COMPLIANCE WITH FDA RECOMMENDATIONS ABOUT OVERDOSING WITH CARBOPLATIN

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BACKGROUND

At the end of the year 2010, FDA issued an alert regarding the utilisation of one new method for serum creatinine determination. This method provided an insufficient dosing over previous methods, most especially in serum creatinine value ≤0.7mg/dl. This could mean an increase in dosing and toxicity of carboplatin. It was therefore recommended the use of fixed maximum doses for each target AUC value.

Overdosage courses

were selected

	U.S. Department of Health & Human Ser	rvices a A	A		
ne year 2010, FDA issued an alert regarding the utilisation of one new method for	U.S. Food and Drug Administration Protecting and Promoting Your Health				
ne determination. This method provided an insufficient dosing over previous	About FDA	Interior Image: Constraint of the state of the sta			
especially in serum creatinine value ≤0.7mg/dl. This could mean an increase in	FDA Organization Office of Medical Products and Tobacco	Carboplatin dosing This communication is to inform members of the oncology community of recent changes in the measurement of serum creatinine which may have an impact on carboplatin dosing. Based on preliminary communications with the National Cancer Institute/Cancer Therapy Evaluation Program, a potential safety issue with			
city of carboplatin. It was therefore recommended the use of fixed maximum doses	About the Center for Drug Evaluation and Research CDER Offices and Divisions	carboplatin dosing has been identified. By the end of 2010, all clinical laboratories in the US will use the new standardized isotope Dilution Mass Spectrometry (IDNIS) method to measure serum creatinine. The IDMS method appears to underestimate serum creatinine values compared to older methods when the serum creatinine values are relatively low (e.g., ~0.7 mg/dL). Measurement of serum creatinine by the IDNIS-method			
	Drug Safety Oversight Board	could result in an overestimation of the Glomerular Filtration Rate (GFR) in some patients with normal renal function. If the total carboplatin dose is calculated based on IDMS-measured serum creatining using the Calcult drenul, acrohoplatin dose in a calculate based on a could accult in screen and drug rated at the calculation of the calculation of			
AUC value.	Jobs at the Center for Drug Evaluation and Research (CDER)	Calvert formula, carboplatin dosing couldbe higher than desired and could result in increased drug-related toxicity.			
	Meeting Presentations (Drugs)	The current label for carboplatin provides safe dosing instructions that are based on actual GFR measurements. Provided that actual GFR measurements are made to assess renal function, carboplatin can be actively deced accerding to the instructions described in the label.			
	Realignment of the Office of Antimicrobial Products within the	be safely dosed according to the instructions described in the label. (http://dailymed.nm.nih.gov/dailymed/druginfo.cfm?id=13328).			
	Office of New Drugs CDER Exclusivity Board	If a patient's GFR is estimated based on serum creatinine measurements by the IDMS method, FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid estimated with due to the service of the serv			
	What We Do (CDER)	potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:			
	FAQs about CDER	Total Carboplatin Dose (mg) = (target AUC) x (GFR +25) [Calvert formula] Maximum Carboplatin Dose (mg) = target AUC (mg·min/mL) x (150 mL/min)			
\sim	Reports & Budgets (CDER)	The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal			
(1) To determine compliance with EDA recommendations about carbonlatin decare	Manual of Policies & Procedures (CDER)	function. No higher estimated GFR values should be used. For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg			
To determine compliance with FDA recommendations about carboplatin dosage	Contact CDER	For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg			
To access the toyicity emerged of decay bigher ton recommended	Resources for You	Principal investigators of ongoing clinical trials should assess whether carboplatin dosing in those trials should be adjusted according to the above information. Healthcare professionals should report all serious adverse events suspected to be associated with the use of one modified and drive to EDA's Medified Reporting Sucher Succemptation a form police of the second secon			
(2) To assess the toxicity emerged at doses higher tan recommended.	 What's New (Hematology/Oncology (Cancer) Approvals & Safety Notifications) 	any medicine and device to FDA's MedWatch Reporting System by completing a form online at http://www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178) or mailing the postage-paid address form provided online, or by telephone (1-800-FDA-1088).			

MATERIALS AND METHODS

Data from Farmis® database

carboplatin dosing >900mg for a target AUC=6

In the event of an

• Overall nu	mber of patients
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- Carboplatin courses
- Sex and age

PURPOSE

- Diagnosis
- Overdosage percentage.

rom January 2011 to September 2013

carboplatin dosing >750mg for a target AUC=5 carboplatin dosing >600mg for a target AUC=4 overdosing, blood tests before the next course were sought.

Pharmacological toxicology (neutropenia and thrombocytopenia) and the need to delay the chemotherapy course were evaluated.

RESULTS	Chemotherapy courses	Overdosage percentage	¿Need to delay the next chemotherapy course?	Adverse events	
	courses	percentage	(1 week)		
	1	2%	No	-	
A total of 195 patients 763 carboplatin courses → 2% overdosed	5	3%	Yes, N=2	Neutropenia, grade 1 (N=3) Neutropenia, grade 2 (N=1)	
	2	7%	Yes, N =1	Neutropenia, grade 3 (N=1)	
Patients afected by overdosing: 3 women	1	9%	No	-	
and 4 men, with an average of 48 years.	1	10%	No	-	
Type of cancer: lung (N=2), stomach (N=1), ovary (N=2) and unknown origin (N=2).	2	13%	No	-	
	1	15%	No	-	
	3	20%	Yes, N =1	Neutropenia, grade 3 (N=1)	
	1	22%	No	-	
	1	29%	No	-	
Of the eighteen next chemotherapy courses with excess dosage, 22.2% were delayed.					

CONCLUSIONS

While the rate of implementation is rather high, it is necessary to set up an automated alert system based on FDA recommendations.

Neutropenia was the only adverse event resulting in delays of chemotherapy; with no thrombocytopenia.

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