose in children receiving HEC
Efficacy of palonosetron monotherapy in children receiving moderately or HEC
Comparison of the efficacy of palonosetron in conjunction with aprepitant in children
Comparison of the efficacy of palonosetron versus other 5-HT_3 antagonists as monotherapy and in conjunction with dexamethasone in children

Delay CINV

- No appropriate studies available in children
- Treat in a manner similar to adults with doses adjusted appropriately for children

Anticipatory vomiting

- Lorazepam 0.04-0.08 mg/kg/dose (max 2 mg)

Breakthrough emesis/Refractory CINV

- Upgrade the next high level of emetogenic risk
- Add Olanzapine 0.1 mg/kg/dose (max 10 mg) (age >3 y/o)
- Alternative : Metochlopramide (for >1 y/o, with diphenhydramine and up to 5 days)
- Consider change ondansetron to palonosetron

Pediatr Blood Cancer 2016;63:1144–1151

Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children With Cancer

Jacqueline Flank, BScPhm, ACPR, MSc,[1,2] Paula D. Robinson, MD, MSc,[3] Mark Holdsworth, PharmD,[4] Robert Phillips, MD,[5,6] Carol Portwine, MD, FRCPC, PhD,[7] Paul Gibson, MD,[8] Cathy Maan, PhD, CPsych,[8] Nancy Stefin, Hons BA, CLSt Dipl, CCLS,[7] Lillian Sung, MD, PhD,[9,10] and L. Lee Dupuis, MScPhm, ACPR, PhD[1,2,10*]

This clinical practice guideline provides an approach to the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and the prevention of refractory CINV in children. It was developed by an international, interprofessional panel and is based on systematic literature reviews. Evidence-based interventions for the treatment of breakthrough and prophylaxis of refractory CINV are recommended. Gaps in the evidence used to support the recommendations made in this clinical practice guideline were identified. The contribution of these recommendations to breakthrough and refractory CINV control in children requires prospective evaluation. Pediatr Blood Cancer 2016;63:1144–1151.

Key words: chemotherapy-induced nausea; chemotherapy-induced vomiting; clinical practice guideline; supportive care