Shaukat Khanum Memorial Cancer Hospital and Research Center

# Pharmacy Newsletter

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## *New Formulary Addition*

1. Posaconazole Tablet / Syrup. (Restricted formulary Drug – Only ID consultants authorized). Will be used for high risk patients with mucor mycosis, where Amphotericin B is either contraindicated or causes intolerable adverse effects.

2. Bendamustine Injection - Regular Formulary Item

## An ADR Update

### Cyclophosphamide - Risk of Rhabdomyolysis

The MHLW/PMDA, Japan has stated that cases of adverse events suggestive of rhabdomyolysis have been reported in patients treated with cyclophosphamide hydrate injections in Japan. Based on expert advice and available evidence, it has been recommended by MHLW/PMDA to include the anomaly to the "Clinically significant adverse reactions" subsection of the "Adverse reactions" section of the package insert. Rhabdomyolysis is characterized by myalgia, feelings of weakness, increased creatine kinase (creatine phosphokinase) and increased myoglobin in the urine and blood. Patients should be carefully monitored and drug should be discontinued if any such abnormality occurs with appropriate management measures to ensue.

# Anticancer therapeutic alternatives

*By Sidrah Andleeb*

| Therapeutic alternatives | | | | |
|---|---|---|---|---|
| **Drug** | **IV (mg)** | **Conversion Drug** | **Dose of Conversion Drug (mg)** | **Example** |
| **Cyclophosphamide** [1] | 1 | Ifosfamide | 2.5-3 | Cyclophosphamide 500mg/m2 is equivalent to Ifosfamide 1250mg/m2 - 1500mg/m2 |
| **Dacarbazine** [2] | 1 | Procarbazine | 1 | Dacarbazine 375mg/m2 D1 & D15 is equivalent to Procarbazine 100mg/m2 D 1-7 |
| **Daunorubicin** [3] | 1 | Doxorubicin | 0.833 | Daunorubicin 60mg/m2 is equivalent to Doxorubicin 50mg/m2 |
| **Epirubicin** [3] | 1 | Doxorubicin | 0.67 | Epirubicin 50mg/m2 is equivalent to Doxorubicin 34mg/m2 |
| **Idarubicin** [3] | 1 | Doxorubicin | 5 | Idarubicin 12mg/m2 is equivalent to Doxorubicin 60mg/m2 |
| **Mitoxantrone** [3] | 1 | Doxorubicin | 4 | Mitoxantrone 8mg/m2 is equivalent to Doxorubicin 32mg/m2 |
| **Peg-asparaginase** [4] | 1IU | Asparaginase (*E. coli*) | 40 IU | Asparaginase 6000 IU/m2 D8, D10, D12, D14, D16, D18 & D20 is equivalent to Peg- asparaginase 1100IU/m2 single dose |


*1. Jing Yang et al. "Clinical pharmacology of cyclophosphamide & Ifosfamide". Current drug therapy, 2006, I, 55-84*
*2. Enrica Marchi et al. "Evaluation & treatment of lymphoma" Pg No. 236. Table 17.4*
*3. J.C Panetta et al. "Comparison of native E. coli and PEG asparaginase pharmacokinetics and pharmacodynamics". Clin Pharmacol Ther. 2009 Dec; 86(6): 651–658.*
*4. www.survivorshipguidelines.org*


# *How to Slay a Dragon: Management of High-Dose Melphalan induced GI Toxicity*

*By Shahbaz Ahmed Khan*

High-dose (HD) melphalan (100mg/m2/day) when used for two consecutive days may lead to severe mucositis and gastro-intestinal injury resulting in nausea, vomiting, diarrhea, cramping, and occasionally acute abdominal pain. The prevalence of WHO grade 3 or 4 gastrointestinal mucositis can be as high as 20%-60%. In recent years recombinant product, palifermin (keratinocyte growth factor), has been approved by US FDA for management severe oral mucositis associated with hematologic malignancies in patients receiving myelotoxic therapy with hematopoietic stem cell support (when the preparative regimen is expected to induce mucositis ≥ grade 3 in most patients). In the phase II trial, palifermin proved to reduce the incidence as well as the median duration of WHO grade 3/ 4 mucositis, as compared to placebo. The major side effects limiting the use of palifermin were cutaneous toxicity and raised amylase and lipase.

HD melphalan induced GI toxicities have also been noticed in SKMCH while treating multiple myeloma patients. Supportive treatment was given for management of diarrhea. In order to minimize these incidents, dose was reduced from 100 mg/m2 to 75 mg/m2/day (on average a 25 % dose reduction) leading to some improvement. Recipients often required narcotic analgesics and parenteral alimentation

due to mucositis; the latter is sometimes associated with opportunistic infections in immune-compromised hosts.

## The Siamese Twins – Intra-venous to Per-oral Therapeutic Equivalency

*By Mariam Nawaz*

| Therapeutically equivalent doses of Intravenous ( IV) & Per oral (PO) dosage forms [1,2,3] | | |
|---|---|---|
| **Drug** | **IV** | **PO** |
| **Acyclovir** | 400 mg Q8H | 800 mg Q5H |
| **Ciprofloxacin** | 400 mg Q12H | 500 or 750 mg Q12H |
| **Cefuroxime** | 500-750 mg Q8H (Cefuroxime sodium) | 250-500 mg Q12H (Cefuroxime axetil) |
| **Clindamycin** | 150-450 mgQ6H | 600-2700 mg in 2-4 divided doses |
| **Chlorpromazine (For nausea & vomiting only)** | IM: 25 to 50 mg Q3H to Q4H | 10 to 25 mg Q4 to 6H |
| **Digoxin** | 0.1-0.4mg OD | 0.125-0.5mg OD |
| **Diltiazem** | Oral dose (mg daily) = [rate of IV dose (mg/hour) x 3 + 3] x 10 | |
| **Erythromycin** | 250 to 500 mg Q6H to Q12H | 15 to 20 mg/kg/day divided Q6H or 500 mg to 1 g Q6H |
| **Granisetron** | 10 mcg/kg 30mins before chemotherapy | 2 mg OD up to 1 hour before chemotherapy |
| **Labetalol** | 20 mg IV push over 2 minutes; max: 40 to 80 mg at 10-minute intervals, titrate to response to up to 300 mg | Upon discontinuation of IV infusion, may initiate oral dose of 200 mg followed by additional dose of 200 to 400 mg in 6-12 hours. Thereafter, give 400 to 2400 mg/day in divided doses depending on blood pressure response. |
| **Levothyroxine** | 50-80 mcg (Not available) | 100mcg |
| **Pethidine** | 75 mg | 300 mg (Not available) |
| **Metoprolol** | 25 mg Q12H | 2.5 to 5 mg IV Q6H. |
| **Morphine** | 10mg | 30mg |
| **Ranitidine** | 50mg Q6-Q8H | 150mg Q12H |

*1.www.med.sanford.edu*
*2.www.ashp.org/DocLibrary*
*3.www.lexicomponline.com*

# News & Updates

## Codeine in pediatric population

In April 2015, the European Medicines Agency announced that codeine is not recommended in children and adolescents between 12 and 18 years who have breathing problems, including those with asthma and other chronic breathing issues. In addition, US FDA has issued a boxed warning about the risk of respiratory depression and death in children who received codeine after tonsillectomy and/or adenoidectomy for post-operative pain management. These patients were found to be ultra-rapid metabolizers of codeine to morphine due to a CYP2D6 polymorphism that led to life threatening amount of morphine in body.

### Galactomannan (GM) & B-D Glucan (BGL) Assays vs. the Drugs – An Interaction Update

There are various drugs that may influence the results of GM and BGL assay for identifying Aspergillus and Candida species respectively. In addition appropriate sample collection time while considering the half-life of a particular interacting drug can also help avoid false positive GM.

**Interacting Drugs**

***GM Assay***: Piperacillin/Tazobactum, Caspofungin, Immunoglobulin

***BGL Assay:*** Ampicillin-Sulbactam, Colistin, Cefazolin, Co-trimoxazole, Cefotaxime, Cefepime, Ertapenem

## Pembrolizumab vs. Ipilimumab for advanced Melanoma

Management of advanced melanoma is being taken upfront with newer targeted chemotherapeutic drugs. In a randomized phase III trial, anti PD1 antibody Pembrolizumab has shown prolonged progression free survival (PFS), overall survival (OS) and lesser high grade toxicity as compared to the immune checkpoint inhibitor Ipilimumab in patients with advanced melanoma. The 6 months PFS with Pembrolizumab 10mg/kg q2weekly, Pembrolizumab 10mg/kg q3weekly and Ipilimumab 3mg/kg q3weekly was 47.3%, 46.4% and 26.5% respectively. While the survival rate for 1 month for the three groups was 74.1%, 68.4% and 58.2% respectively. Efficacy was similar in the two Pembrolizumab groups. Response rate was better with fewer grade 3 -5 toxicities in Pembrolizumab groups as compared to Ipilimumab. Adverse effects commonly associated with Pembrolizumab are peripheral edema, fatigue, metabolic abnormalities, anemia and arthralgia. Whereas, common side effects exhibited with Ipilimumab are fatigue, pruritus, GI abnormalities and anemia.

## Good news for the Obese- Liraglutide

In a recent randomized controlled SCALE trial, Liraglutide – a glucagon-like-peptide-1 analogue at dose higher than that recommended for type 2 Diabetes mellitus, i.e., 3mg per day, in conjunction with diet and exercise has shown potential benefit in weight reduction. Another study has shown that treatment with Liraglutide increased bone formation by 16% and prevented bone loss after weight loss through a low calorie-diet. This supports the role of Liraglutide as a safe weight- lowering agent while minimizing the occurrence of osteoporosis and bone fracture especially in menopausal women.

## New Arrivals *to be:* Alirocumab and Evolocumab

One of their kind intravenous low density lipoprotein & cholesterol lowering drugs - proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, Alirocumab and Evolocumab, are up for approval by US FDA. According to the Endocrinology and Metabolic Drugs Advisory Committee, these drugs have shown to be both effective and well-tolerated in lowering LDL cholesterol in patients at risk for cardiovascular events, especially in patients who cannot tolerate statins. Studies have found that Alirocumab reduces LDL cholesterol by 40% to 60%, compared with placebo, while Evolocumab was associated with roughly 60% LDL reduction. However, full results from the large ODYSSEY-Outcomes, expected to be released by 2018, will give more insight that whether the clinical outcomes are as promising as the initial studies suggest. Nevertheless an early approval for Alirocumab is favored, prior to information on hard outcomes, due to favorable response in 10 phase 3 trials.

## An Atlatl against Refractory H. pylori

Rifabutin-based triple therapy: Proton pump inhibitor + Rifabutin 150 mg BID + Amoxicillin 1g BID for 7-10 days. Rifabutin based regimen has shown to be similarly effective or even more effective and well tolerated than the quadruple therapy on patients who had failed eradication after standard triple therapy. Patients on Rifabutin had exhibited relatively lesser side effects with no incidence of treatment discontinuation. Moreover, similar high intention-to-treat eradication rates (91%) had been reported with both the regimens making Rifabutin a considerable second- line treatment choice in refractory cases.