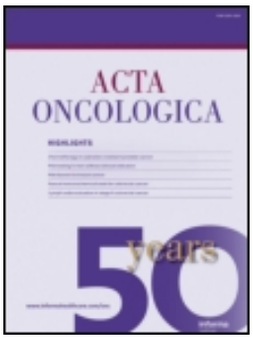

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# Mangafodipir as a cytoprotective adjunct to chemotherapy – a case report

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lesions enlarged and finally progressed to Stevens-Johnson Syndrome. She developed severe leucopenia ($0.1 \times 10^9$/L) and thrombocytopenia ($10 \times 10^9$/L) and was treated with filgrastim and thrombocyte-substitution, respectively. She became febrile and, despite empiric broad spectrum antibiotics, developed septic shock resistant to vaso-active agents. After a comatose state, she finally died on the 12th day of hospitalization, 3 weeks after onset of her first symptoms.

Capecitabine is an oral 5-fluorouracil (5-FU) prodrug mainly used for the treatment of CRC and breast cancer. The drug is activated in a 3-step process, yielding the active agent 5-FU (Figure 1). The final step of activation into 5-FU occurs preferentially in malignant cells. Main adverse reactions of 5-FU are myelotoxicity, mucositis and a hand-foot-syndrome. More than 80% of 5-FU is metabolized by dihydropyrimidine-dehydrogenase (DPD), the rate limiting step of 5-FU inactivation (Figure 1) [1].

Brivudine ((E)-5-(2-bromovinyl)-2′-deoxyuridine; BVDU) is a thymidine analogue for treatment of herpes zoster virus infections. Brivudine is hepatically converted to bromovinyluracil (BVU) and 2-deoxyribose-1-phosphate (Figure 1). Non-metabolized brivudine is phosphorylated by viral deoxythymidinekinase to BVDU monophosphate (BVDU-MP) and BVDU diphosphate (BVDU-DP). The latter is trapped in infected cells and is activated to BVDU triphosphate (BVDU-TP), inhibiting viral replication. Of note, BVU is an irreversible inhibitor of DPD, decreasing DPD activity by $\geq 90$, which normalizes only within 18 days. This inhibition is associated with a 5-15 fold increase in 5-FU-concentrations [2,3]. Due to enhanced 5-FU toxicity, the combination of these drugs is absolutely contraindicated. In 1993, fifteen fatal DDI with the antiviral sorivudine, another irreversible DPD-inhibitor, and the 5-FU-prodrug tegafur were reported in Japan [4].

In our patient, the combination of brivudine and capecitabine occurred despite clearly visible warning labels on the package. This is the first report of a fatal DDI between capecitabine and brivudine and the only case reported to the Swiss National Pharmacovigilance Center Swissmedic [6]. Alertness of the prescribers and optimal communication between health care providers are essential to prevent concomitant prescription of these drugs.

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# Mangafodipir as a cytoprotective adjunct to chemotherapy – a case report


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## To the Editor

The contrast agent mangafodipir (Teslascan®, GE Healthcare) for MRI of the liver has been in clinical use with a low profile of side effects for more than a decade. As a chelate of mangenese ion bound to fodipir, it also posesses superoxide dismutase (SOD)


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like properties which might be utilized in therapy [1–3]. Animal studies have shown that the agent protects mice against doxorubicin-induced cardiotoxocity and acetaminophen-induced hepatic failure. Furthermore, mangafodipir preserves blood cells during *in vitro* treatment with anticancer drugs like paclitaxel and oxaliplatin while enhancing cytotoxicity to cancer cells, as presented by Alexandre et al. in Journal of the National Cancer Institute (JNCI) in 2005 [4]. An editorial in the same issue of JNCI, recommended this agent to be tried out in a clinical setting [5]. On this background, and after thorough discussion, we decided to give mangafodipir to a young, critically ill patient with metastatic colon cancer in combination with oxaliplatinum-based chemotherapy. Hence, in this single case report, our experience with mangafodipir as a cytoprotective adjunct to chemotherapy is presented. As far as we know, this is the first human to receive this combination of pre-treatment and chemotherapy. The treatment was undertaken with the utterly informed consent of the patient and approved by the local ethical committee and the Norwegian Medicines Agency (NoMA).

In January 2003, a 21-year-old male with a previous history of Crohn's disease and primary sclerotic cholangitis (PSC), was diagnosed with right-sided colon cancer Duke's stage C. He was subsequently treated with hemicolectomy and adjuvant chemotherapy with 5-fluorouracil (5-FU) and levofolinate. Thirty-five months thereafter the disease had relapsed with metastases to the pelvic cavity, and severe abdominal and back pain required epidural administration of analgetics. Seven following cycles of palliative chemotherapy with irinotecan, 5-FU and levofolinate had little impact on the disease. Liver metastases were now detected, and the patient was confined to bed rest. Therefore, chemotherapy was changed to the "Nordic FLOX-regimen" [6] consisting of oxaliplatin (2 hour i.v. infusion of 85 mg/m$^2$ on day 1), 5-FU (500 mg/m$^2$ bolus i.v. on days 1–2) and levofolinate (60 mg/m$^2$ bolus i.v. on days 1–2). To this, mangafodipir (5 μmol/kg) was added as an i.v. infusion half an hour before chemotherapy on both days, based on the pre-clinical findings by Alexandre et al. [4]. Over the following 8 months the patient received a total of 15 cycles of FLOX, 14 of these with mangafodipir included. The response to treatment was monitored by CT scans after every second cycle and by regular blood measurements, including CEA.

No side effects were seen during pre-infusion of mangafodipir. After the 7$^{th}$ cycle and onward the patient presented occasional hand tremor and complained of insomnia. More importantly, no severe side effects of FLOX like neutropenic fever or mucositis occurred. Only during the 5$^{th}$ cycle when mangafodipir was deliberately left out did the patient experience peripheral sensory neuropathy (grade 1–2). After five cycles the performance status was drastically improved and the demand for analgetics was greatly reduced. Neutropenia or thrombocytopenia never occurred (Table I) and no chemotherapy-cycle was delayed due to laboratory findings. Serum bilirubin, ASAT, ALP and GT were slightly elevated before start of treatment and increased during the treatment period, especially after removal of a stent in the bile duct. Serum values of CRP and CEA were elevated and albumin low. MRI of the brain after the 14$^{th}$ cycle showed increased T1 signal intensity in corpus callosum, pituitary gland, medulla oblongata, spine and basal ganglia, and may be suspected to be caused by accumulation of manganese in these structures. After nine cycles progression of disease and symptoms again became evident, although only minor objective findings were present at CT or by CEA elevation. Due to continued effect on performance status and pain, we decided to continue treatment despite these signs of progression. In March 2007 at the age of 25 the patient died, 52 months after the primary disease was diagnosed and 15 months after detection of metastases.

Altogether, chemotherapy was safe and well tolerated in this young patient who received pre-infusion of mangafodipir. Although speculative, absence of neutropenia, neurotoxicity and mucositis in this single patient receiving a very high accumulated dose of oxaliplatin (1 275 mg/m$^2$) may be consistent with cytoprotective activity by mangafodipir. Treatment response of FLOX in combination with mangafodipir was rapid with a strikingly lowered level of

Table I. Hematological and biochemical findings. Median value and range for different parameters derived from all blood samples taken during the FLOX treatment. ALAT: Alanine transaminase; ASAT: Aspartate transaminase; GT: Gamma-glutamyl transferase; CRP: C-reactive protein; CEA: Carcinoembryonic antigen.

| Parameter (normal limits) | Median value (range) |
|---|---|
| Hemoglobin (13.4–17.0 g/dl) | 13.0 (10.7–15.2) |
| Total white blood cell count (3.5–8.8 ×109/l) | 13.4 (8.0–28.2) |
| Total platelet count (145–348 ×109/l) | 216 (146–637) |
| Neutrophiles (1.3–5.1 ×109/l) | 8.3 (4.4–22.4) |
| Total bilirubin (5–25 μmol/l) | 195 (43–295) |
| Creatinine (60–105 μmol/l) | 42 (28–59) |
| ASAT (15–45 U/l) | 109 (48–196) |
| ALAT (10–70 U/l) | 65 (37–129) |
| Lactate dehydrogenase (105–205 U/l) | 164 (111–283) |
| GT (10–80 U/l) | 408 (187–1072) |
| Alkaline phosphatase (35–105 U/l) | 346 (231–779) |
| CRP (0–5 mg/l) | 42 (15–103) |
| Total albumin (36–48 g/l) | 23 (12–30) |
| CEA (0–5 μmol/l) | 8 (5–19) |

pain and improved performance status. Thus the patient tolerated a total dose of oxaliplatin about 50% higher than a proposed limit (780–850 mg/m$^2$) for accumulated neuropathy grade 2–3 [7] and about twice the dose inducing peripheral neuropathy and neutropenia in patients treated with a much similar FOLFOX4 regimen for colorectal cancer [8].

To our knowledge the patient is the first human to receive mangafodipir repeatedly and over such a long time period. Thus the accumulated dose (140 μmol/kg) was 5–6 times higher than the highest single dose given in liver MRI (25 μmol/kg). Concern has been raised that accumulation of manganese ions in basal ganglia predispose for Parkinsonism-like motoric disturbances, psychiatric disorders and symptoms like headache, apathy, and insomnia [9]. Such manifestations have been reported in miners and welders after chronic exposure to manganese by inhalation with secondary high concentrations in the brain. The present patient experienced insomnia and a light hand tremor which might correspond to manganese accumulation in specific brain structures as was documented by MRI. However, these symptoms could also be caused by chemotherapy, particularly to the high accumulated dose of oxaliplatin [7] or by disease progression as such.

Of future importance, the dose of mangafodipir (10 μmol/kg) applied in each cycle was probably much higher than that needed for therapeutic effects. Eagerly awaiting therefore are results from an ongoing Phase II trial in Sweden applying mangafodipir at a considerably lower dose (2 μmol/kg/cycle) as an adjunct to FOLFOX4 in patients with colon cancer. In conclusion, this case report may strengthen the possibility, as documented in preclinical studies, of using mangafodipir as an effective adjunct to chemotherapy with oxaliplatin and other anticancer drugs.

***Declaration of interest:*** Per Jynge is shareholder in a holding company owning shares in PledPharma AB, a Swedish R&D company promoting mangafodipir for use in therapy.

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# An unusual presentation of hand-foot syndrome at the hidden area: The scrotum and penis

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