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Platinum Coordination Complexes

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OVERVIEW

The platinum coordination complexes are a group of antineoplastic agents that are usually classified as alkylating agents, but which have distinctive features. Their anticancer activity appears to relate to the cross linking of DNA molecules in a fashion similar to standard alkylating agents. The DNA adducts formed by the platinum-containing complexes inhibit DNA replication and lead to strand breaks and miscoding, thereby eliciting apoptosis as well as inhibition of RNA and protein synthesis.

The first of the platinum coordination complex with alkylating activity introduced into clinical medicine was cisplatin. Cisplatin was first described in 1845 as Peyrone's salt and in 1893 its chemical structure was elucidated. In the 1960s, cisplatin was shown to have anticancer activity in vitro and in vivo. Upon this discovery, multiple platinum containing compounds were synthesized and studied for anticancer activity in screening assays. Cisplatin was found to have the most potency. Cisplatin (Platinol) was approved for use in the United States in 1978 and became an important component of therapies of ovarian, testicular, bladder, head and neck, esophagus, lung and colon cancer. Carboplatin (Paraplatin) was approved for treatment of ovarian cancers in 1989 and oxaliplatin (Eloxatin) for colorectal cancer in 2003. The platinum coordination complexes have similar antineoplastic activities and are used largely for advanced cancer and in combination with other agents. All must be given by intravenous infusion, and all are associated with significant renal, intestinal, bone marrow and neurologic toxicities. The platinum-containing agents are also mutagenic, teratogenic and carcinogenic, and their use has been associated with an increased risk of secondary leukemias.

Cisplatin and carboplatin are rare causes of liver injury, while oxaliplatin has been associated with a high rate of histological changes when used prior to hepatic resection of colorectal cancer liver metastases. The most common changes linked to oxaliplatin are sinusoidal dilatation and vascular injury that may precede the ultimate development of nodular regenerative hyperplasia and noncirrhotic portal hypertension. The histological changes have little clinical significance, but progression to nodular regenerative hyperplasia can result in complications of ascites, variceal hemorrhage and hepatic decompensation. Once chemotherapy is stopped, the histological changes usually regress and nodular regenerative hyperplasia generally improves and rarely progresses. The platinum coordination complexes have other toxicities that are clinically significant and often overshadow the effects on the liver.

Each of the platinum coordination complexes is described separately, but references to their pharmacology and hepatotoxicity are given together after this introductory section.

Drug Class: Antineoplastic Agents; Subclass: Alkylating Agents

ANNOTATED BIBLIOGRAPHY

References updated: 20 January 2014

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999; mentions that cisplatin had been reported to cause dose related serum enzyme elevations and has been linked to steatosis and necrosis, whereas carboplatin has been linked to rare instances of cholestatic and hepatocellular injury).

DeLeve LD. Liver sinusoidal endothelial cells and liver injury. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 139-43.

(Review of liver injury to sinusoidal endothelial cells caused by medications mentions that oxaliplatin as capable of causing sinusoidal dilatation, peliosis hepatis, nodular regenerative hyperplasia (NRH) and sinusoidal obstruction syndrome [SOS]).

Chabner BA, Bertino J, Clearly J, Ortiz T, Lane A, Supko JG, Ryan DP. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1677-730.

(Textbook of pharmacology and therapeutics).

Peyrone M. Ueber die einwirkung des ammoniaks auf platinchlorür. der Chemie und Pharmacie 1844; 51: 1-29. Not in PubMed

(Initial description of cisplatin).

Lippman AJ, Helson C, Helson L, Krakoff IH. Clinical trials of cis-diamminedichloroplatinum (NSC-119875). Cancer Chemother Rep 1973; 57: 191-200. PubMed PMID: 4126381.

(Pilot study of cisplatin in 26 patients with advanced malignancies; 1 [4%] patient on high doses had transient mild elevations in AST with resolution in 5 days).

Hill JM, Loeb E, MacLellan A, Hill NO, Khan A, King JJ. Clinical studies of platinum coordination compounds in the treatment of various malignant diseases. Cancer Chemother Rep 1975; 59: 647-59. PubMed PMID: 1203889.

(Among 78 patients with cancer treated with cisplatin, side effects included nausea, vomiting, diarrhea, tinnitus, hearing loss, bone marrow suppression, nephropathy, and minor elevations of AST [peak value 81 U/L]).

Hayes DM, Cvitkovic E, Golbey RB, Scheiner E, Helson L, Krakoff IH. High dose cis-platinum diammine dichloride. Cancer 1977; 39: 1372-81. PubMed PMID: 856437.

(Among 60 patients treated with escalating doses of cisplatin, 2 had transient AST elevations without jaundice or change in Alk P).

Jacobs C, Bertino JR, Fogginet DR, Fee WE, Goode RL. 24-hour infusion of cis-platinum in head and neck cancers. Cancer 1978; 42: 2135-40. PubMed PMID: 719601.

(Among 18 patients given 34 courses of cisplatin for advanced head and neck cancers, 2 had transient AST elevations; no details provided on symptoms or jaundice).

Cavalli F, Tschopp L, Sonntag RW, Zimmermann A. A case of liver toxicity following cis-dichlorodiammineplatinum(II) treatment. Cancer Treat Rep 1978; 62: 2125-6. PubMed PMID: 751721.

(47 year old man developed jaundice 4 weeks after an initial cycle of cisplatin [bilirubin 2.2 mg/dL, AST 58 U/L, Alk P 55 U/L], values falling to normal 4 weeks later, and similar elevations occurring with subsequent cycles until a peak bilirubin 9.8 mg/dL after fifth course [AST 144 U/L, biopsy showing fatty change, focal necrosis and cholestasis]: cisplatin Case 1).

Canetta R, Franks C, Smaldone L, Bragman K, Rozencweig M. Clinical status of carboplatin. Oncology (Williston Park) 1987; 1: 61-70. PubMed PMID: 3079484.

(Summary of clinical studies of carboplatin, a cisplatin derivative; carboplatin and cisplatin have similar efficacy against ovarian, cervical, and small cell lung cancer, but carboplatin is better tolerated; ALT elevations in 16% of patients, bilirubin in 4%, no mention of clinically apparent hepatotoxicity).

Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, Vogelsang GB, et al. Veno-occlusive disease of the liver following bone marrow transplantation. Transplantation 1987; 4: 778-83. PubMed PMID: 3321587.

(Among 235 patients undergoing bone marrow transplantation between 1982 and 1985, sinusoidal obstruction syndrome [SOS] developed in 52 [22%] of whom half died, making SOS the third most common cause of death in this population).

Canetta R, Bragman K, Smaldone L, Rozencweig M. Carboplatin: current status and future prospects. Cancer Treat Rev 1988; 15B: 17-32. PubMed PMID: 2841021.

(Summary of results of prelicensure trials of carboplatin; no mention of ALT elevations or hepatotoxicity).

Hruban RH, Sternberg SS, Meyers P, Fleisher M, Menendez-Botet C, Boitnott JK. Fatal thrombocytopenia and liver failure associated with carboplatin therapy. Cancer Invest 1991; 9: 263-8. PubMed PMID: 1913229.

(18 year old man with acute lymphocyte leukemia and cirrhosis developed severe thrombocytopenia within 6 days of starting carboplatin [platelet count 15,000/μL, bilirubin 5.6 mg/dL, AST 4690 U/L, Alk P 150 U/L] and death from multiorgan failure 10 days later; autopsy showed cirrhosis and marked centrolobular necrosis).

Tran A, Housset C, Boboc B, Tourani J-M, Carnot F, Berthelot P. Etoposide (VP 16-213) induced hepatitis: report of three cases following standard dose treatments. J Hepatol 1991; 12: 36-9. PubMed PMID: 2007774.

(3 patients, ages 52-73 years, developed jaundice 1-5 months after starting etoposide with several other cyclic antineoplastic agents including cisplatin and cyclophosphamide in two [bilirubin 4.2-13.0 mg/dL, ALT 790-2270 U/L, Alk P 181-280 U/L], resolving in 4-10 weeks and no recurrence on a similar regimen without etoposide in one patient).

Bishop JF. Current experience with high-dose carboplatin therapy. Semin Oncol 1992; 19: 150-4. PubMed PMID: 1411626.

(Dose limiting toxicities of high dose carboplatin followed by bone marrow transplantation were reversible cholestatic hepatitis, renal dysfunction and ototoxicity).

Washington K, Lane KL, Meyers WC. Nodular regenerative hyperplasia in partial hepatectomy specimens. Am J Surg Pathol 1993; 17: 1151-8. PubMed PMID: 8214260.

(Pathological review of liver resections from 72 patients showed nodular regenerative hyperplasia in 5, all of whom had colon cancer metastases and had been treated with chemotherapy: usually 5-fluorouracil; 9 patients had hyperplastic foci some of whom had received cisplatin and other agents including cyclophosphamide, VP-16 and carmustine).

Cersosimo RJ. Hepatotoxicity associated with cisplatin chemotherapy. Ann Pharmacother 1993; 27: 438-41. PubMed PMID: 8477119.

(69 year old man developed liver enzyme elevations during second day of each cycle of cisplatin therapy).

Ayash LJ, Elias A, Wheeler C, Reich E, Schwartz G, Mazanet R, Tepler I, et al. Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: a feasibility study. J Clin Oncol 1994; 12: 37-44. PubMed PMID: 7505807.

(Among 29 men with advanced testicular cancer receiving carboplatin and etoposide, 6 [21%] developed "elevation of liver function tests" but no mention of veno-occlusive disease).

Hartmann JT, Lipp H-P. Toxicity of platinum compounds. Expert Opin Pharmacother 2003; 4: 889-901. PubMed PMID: 12783586.

(Review of pharmacology, mechanism of action, adverse effects and tolerance of platinum containing alkylating agents; "Mild reversible increases in liver function tests can occur in patients who have received platinum compounds. However, the platinum compounds are generally not classified as hepatotoxic drugs").

Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004; 15: 460-6. PubMed PMID: 14998849.

(Among 153 patients undergoing hepatic resection for colon cancer, centrolobular congestion and necrosis was found in nontumor liver tissue in 51% of those who received neoadjuvant chemotherapy, but in none undergoing surgery alone; oxiplatin as the most frequently implicated agent; follow up biopsies often showed fibrosis).

Sebagh M, Plasse M, Lévi F, Adam R. Severe hepatic sinusoidal obstruction and oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer: a real entity? Ann Oncol 2005; 16: 331; author reply 332-3. PubMed PMID: 15668292.

(Letter in response to Rubbia-Brandt [2004] questioning the clinical significance of the histological findings; among 700 patients treated "mainly" by oxaliplatin, the authors mention no increase in operative mortality).

Tisman G, MacDonald D, Shindell N, Reece E, Patel P, Honda N, Nishimora EK, et al. Oxaliplatin toxicity masquerading as recurrent colon cancer. J Clin Oncol 2004; 22: 3202-4. PubMed PMID: 15284280.

(69 year old man with adenocarcinoma of the rectum developed ascites after radiation and a fourth course of chemotherapy with capecitabine and oxaliplatin, with a hepatic venous pressure gradient of 18 mm Hg and liver biopsy showing sinusoidal obstruction syndrome and no cirrhosis [bilirubin and Alk P elevated but ALT normal], with progressive hepatic and multiorgan failure and death).

Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005; 200: 845-53. PubMed PMID: 15922194.

(A

mong patients undergoing hepatic resections for colorectal cancer metastases, steatohepatitis and liver injury was more common among the 14 who received oxaplatin and/or irinotecan than 10 who received 5-FU alone or 13 given no chemotherapy).

Rubbia-Brandt L, Mentha G, Terris B. Sinusoidal obstruction syndrome is a major feature of hepatic lesions associated with oxaliplatin neoadjuvant chemotherapy for liver colorectal metastases. J Am Coll Surg 2006; 202: 199-200. PubMed PMID: 16377516.

(Letter in response to Fernandez [2005] suggesting that some of the hepatic changes represented sinusoidal obstruction syndrome).

Lu Y, Cederbaum AI. Cisplatin-induced hepatotoxicity is enhanced by elevated expression of cytochrome P450 2E1. Toxicol Sci 2006; 89: 515-23. PubMed PMID: 16251482.

(Prooxidants and stimulation of CYP 2E1 enhanced while glutathione repletion decreased injury to hepatocytes by cisplatin in vitro).

Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, Azoulay D, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006; 24: 4983-90. PubMed PMID: 17075116.

(Among 92 patients undergoing resection of colorectal liver metastases, those who received chemotherapy [mostly oxaliplatin and fluorouracil] were more likely to have vascular changes, but had similar rates of steatosis compared to those who did not receive chemotherapy).

Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, Xiong HQ, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006; 24: 2065-72. PubMed PMID: 16648507.

(Among 406 patients undergoing hepatic resection for colorectal metastases, preoperative chemotherapy with oxaliplatin was associated with sinusoidal dilatation [19% vs 2%], whereas irinotecan was associated with steatohepatitis [20% vs 4.4%] which was associated with higher 90 day mortality rates).

Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006; 243: 1-7. PubMed PMID: 16371728.

(Retrospective analysis of 67 patients undergoing hepatic resection of colorectal liver metastasis, found preoperative chemotherapy was associated with higher rates of complications [38% vs 14%] and hepatic failure [11% vs 0%] compared to no chemotherapy, despite no difference in degree of elevation of liver tests during first 10 postoperative days).

Higashiyama H, Harabayashi T, Shinohara N, Chuma M, Hige S, Nonomura K. Reactivation of hepatitis in a bladder cancer patient receiving chemotherapy. Int Urol Nephrol 2007; 39: 461-3. PubMed PMID: 17171423.

(A 59 year old woman with bladder cancer who was an HBV carrier developed severe reactivation of hepatitis B after 2 cycles of chemotherapy with methotrexate, epiadriamycin and cisplatin, resolving with lamivudine and prednisolone therapy).

Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey J-N, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Brit J Surg 2007; 94: 274-86. PubMed PMID: 1731528.

(Systematic review of liver toxicity occurring after preoperative systemic chemotherapy for colorectal liver metastases, oxilatin has been linked to histological changes in microvasculature of the liver but not with increased mortality rate or hepatic failure).

Liao Y, Lu X, Lu C, Li G, Jin Y, Tang H. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacol Res 2008; 57: 125-31. PubMed PMID: 18282716.

(Analysis of factors that decreased hepatotoxicity of cisplatin in animal model found antioxidants and glutathione precursors were effective in decreasing ALT elevations during therapy).

Schouten van der Velden AP, Punt CJ, Van Krieken JH, Derleyn VA, Ruers TJ. Hepatic veno-occlusive disease after neoadjuvant treatment of colorectal liver metastases with oxaliplatin: a lesson of the month. Eur J Surg Oncol 2008; 34: 353-5. PubMed PMID: 17207961.

(54 year old man with colon cancer metastatic to liver underwent attempt at resection followed by 11 cycles of chemotherapy [5-fluorouracil, and oxaliplatin] and repeat hepatic resection, but developed liver failure and died postoperatively, autopsy showing absence of central hepatic vein in the area of the resected tumor).

Morris-Stiff G, Tan YM, Vauthey JN. Hepatic complications following preoperative chemotherapy with oxaliplatin or irinotecan for hepatic colorectal metastases. Eur J Surg Oncol 2008; 34: 609-14. PubMed PMID: 17764887.

(Systematic review of the literature on oxaliplatin and liver injury; histological vascular changes with sinusoidal damage occurs in at least 20% of patients treated with oxilaplatin, but it is not associated with an increase in mortality in most studies).

Khan AZ, Morris-Stiff G, Makuuchi M. Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. J Hepatobiliary Pancreat Surg 2009; 16: 137-44. PubMed PMID: 19093069.

(Review of liver injury from neoadjuvant therapy of colon cancer metastases; oxilaplatin is frequently associated with sinusoidal injury, but rarely with clinically significant sinusoidal obstruction syndrome).

Brouquet A, Benoist S, Julie C, Penna C, Beauchet A, Rougier P, Nordlinger B. Risk factors for chemotherapy-associated liver injuries: A multivariate analysis of a group of 146 patients with colorectal metastases. Surgery 2009; 145: 362-71. PubMed PMID: 19303984.

(Analysis of factors predictive of steatosis, steatohepatitis and sinusoidal dilatation in liver tissue from 146 patients undergoing liver resection of colorectal metastases found that oxaliplatin based chemotherapy was a risk factor for sinusoidal changes [Hazard ratio 4.4]).

Kudo D, Tsutsumi S, Akasaka H, Jin H, Ohashi T, Muroya T, Hasebe T, et al. [Predictive factors for histopathological liver injury in the patients who received preoperative systemic chemotherapy for colorectal liver metastases]. Gan To Kagaku Ryoho 2009; 36: 2025-7. Japanese. PubMed PMID: 20037312.

(Abstract only: Among 47 patient undergoing hepatic resections for metastatic colorectal cancer, sinusoidal dilation but not steatohepatitis was more common among those who received preoperative oxaliplatin chemotherapy).

van den Broek MA, Olde Damink SW, Driessen A, Dejong CH, Bemelmans MH. Nodular regenerative hyperplasia secondary to neoadjuvant chemotherapy for colorectal liver metastases. Case Report Med 2009; 457975. PubMed PMID: 19997518.

(Two men, ages 68 and 51 years, developed nodular regenerative hyperplasia after 6 cycles of oxaliplatin/capecitabine with minimal liver test abnormalities [bilirubin 2.3 and 1.2 mg/dL, ALT 23 and 57 U/L, Alk P 237 and 205 U/L], one dying of hepatic failure after partial hepatectomy of residual tumor, and the second developing variceal hemorrhage and encephalopathy after one resection but eventually recovering and tolerating a repeat hepatic resection 18 months later).

Cleary JM, Tanabe KT, Lauwers GY, Zhu AX. Hepatic toxicities associated with the use of preoperative systemic therapy in patients with metastatic colorectal adenocarcinoma to the liver. Oncologist 2009; 14: 1095-105. PubMed PMID: 19880627.

(Review of hepatic complications of oxaliplatin chemotherapy for colorectal cancer; sinusoidal dilation reported in 10-61% of patients sometimes with greater postoperative morbidity, but with no greater mortality).

Slade JH, Alattar ML, Fogelman DR, Overman MJ, Agarwal A, Maru DM, Coulson RL, et al. Portal hypertension associated with oxaliplatin administration: clinical manifestations of hepatic sinusoidal injury. Clin Colorectal Cancer 2009; 8: 225-30. PubMed PMID: 19822514.

(Six patients developed noncirrhotic portal hypertension after 6 to 12 cycles of oxaliplatin and 5-FU chemotherapy [6-15 months] for metastatic colorectal cancer, including 3 men, 3 women, ages 37 to 69 years, all of whom developed thrombocytopenia [53-128,000/μL], splenomegaly and varices, 2 with variceal hemorrhage and 2 with ascites).

McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology 2010; 51: 1450-60. PubMed PMID: 20373370.

(Review of liver complications of bone marrow [hematopoietic cell] transplantation, which have become less frequent with better understanding of their causes and means of prevention; the rate of sinusoidal obstruction syndrome [SOS] has decreased because of avoidance of more aggressive ablative therapies [total body irradiation and high doses of cyclophosphamide] and better understanding of pharmacokinetics of the alkylating agents).

Soubrane O, Brouquet A, Zalinski S, Terris B, Brézault C, Mallet V, Goldwasser F, Scatton O. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin-based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. Ann Surg 2010; 251: 454-60. PubMed PMID: 20160638.

(Among 78 patients undergoing resection of hepatic metastases from colon cancer after oxaliplatin neoadjuvant therapy, vascular changes occurred in 46 [59%] and 5 had fibrosis; AST elevations occurred in 61% of patients with vascular changes and 25% of those without).

Pessaux P, Chenard MP, Bachellier P, Jaeck D. Consequences of chemotherapy on resection of colorectal liver metastases. J Visc Surg 2010; 147: e193-201. PubMed PMID: 20655821.

(Review of the role and liver toxicity of chemotherapy for colorectal metastases; oxaliplatin is associated with sinusoidal injury and irinotecan with chemotherapy induced steatohepatitis [CASH]).

Takamoto T, Hashimoto T, Sano K, Maruyama Y, Inoue K, Ogata S, Takemura T, et al. Recovery of liver function after the cessation of preoperative chemotherapy for colorectal liver metastasis. Ann Surg Oncol 2010; 17: 2747-55. PubMed PMID: 20425145.

(Indocyanine green [ICG] testing of 55 patients receiving chemotherapy before hepatic resection for colorectal cancer metastases showed improvements in ISG clearance within 4 weeks of stopping therapy).

Ryan P, Nanji S, Pollett A, Moore M, Moulton CA, Gallinger S, Guindi M. Chemotherapy-induced liver injury in metastatic colorectal cancer: semiquantitative histologic analysis of 334 resected liver specimens shows that vascular injury but not steatohepatitis is associated with preoperative chemotherapy. Am J Surg Pathol 2010; 34: 784-91. PubMed PMID: 20421779.

(Among 334 patients undergoing hepatic resection for colorectal cancer metastases, marked hepatic steatosis was uncommon [9%] and correlated with BMI rather than chemotherapy, while sinusoidal lesions were present in 35% of cases and correlated with oxaliplatin use; neither correlated with immediate operative outcome).

Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, Eng C, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010; 28: 2549-55. PubMed PMID: 20406923.

(Spleen size as measured by CT increased [by an average of 22%] in 86% of 96 patients treated with oxaliplatin and 5FU for colorectal cancer and correlated with thrombocytopenia and sinusoidal injury seen on subsequent liver biopsy of 60 patients).

Komori H, Beppu T, Baba Y, Horino K, Imsung C, Masuda T, Hayashi H, et al. Histological liver injury and surgical outcome after FOLFOX followed by a hepatectomy for colorectal liver metastases in Japanese patients. Int J Clin Oncol 2010; 15: 263-70. PubMed PMID: 20238233.

(Comparison of 15 patients who received oxaliplatin to 12 who received no chemotherapy before hepatic resection of metastatic colorectal cancer showed higher rates of marked sinusoidal dilatation [33% vs 8%] and "blue liver" [47% vs 0%], but similar rates of steatosis [40% vs 33%] in oxaliplatin treated subjects).

Heo J, Shin KY, Kwon YH, Park SY, Jung MK, Cho CM, Tak WY, Kweon YO. [A case of portal hypertension after the treatment of oxaliplatin based adjuvant chemotherapy for rectal cancer]. Korean J Gastroenterol 2011; 57: 253-7. Korean. PubMed PMID: 21519180.

(A

bstract only: 35 year old woman developed portal hypertension after 12 cycles of oxaliplatin for rectal cancer).

Makowiec F, Möhrle S, Neeff H, Drognitz O, Illerhaus G, Opitz OG, Hopt UT, zur Hausen A. Chemotherapy, liver injury, and postoperative complications in colorectal liver metastases. J Gastrointest Surg 2011; 15: 153-64. PubMed PMID: 21061183.

(Among 102 patients undergoing hepatic resections for colorectal cancer metastases, steatosis was most common in those who had preoperative chemotherapy regardless of regimen [46% vs 18%], but BMI was a stronger risk factor and steatosis did not correlate with poor outcome; none of 22 patients who received oxaliplatin died or developed hepatic insufficiency).

Tamandl D, Klinger M, Eipeldauer S, Herberger B, Kaczirek K, Gruenberger B, Gruenberger T. Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. Ann Surg Oncol 2011; 18: 421-30. PubMed PMID: 20844968.

(Among 199 patients undergoing hepatic resection for colorectal metastases, findings of hepatic steatosis did not correlate with decreased survival, whereas severe sinusoidal lesions [found in 18% of oxaliplatin recipients vs 6% of controls] were associated with markedly reduced survival).

Vincenzi B, Daniele S, Frezza AM, Berti P, Vespasiani U, Picardi A, Tonini G. The role of S-adenosylmethionine in preventing oxaliplatin-induced liver toxicity: a retrospective analysis in metastatic colorectal cancer patients treated with bevacizumab plus oxaliplatin-based regimen. Support Care Cancer 2012; 20: 135-9. PubMed PMID: 21229271.

(Among 78 patients with metastatic colon cancer who received 3 cycles of oxaliplatin, capecitabine and bevacizumab with or without S-adenosyl-methionine [SAMe], those on SAMe had lower peak ALT levels [98 vs 179 U/L] and less frequent discontinuations).

Nam SJ, Cho JY, Lee HS, Choe G, Jang JJ, Yoon YS, Han HS, et al. Chemotherapy-associated hepatopathy in korean colorectal cancer liver metastasis patients: oxaliplatin-based chemotherapy and sinusoidal injury. Korean J Pathol 2012; 46: 22-9. PubMed PMID: 23109974.

(Among 89 patients with colorectal cancer undergoing hepatic resection for metastases, sinusoidal dilation, centrolobular fibrosis, small vessel obliteration and hepatocyte plate disruption were more frequent after oxaliplatin than fluorouracil chemotherapy and correlated with number of cycles).

Viganò L, Ravarino N, Ferrero A, Motta M, Torchio B, Capussotti L. Prospective evaluation of accuracy of liver biopsy findings in the identification of chemotherapy-associated liver injuries. Arch Surg 2012; 147: 1085-91. PubMed PMID: 22910896.

(Prospective study of 100 patients with colorectal cancer and hepatic metastases found liver biopsy was accurate in demonstrating marked steatosis [>30%] but not in detecting sinusoidal dilation [28% in oxaliplatin recipients] or steatohepatitis [19% in irinotecan recipients]).

Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-associated liver injury in patients with colorectal liver metastases: a systematic review and meta-analysis. Ann Surg Oncol 2012; 19: 4287-99. PubMed PMID: 22766981.

(Systematic review of literature on chemotherapy induced liver injury in patients with colorectal cancer; isoplatinin regimens are associated with a higher rate of sinusoidal injury [17% vs 6%] but not steatosis [11.5% vs 9.8%], and rates are reduced by concurrent bevacizumab therapy).

Vreuls CP, Van Den Broek MA, Winstanley A, Koek GH, Wisse E, Dejong CH, Olde Damink SW, et al. Hepatic sinusoidal obstruction syndrome (SOS) reduces the effect of oxaliplatin in colorectal liver metastases. Histopathology 2012; 61: 314-8. PubMed PMID: 22571348.

(Among 50 patients with hepatic resection for colorectal cancer after 1 to 12 cycles [mean = 6] of oxaliplatin, 32 [64%] had changes of sinusoidal obstruction syndrome among whom tumor regression scores were reduced compaired to patients without the sinusoidal histological changes; no discussion of survival).

Robinson SM, White SA. Hepatic sinusoidal obstruction syndrome reduces the effect of oxaliplatin in colorectal liver metastases. Histopathology 2012; 61: 1247-8. PubMed PMID: 23043422.

(Editorial in response to Vreuls [2012]).

Bissonnette J, Généreux A, Côté J, Nguyen B, Perreault P, Bouchard L, Pomier-Layrargues G. Hepatic hemodynamics in 24 patients with nodular regenerative hyperplasia and symptomatic portal hypertension. J Gastroenterol Hepatol 2012; 27: 1336-40. PubMed PMID: 22554152.

(Among 24 patients with various forms of nodular regenerative hyperplasia [NRH], wedged hepatic venous pressure gradients [HVPG: range 2 to 17, mean = 8.9 mm Hg] were lower than directly obtained portal venous pressure gradients [range 16 to 35, mean = 20.5 mmHg], indicating that HVPG measurements are inaccurate in NHR).

Jardim DL, Rodrigues CA, Novis YA, Rocha VG, Hoff PM. Oxaliplatin-related thrombocytopenia. Ann Oncol 2012; 23: 1937-42. PubMed PMID: 22534771.

(Review of thombocytopenia related to oxaliplatin therapy which has three possible causes: myleosuppression, immune destruction or portal hypertension and liver disease).

Pilgrim CH, Thomson BN, Banting S, Phillips WA, Michael M. The developing clinical problem of chemotherapy-induced hepatic injury. ANZ J Surg 2012 ; 82: 23-9. PubMed PMID: 22507491.

(Review of types of liver injury from chemotherapy; oxaliplatin is associated with vascular and sinusoidal injury whereas irinotecan is linked to steatohepatitis).

Benavides M, Pericay C, Valladares-Ayerbes M, Gil-Calle S, Massutí B, Aparicio J, Dueñas R, et al. Oxaliplatin in combination with infusional 5-fluorouracil as first-line chemotherapy for elderly patients with metastatic colorectal cancer: a phase II study of the Spanish Cooperative Group for the Treatment of Digestive Tumors. Clin Colorectal Cancer 2012; 11: 200-6. PubMed PMID: 22421001.

(Among 129 elderly patients with metastatic colorectal cancer treated with oxaliplatin and fluorouracil, 21 [16%] had ALT or AST elevations, but levels >5 times ULN occurred in only 3 [2%]).

Narita M, Oussoultzoglou E, Chenard MP, Fuchshuber P, Rather M, Rosso E, Addeo P, et al. Liver injury due to chemotherapy-induced sinusoidal obstruction syndrome is associated with sinusoidal capillarization. Ann Surg Oncol 2012; 19: 2230-7. PubMed PMID: 22402811.

(Among 98 patients with colorectal cancer undergoing hepatic resection for metastases, 39 [36 of whom had received oxaliplatin] had changes of sinusoidal obstruction syndrome and degree of changes correlated with isocyanine green [ICG] retention and overexpression of CD34 indicating capillarization of hepatic sinusoids).

Vietor NO, George BJ. Oxaliplatin-induced hepatocellular injury and ototoxicity: a review of the literature and report of unusual side effects of a commonly used chemotherapeutic agent. J Oncol Pharm Pract 2012; 18: 355-9. PubMed PMID: 22333669.

(46 year old woman with colorectal cancer developed ototoxicity and marked ALT elevations [~850 U/L] during cycle 2 of fluorouracil, oxaliplatin and leucovorin, that resolved when oxaliplatin was held, and then recurred despite a reduced dose of oxaliplatin).

Agostini J, Benoist S, Seman M, Julié C, Imbeaud S, Letourneur F, Cagnard N, et al. Identification of molecular pathways involved in oxaliplatin-associated sinusoidal dilatation. J Hepatol 2012; 56: 869-76. PubMed PMID: 22200551.

(Analysis of differences in gene expression in livers of patients with and without sinusoidal dilation after oxaliplatin therapy identified increased expression of genes involved with angiogenesis, inflammation and collagen production in response to sinusoidal injury).

Hoff PM, Saad ED, Costa F, Coutinho AK, Caponero R, Prolla G, Gansl RC. Literature review and practical aspects on the management of oxaliplatin-associated toxicity. Clin Colorectal Cancer 2012; 11: 93-100. PubMed PMID: 22154408.

(Review of adverse effects of oxaliplatin including hepatotoxicity which appears to be due to sinusoidal cell injury).

Tsimberidou AM, Leick MB, Lim J, Fu S, Wheler J, Piha-Paul SA, Hong D, et al. Dose-finding study of hepatic arterial infusion of oxaliplatin-based treatment in patients with advanced solid tumors metastatic to the liver. Cancer Chemother Pharmacol 2013; 71: 389-97. PubMed PMID: 23143207.

(Among 76 patients with hepatic metastases of different cancers given hepatic artery infusions of oxaliplatin [369 cycles], 26 [34%] had ALT elevations [5% were >5 times ULN] and 11 [14%] had bilirubin elevations).

van den Broek MA, Vreuls CP, Winstanley A, Jansen RL, van Bijnen AA, Dello SA, Bemelmans MH, et al. Hyaluronic acid as a marker of hepatic sinusoidal obstruction syndrome secondary to oxaliplatin-based chemotherapy in patients with colorectal liver metastases. Ann Surg Oncol 2013; 20 (5): 1462-9. PubMed PMID: 23463086.

(Among 40 patients with colorectal cancer undergoing hepatic resection for metastases after oxaliplatin based chemotherapy, 23 had sinusoidal obstruction syndrome which was severe in 11 patients who had higher hyaluronic acid levels than the 29 with mild or no injury [52 vs 29 ng/mL]).

Rahbari NN, Weitz J. Hyaluronic acid as a marker of sinusoidal obstruction syndrome after oxaliplatin-based chemotherapy for colorectal liver metastases: Don't forget the tumor. Ann Surg Oncol 2013; 20 (5): 1405-7. PubMed PMID: 23463087.

(Editorial in response to van den Broek [2013]).

Hubert C, Sempoux C, Humblet Y, van den Eynde M, Zech F, Leclercq I, Gigot JF. Sinusoidal obstruction syndrome (SOS) related to chemotherapy for colorectal liver metastases: factors predictive of severe SOS lesions and protective effect of bevacizumab. HPB (Oxford) 2013; 15 (11): 858-64. PubMed PMID: 23458554.

(Retrospective analysis of 151 patients with colorectal cancer and hepatic metastases; sinusoidal obstruction syndrome occurred in 60 of 67 [90%] of those who received oxaliplatin and fluorouracil alone and was severe in 37 [55%]; but arose in only 6 of 10 who received both oxaliplatin and bevacizumab and was severe in only 1 [10%]).

Wolf PS, Park JO, Bao F, Allen PJ, DeMatteo RP, Fong Y, Jarnagin WR, et al. Preoperative chemotherapy and the risk of hepatotoxicity and morbidity after liver resection for metastatic colorectal cancer: a single institution experience. J Am Coll Surg 2013; 216: 41-9. PubMed PMID: 23041049.

(Among 506 patients undergoing hepatic resection for colorectal cancer, histologic evaluation of non-tumor parenchyma showed that steatohepatitis was associated with irinotecan regimens, higher BMI and diabetes, whereas sinusoidal dilatation was not associated with chemotherapy; neither chemotherapy or liver histology correlated with complications or deaths).

Urdzik J, Bjerner T, Wanders A, Duraj F, Haglund U, Norén A. Magnetic resonance imaging flowmetry demonstrates portal vein dilatation subsequent to oxaliplatin therapy in patients with colorectal liver metastasis. HPB (Oxford) 2013; 15: 265-72. PubMed PMID: 23458313.

(Prospective monitoring by magnetic resonance imaging found that oxaliplatin chemotherapy was associated with portal vein dilatation independent of sinuosoidal injury, but that a combination of measurements of portal velocity and cross sectional area was predictive of the finding of sinusoidal injury).

Béchade D, Désolneux G, Fonck M, Soubeyran I, Bécouarn Y, Evrard S. [Regenerative nodular hyperplasia of the liver related to oxaliplatin-based chemotherapy]. Presse Med 2013; 42: 102-7. PubMed PMID: 22770975.

(Two cases of nodular regenerative hyperplasia [NRH] in a man and woman, age 60 years, with metastatic colorectal cancer after 17 and 12 courses of oxaliplatin based chemotherapy).

Vreuls CP, Olde Damink SW, Koek GH, Winstanley A, Wisse E, Cloots RH, van den Broek MA, et al. Glutathione S-transferase M1-null genotype as risk factor for SOS in oxaliplatin-treated patients with metastatic colorectal cancer. Br J Cancer 2013; 108: 676-80. PubMed PMID: 23287989.

(Among 55 patients with metastatic colorectal cancer who received oxaliplatin chemotherapy, the glutathione S-transferase [GST] M1-null polymorphism was frequent in those who developed moderate or severe sinusoidal injury [12 of 17: 70%] than in those with no or mild injury [13 of 38: 34%]).

Morris-Stiff G, White AD, Gomez D, Cameron IC, Farid S, Toogood GJ, Lodge JP, et al. Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases. Eur J Surg Oncol [Epub ahead of print] PubMed PMID: 24370284.

(Retrospective review of 978 patients who underwent hepatic resection for colorectal cancer metastases at a single institution in the UK between 2000 and 2010, identified 5 who developed clinically apparent NRH, all had received at least 6 cycles of oxilaplatin and fluorouracil, but only 1 had hepatic failure which was reversible and the all deaths [n=4] were due to cancer recurrence).

Ogata H, Gushima T, Maruoka S, Takasaki S, Tanaka R, Matsuura T, Aishima S, et al. A case of portal hypertension after 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) chemotherapy. Nihon Shokakibyo Gakkai Zasshi 2013; 110: 2119-26. PubMed PMID: 24305101.

(46 year old man developed noncirrhotic portal hypertension after 10 cycles of oxaliplatin and fluorouracil for colorectal cancer metastases, and required endoscopic ligation and transvenous obliteration of bleeding esophageal varices).

Uchino K, Fujisawa M, Watanabe T, Endo Y, Nobuhisa T, Matsumoto Y, Kai K, et al. Oxaliplatin-induced liver injury mimicking metastatic tumor on images: a case report. Jpn J Clin Oncol 2013; 43: 1034-8. PubMed PMID: 23958518.

(47 year old man developed radiologically apparent hepatic masses after 6 cycles of oxaliplatin and fluorouracil for metastatic colorectal cancer which, on resection, were not tumors but represented severe sinusoidal dilatation and congestion).

Lu QY, Zhao AL, Deng W, Li ZW, Shen L. Hepatic histopathology and postoperative outcome after preoperative chemotherapy for Chinese patients with colorectal liver metastases. World J Gastrointest Surg 2013; 5: 30-6. PubMed PMID: 23556058.

(Retrospective analysis of 106 patients undergoing hepatic resection for colorectal cancer at a single Chinese medical center over a 10 year period, found that oxaliplatin based regimens were associated with sinusoidal dilation [42%] compared to surgery only controls [21%], but perioperative complication rates were similar).

Morine Y, Shimada M, Utsunomiya T. Evaluation and management of hepatic injury induced by oxaliplatin-based chemotherapy in patients with hepatic resection for colorectal liver metastasis. Hepatol Res 2014; 44: 59-69. PubMed PMID: 23551330.

(Review of the frequency, clinical significance and management of hepatic effects of oxaliplatin therapy in patients undergoing liver resection for colorectal cancer metastases).

Nguyen-Khac E, Lobry C, Chatelain D, Fuks D, Joly JP, Brevet M, Tramier B, et al. A Reappraisal of chemotherapy-induced liver injury in colorectal liver metastases before the era of antiangiogenics. Int J Hepatol 2013; 2013: 314868. PubMed PMID: 23533786.

(Among 50 patients with colorectal cancer undergoing hepatectomy after chemotherapy, 55% of those who received oxaliplatin developed sinusoidal dilatation and 23% had evidence of NRH compared to 23% and 6% of controls; however, there was no difference in overall mortality or outcomes).

Schwarz RE, Berlin JD, Lenz HJ, Nordlinger B, Rubbia-Brandt L, Choti MA. Systemic cytotoxic and biological therapies of colorectal liver metastases: expert consensus statement. HPB (Oxford) 2013; 15: 106-15. PubMed PMID: 23297721.

(Summary of current optimal therapies of patients with colorectal liver metastases and the problem of chemotherapy associated liver injury, particularly to oxaliplatin [SOS, NRH] and irinotecan [steatosis] leading to recommendation that, if possible, preoperative chemotherapy be limited to 3 months).