Shaukat Khanum Memorial Cancer Hospital and Research Center

Pharmacy Newsletter

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ADR Updates

Ibuprofen - Small increase in cardiovascular risk with daily doses ≥ 2,400mg

Recent EU review by the Pharmaco-vigilance risk assessment committee (PRAC) has confirmed a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) in patients taking high doses of ibuprofen (≥ 2,400mg/day). Health-care professionals are advised to consider the following:

- Ibuprofen should be prescribed at the lowest dose for the shortest duration possible.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) must be avoided.
- For patients at risk of cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, and smoking) careful consideration should also be exercised before initiating long-term treatment with ibuprofen, particularly if high dose, i.e. 2400 mg/day, is required.

Reference: *WHO Pharmaceuticals Newsletter No.3, 2015 for Risk of serious heart and stroke adverse events at high doses in Canada*

Severe joint pain with dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Sitagliptan)

The US FDA has added a warning and precaution to the labels of all DPP-4 inhibitors about the risk of severe disabling joint pain. Health care professionals are advised to consider discontinuing DPP-4 inhibitors if severe joint pain occurs. According to FDA adverse event reporting system database, patients started having symptoms from 1 day to years after initiating DPP-4 inhibitor therapy for type-2 diabetes. Symptoms were relieved, usually in less than a month, upon discontinuing the drug.

Folinic acid rescue dosing post methotrexate administration

Folinic acid (also known as leucovorin) is used along with hydrations to reduce methotrexate (MTX) toxicity. It counteracts folic acid antagonist and restores folate required for DNA and RNA synthesis. Folinic acid is chosen for MTX rescue rather than folic acid as the latter is incapable of bypassing the methotrexate-dihydrofolate reductase complex. Folinic acid rescue and monitoring of MTX levels may be required depending on MTX dose used as shown in the following table [1]:

MTX dose	100-500mg/m^2	500-1000 mg/m^2	≥1000mg/m^2
Folinic acid rescue	Consider*	Yes	Yes
MTX levels	-	Consider*	Yes

*In case of other risk factors (e.g. Renal failure, hypo-albuminemia, concurrent use of interacting drugs) [2]

The adjustment of folinic acid dose, in view of MTX levels, is shown in table below [3]:

MTX plasma concentration(µM/L)	Time after starting MTX		
	24 hrs	48hrs	72hrs
<0.20	-	-	-
0.20-0.70	15mg/ m^2q6h	15mg/ m^2 q6h	30mg/ m^2 q6h
0.71-2.00	15mg/ m^2 q6h	15mg/ m^2 q6h	150 mg/ m^2 q6h
2.10-19.90	15mg/ m^2 q6h	150 mg/ m^2 q6h	750 mg/ m^2 q3h
20.00-100.00	60 mg/ m^2 q6h	300 mg/ m^2 q3h	3000 mg/ m^2 q3h
>100.00	Adjust with formula	Adjust with formula	Adjust with formula

If the MTX levels are greater than 100µM/L then discuss with consultant. The appropriate dose is calculated from the following formula:

$$Total\ daily\ dose\ of\ Folinic\ acid * = \frac{Patient's\ actual\ serum\ MTX\ \times\ standard\ daily\ dose\ of\ folinic\ acid}{Upper\ limit\ of\ serum\ MTX\ for\ the\ actual\ day\ and\ time+}$$

*Higher doses are given intravenously q3h

+Where, upper limits of serum MTX: At 24hrs = 20.00 µM/L, at 48hrs = 2.00 µM/L, at 72hrs = 0.20 µM/L

Following table describes monitoring for the targeted levels in high-dose MTX (greater than 1g/m^2) protocols:

Chemotherapy Protocol	MTX level monitoring	Targeted serum MTX level
Hyper-CVAD	Check MTX levels & start folinic acid at 48hrs after start of MTX infusion and continue at 48, 72 and 96 hrs until MTX levels < 0.05 micromole/L.	<0.05 µM/L
MAP	Check MTX levels & start folinic acid at 24 hrs after start of MTX infusion and continue at 48, 72 and 96 hrs. until MTX levels < 0.1 micromole/L.	<0.1 µM/L

References:

1. *Cancer Care Ontario, drug monograph for methotrexate 2015.*

2. Kivity, et al. Clinical characteristics and risk factors for low dose methotrexate toxicity: a cohort of 28 patients. Autoimmun Rev. 2014 Nov; 13(11):1109-13.

3. Ivo M Hennig .Nottingham University Hospital, Guidelines for the use of high dose methotrexate 12g/m2 within the Euromos-1 trial protocol in the department of oncology 2013.

News & Updates

Paracetamol vs. vaccines – An interaction Update

Paracetamol may reduce the efficacy of vaccines in children, when co-administered. The proposed mechanism for this interaction involves acetaminophen associated suppression of the inflammatory response, which is important for the host response to vaccine administration. In a randomized trial, 226 healthy infants received acetaminophen (80-125 mg/dose, weight-based) Q6-8 hours post vaccination and were then assessed for antibody response. The specific vaccines included a ten-valent pneumococcal *Haemophilus influenzae* protein D-conjugate vaccine co-administered with a diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*H. influenzae* type b vaccine and an oral rotavirus vaccine. After primary prophylaxis the antibody geometric mean concentrations (GMCs) were significantly lower for all 10 pneumococcal serotypes, protein D, anti-diphtheria, anti-tetanus, and anti-pertactin that persisted after booster doses. However, in two other studies of children receiving diphtheria-tetanus-pertussis (DTP) or DTP-inactivated poliovirus vaccines, GMC was not significantly different. The degree of impact on various vaccines and the discrepancy between studies is unclear, but this interaction requires consideration while treating infants relative to adults.

Immediate infusion reactions to Folinic acid

Infusion reactions to folinic acid are rarely reported and the reaction may also be under recognized because it is often administered simultaneously with other reaction causing chemotherapy agents. In a study of 44 patients receiving folinic acid based regimen for metastatic colorectal cancer, five patients developed an immediate infusion reaction associated with folinic acid and not the co- administered drug, i.e. Oxaliplatin and Irinotecan. Re- challenge with folinic acid reproduced the symptoms in all five patients, whereas separate re- challenge with the co-administered drugs did not. All patients also reacted similarly to a challenge with LEVOfolinic acid, suggesting that the L-isomer cannot necessarily be substituted for the more commonly used racemic folinic acid. Desensitization can facilitate to continue folinic acid therapy.

New and simplified Pneumococcal vaccine recommendations for immune-competent elderly patients by CDC- ACIP

Following is the schedule for 13-valent pneumococcal conjugate vaccine (PCV13, Prevanar 13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax 23) in immune-competent adults aged ≥ 65 years by CDC's Advisory committee on Immunization practices (ACIP), 2015.

Current age	Age of previous vaccination	Vaccine		Recommendation
		PCV13	PPSV23	
≥ 65 years	Not vaccinated	×	×	First PCV13 followed by PPSV23 at least 1 year later
	≥ 65	×	√	PCV13 at least 1 year after PPSV 23
		√	×	PPSV 23 at least 1 year after PCV13
	< 65	×	√	First PCV13 followed by PPSV23 at least 1 year later
		√	×	PPSV23 (minimum gap of 1 year from previous vaccination

Flu vaccination of health- care workers– How strict to go about it?

Recent study conducted at University of New Mexico Health Sciences Center reports that once the percentage of influenza vaccinated health-care workers reaches about 50%, there is no further reduction in the rate of hospital acquired influenza. They presented the following data:

Flu Season	Health-care worker vaccination %age	Hospital acquired influenza %age
2010/11	47.0	9.0
2011/12	56.5	4.9
2012/13	64.9	4.3
2013/14	91.7	5.2
2014/15	89.9	4.8

Rate of hospital acquired influenza, defined as infections diagnosed at least 48hrs after admission in patients who presented to the hospital without influenza like symptoms in previous 24hrs, plateaued once about half the health care personnel were vaccinated. These findings contradict with the Healthy People 2020 Objective; however, further studies are proposed to develop evidence.

New arrivals

Daclatasvir-based regimens for genotype 3 HCV infection

Recently, the US FDA approved the use of daclatasvir, a novel NS5A inhibitor, in combination with sofosbuvir as preferred regimen for genotype 3 hepatitis C virus infected patients. The duration of therapy for patients without cirrhosis is 12 weeks. In an open-label study that included 120 patients, sustained virologic response (SVR) rates were 96% with this regimen. In 32 patients with cirrhosis, the SVR rates were only 63 % but limited evidence suggests that efficacy is enhanced with the addition of ribavirin to the regimen. Thus, daclatasvir along with sofosbuvir and weight-based ribavirin is the preferred regimen for genotype 3-infected patients with cirrhosis; the regimen is given for 12 to 24 weeks, although the optimal duration is uncertain.

New Drug Combination for Colorectal Cancer:

Trifluridine/Tripiracil is the newly approved drug combination for metastatic colorectal cancer with wild type RAS, progressed on flouro-pyrimidine, Oxaliplatin and Irinotecan based chemotherapy, an anti-VEGF biologic product, and an anti-EGFR monoclonal antibody. A multicenter, double-blind, placebo-controlled trial (TPU-TAS-102-301) showed improved over-all survival of ~ 7.1 months in the trifluridine/tripiracil group vs. 5.3 months in the placebo group with a 32% reduction in the risk of death. The recommended dose and schedule for trifluridine/tipiracil is 35 mg/m^2 (based on trifluridine component) orally twice daily within one hour of completion of morning and evening meals on days 1to 5 and days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity. Most common adverse effects were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. Considering that chemotherapeutic options for colorectal cancer refractory to standard regimens are limited, trifluridine/tripiracil appears as a good oral treatment option.