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Treatment of High Dose Methotrexate Toxicity with Glucarpidase

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Abstract

High Dose Methotrexate (HD-MTX) toxicity can cause renal dysfunction in patients due to a presence of risk factors such as body mass index >25 kg/m^2, comedication (salicylates, NSAID`s, sulfonamides, beta-lactam antibiotics, aminoglycosides), urine pH<7, iv fluid intake <3 l/m^2/24 hours, hepatic dysfunction, renal insufficiency prior to HD-MTX, diarrhea and pleural effusions. To prevent renal dysfunction and further MTX toxicity Glucarpidase can be used which degrades MTX to its metabolites.

Cases: A 17 year-old and a 14 year-old boy were treated with HD-MTX, developed renal insufficiency and were treated with Glucarpidase. In both patients unexpected renal dysfunction was seen still 3-4 weeks after treatment with Glucarpidase. A theoretic concern regarding the use of Glucarpidase is that the rapid formation of MTX metabolite called DAMPA, which is almost 10-fold less soluble than MTX, may lead to further renal toxicity by precipitation in the renal tubules. If we compare our patient data with data we found in the literature there is almost no difference in renal dysfunction duration between patients who got Glucarpidase (21 days) and those with only supportive therapy (19 and 12 days). After treatment with Glucarpidase the question on how and when to restart HD-MTX therapy raised. The safe option for our two patients would be first a rechallange with 50-75% HD-MTX after a full recovery of the renal function. After the first rechallange kindey function and MTX levels should be closely monitored and if no problems are observed the second rechallange should be with 100% HD-MTX. If we closely look at our data and available data from the published articles there is a concern on how effective and safe Glucarpidase is. Glucarpidase should be given only in cases if supportive therapy is not effective enough in lowering MTX plasma levels. Even then, health care professionals should use Glucarpidase cautiously because of its uncertain benefits unpredictable side effect.

Keywords: Methotrexate; Glucarpidase; Voraxaze; Child; Intoxication; Toxicity

Introduction

Methotrexate (MTX) is one of the most widely used anticancer agents. High Dose Methotrexate (HD-MTX) followed by Leucovorin (LV) rescue is an important component in the treatment of a variety of childhood and adult cancers. HD-MTX can be safely administered to patients with normal renal function using of alkalinasation, hydration and pharmacokinetically guided LV rescue. Despite these measures HD-MTX-induced renal dysfunction continues to occur in approximately 1.8% of patients. The mortality among patients who developed renal dysfunction was 4.4%. In the 1970s, prior to routine monitoring of plasma MTX concentrations and PK guided adjustment of LV, the mortality associated with HD-MTX infusions ranged between 4.6% and 6% [1,2].

MTX-induced renal dysfunction is believed to be mediated by the precipitation of MTX and its metabolites in the renal tubules or via a direct toxic effect of MTX on the renal tubules. Without safety measures following HD-MTX infusion patients present following a delay of several days with severe mucositis, profound bone marrow depression and less commonly dermatitis. Rescue attempts with High Dose Leucovorin had small effect on relieving MTX toxicities. In addition to conventional treatment approaches, dialysis-based methods have been used to remove MTX with limited effectivness.

More recently Glucarpidase (Voraxaze®) has become been available for the treatment of HD-MTX (>1g/m^2) induced renal dysfunction [3].

Glucarpidase is a recombinant bacterial enzyme that rapidly hydrolyzes MTX to inactive metabolites (-95% in 15 minutes). It is not registered in the EU due to allocation of the production site while pending at the European Medicine Agency. Glucarpidase1000 IE powder for injection is priced at € 14431, 64 (vat incl) per vial and must be ordered per set of two vials. It should be dosed at 50 IE/kg, dissolved in 1 ml NaCl 0, 9% and injected as an intravenous bolus in 5 minutes. Two hours before and after administration of Glucarpidase no Leucovorin should be administered due to the fact that Leucovorin itself is a substrate for Glucarpidase [4].

Before the treatment with Glucapridase is started there should be a consultation between the physician and the hospital pharmacist where they can decide, using the most recent MTX blood concentrations and the patient characteristics (clearance, signs of intoxication such as mucositis, etc.), if and how the patient should be treated. In the University Medical Centre Groningen we use a Glucarpidase protocol in which the initiation of treatment depends on the given MTX dosage, the MTX infusion duration and measured MTX blood concentrations (Table 1).

After the patient treatement with Glucarpidase some questions raised about:

- The mechanism behind MTX induced nephrotoxicity
- The duration of elevated creatinine levels after treatment with Glucarpidase and the cause of it
- Resumption of HD-MTX therapy after nephrotoxicity
- Criteria/protocol when and how to use Glucarpidase

MTX dose	**1 g/m^2**	**2 g/m^2**	**5 g/m^2**	**4 g/m^2**	**8 g/m^2**	**12 g/m^2**
Infusion duration	24 hours			4 hours		
Hours after start MTX administration	Limit levels of MTX blood concentrations (µmol/L)					
12 hours	≥ 50	≥ 100	≥ 250	≥ 160	≥ 310	≥ 470
24 hours	≥ 50	≥ 100	≥ 250	≥ 25	≥ 50	≥ 75
36 hours	≥ 7.5	≥ 15	≥ 35	≥ 5	≥ 10	≥ 16
42 hours	≥ 3	≥ 6	≥ 16	≥ 3	≥ 6	≥ 9
48 hours	≥ 1.5	≥ 3	≥ 7.5	≥ 2	≥ 4	≥ 6
>60 hours	≥ 1	≥ 1	≥ 2.5	≥ 1	≥ 2	≥ 3

Tabel 1: Glucarpidase protocol: MTX limit levels at which Glucarpidase should be given (1 µmol/L=454 µg/L).

Case 1

Patient 1, 17 years old, threated with SKION-EURAMOS 01-M chemotherapy (10 treatment cycles with a month period between each cycles) with 24 grams of Methotraxate iv (12 g/m^2 in 4 hours, iv), for osteosarcoma, developed nephrotoxicity with hyperkaliemia after the tenth treatment cycle.

Date	**MTX blood level µmol/l**	**Creatinine µmol/l**	**Therapy**
Day 0		62	HD-MTX 24 g iv in 4 hours
Day 2; 14 pm	36	not measured	Supportive care
Day 2; 17 pm	26	143	
Day 2; 22 pm	18	141	
Day 3; 9 am	7.3	133	Glucarpidase1000 IE
Day 3; 12am	4	137	Hyperhydration continued
Day 4	2.2 LC/MS MTX level was 0.81 µmol/l	126	
Day 5	1.4 LC/MS MTX level was 0.30 µmol/l	122	
Day 8	0.8	129	Hyperhydration stop
Day 7	0.7	147	
Day 14	0.3	121	
Day 25	Not measured	112	

Table 2: Laboratory results and therapies applied to the patient.

Before each HD-MTX therapy the attending physicians confirmed that kindey and liver function were normal, there was no mucositis present and blood cell counts (leucocytes, granulocytes and trombocytes) where normal. Urine pH level was at least 7.

2 days after HD-MTX infusion a MTX level in blood sample was analysed according to the protocol. Measured blood level was 36 µmol/L (ref >1.5 µmol/L) and creatinine level 143 µmol/L. There was no evident reason for such a high level of MTX. Hyperhydration level and Leucovorin dose were raised and shortly thereafter resulted in a decline of MTX blood level (see Table 2). In regards to our own Glucarpidase protocol and MTX blood levels after 48 hours, use of Glucarpidase was indicated. Glucarpidase was immediately ordered through international channels and administered almost 72 hours after the initial MTX dose. Shortly after the administration of Glucarpidase there was no sharp decline in MTX level or improvement of kidney function at a long term. At day 7 there was even a decline in kidney function. Even 2 weeks after initial treatment with Glucapridase, creatinine levels did not return to a level before the last HD-MTX administration. Physicians were not sure how and when they could restart next MTX chemotherapy.

Case 2

Patient 2, 14 years old, threated according to the SKION ALL 11 HD-MTX chemotherapy (5,000 mg/m2/dose, i.v., over 24 hours, days 8, 22, 36, 50) protocol was treated with 10 grams of Methothrexate (5gr/m^2 in 24 hours) for acute limphoblastic leukemia. He developed nephrotoxicity after the second cycle. There was no evident reason for such a high level of MTX. Creatinine level before treatment was 64 µmol/l and there were no signs of side-effects caused by the previous MTX therapy. At day 2 MTX level (67 µmol/l (ref >1.5 µmol/L) and creatinine level were measured (295 µmol/l) (see Table 3).

It is unknown if supportive therapy/care was given during and after this period. At day 2 at 22 pm Glucarpidase 1000 IE was given. At day 3 there was a sharp decline in MTX level while creatinine levels stayed unchanged. At day 4 there was a rebound of MTX because Glucarpidase doesn`t penetrate the cells in which MTX is stored. The outflow of MTX from the cells caused an incline in MTX blood levels. At day 10 there was an acceptable MTX level while for creatinine level it tooked 19 days to return to a level comparable with day 0. Same as with case 1, physicians were not sure how and when they could restart next MTX chemotherapy.

Discussion

The bacterial carboxylasepeptidase-G class of enzymes hydrolyze the terminal glutamate from MTX. A recombinant form of bacterial carboxypeptidase, glucarpidase has been developed to treat patients with HDMTX-induces acute kidney injury. Glucarpidase converts MTX to, what is believed ``non-toxic`` metabolites such as DAMPA (4-([2,4-diamino-6-(pteridinyl)methyl]-methylamino-benzoic acid)

and glutamic acid. It is reported that glucarpidase rapidly reduces systemic MTX concentration by >95% within 1 hour of administration and causes little rebound in systemic MTX concentration. Aside allergic type reaction glucarpidase it`s believed that it has little treatment-related toxicity [1,2].

Date	MTX blood level µmol/l	Creatinine µmol/l	Therapy
Day 0		64	HD-MTX 10 gr iv in 24 hours
Day 2; 14 pm	67		
Day 2; 20 pm	54	295	
Day 2; 22 pm	50	312	Glucarpidase 1000 IE
Day 3	0.2	316	
Day 4	8.9	293	
Day 5	4.4	276	
Day 6	2.4	311	
Day 7	2	313	
Day 8	2.1	278	
Day 9	1.7	243	
Day 10	1.0	210	
Day 11		157	
Day 12		136	
Day 13		117	
Day 14		111	
Day 15		86	
Day 16		83	
Day 19		64	

Table 3: Laboratory results and therapies applied to the patient.

One of the unexpected consequences of Glucarpidase therapy in both patients was a prolonged renal dysfunction. If we compare our patient data with data we found in the literature there is almost no difference in duration between patients who got Glucarpidase (median 21 days until full renal recovery) and those with only supportive therapy (19 and 12 days) [5]. A theoretic concern regarding the use of Glucarpidase is that the rapid formation of a MTX metabolite called DAMPA, which is almost 10-fold less soluble than MTX, may lead to further renal toxicity by precipitation in the renal tubules [5]. One of the ways to minimize this risk, which should be further investigated, is probably to administer Glucarpidase in more than 5 minutes together with hydration. In this way the forming of huge amounts of DAMPA in short period of time could be prevented. The use of supportive therapy should always be advised. Our current Glucapridase protocol will be updated with data on how long it takes for kidney function to fully recover.

On reviewing the literature we found that almost 19% of the patients treated with Glucarpidase continued to have grade III-IV renal toxicity after HD-MTX therapy. In the same article 60% of the treated patients developed grade III-IV hematological toxicities [2]. There is no data available which compares the occurrence of toxicities between patients who were treated with Glucarpidase or with supportive therapy only. If we closely look at our data and available data from the published literature there is a serious concern about effectiveness and safety of Glucarpidase.

Our second concern was if the measures taken to prevent the intoxication were appropriate. Before HDMTX therapy renal and liver function of both patients were screened en there were no signs of MTX side effects from previous therapies. Schwartz et al. analyzed the risk factors contributing to delayed MTX clearance in 43 patients treated with Glucarpidase [3]. The largest risk factor was a body mass index >25 kg/m^2 followed by relevant comedication (salicylates, NSAID`s, sulfonamides, beta-lactam antibiotics, aminoglycosides), urine pH<7, iv fluid intake <3l/m^2/24 hours, hepatic dysfunction, renal insufficiency prior to HD MTX, diarrhea and pleural effusions. None of the above mentioned risk factors were present in our cases. The check for relevant comedication is one of the factors that are missing in our current Glucarpidase protocol.

After treatment with Glucarpidase the question on how and when to restart HD-MTX therapy arised. Christensen et al. analyzed 13 of 20 patients who received Glucarpidase [2]. These 13 were rechallanged with HD-MTX within an average period of 28 days after Glucarpidase therapy. The next HD-MTX therapies (average 39 days) were given after kidney function fully recovered. 4 of the 13 patients got the full recommended HD-MTX dose. The rest (9 patients) received a reduced HD-MTX dose (50-75%). One of the patients who received a reduced dose developed acute kidney injury and another one developed neurotoxicity. The conclusion was that the restart of the HD-MTX therapy after Glucarpidase administration was well tolerated although close monitoring of both renal function and plasma MTX levels was necessary. A safe option for our two patients would be first a rechallenge with 50-75% HD-MTX after full recovery of the renal function. After first rechallenge kindey function and MTX levels should be closely monitored and if this goes well the second rechallenge should be with 100% HD-MTX.

One should also realize that MTX levels analyzed for these patients, using an immunoassay, not only measure MTX levels but also the metabolite DAMPA due to cross-reactivity. MTX levels measured by liquid chromatography mass spectrometry (LC-MS) showed lower levels of MTX present after the use of Glucarpidase. In patient 1 levels of MTX (day one and day 2 after Glucarpidase administration) were three to five times lover when analyzed by LC/MS. An LC/MS method for analyzing MTX is not present in each hospital due to its complexity and costs, so analyzing these samples on time acquires adequate logistics and communication [6,7].

If we look closely at the MTX levels of patient 1 before and after Glucarpidase therapy we doubt if there is added value of Glucarpidase in this setting. We see a decline in MTX levels probably caused by the supportive therapy. After the moment at which Glucarpidase was given there was no sharp decline in MTX levels compared to patient in case report 2. Glucarpidase should be given only in cases if supportive therapy is not effective enough in lowering MTX plasma levels.

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