Oxaliplatin Induced Hemolytic Anemia

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A 45-year-old male patient with TNM stage III rectal cancer presented with fatigue, dyspnea, icterus and darkening of urine for the last 1-2 days. He had been operated for rectal adenocarcinoma (low anterior resection) 7 months ago and had received pelvic radiotherapy and 11 cycles of FOLFOX-4 regimen thereafter. No serious adverse event had been observed, except for mild neuropathy. One day after the last dose of oxaliplatin administration (cycle 12), while the patient was on 5-FU infusion, he developed fatigue, scleral ictericus and darkly coloured urine. He did not have any other systemic diseases and denied using any other drugs except ondansetron. Laboratory results were as follows: hemoglobin 5.7 g/dL (10.7 g/dL before the cycle) , indirect/direct biliruibin 3.74/0.5 mg/dL, LDH 750 U/mL, reticulocyte 3.6% and haptoglobulin levels undetectable. Direct coombs test was positive, indirect coombs test was negative. Three packs of red blood cells were transfused and treatment with prednisone 40 mg/day for 7 days was started with the diagnosis of acute autoimmune hemolytic anemia (AIHA). At the end of 7 days, hemoglobin level was 10.4 g/dL and bilirubin and LDH levels returned to normal. As this was already the last planned cycle, chemotherapy was discontinued.

FOLFOX-4 is the standard adjuvant treatment in lymph node positive colorectal cancer. It consists of bolus infusions of oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 and 5-fluorouracil (5-FU) 400 mg/m^2 followed by 22-hours continuous infusion of 600 mg/m^2 5-FU via a portable pump on day 1 and day 2, every 15 days. Common side effects are cumulative sensory neuropathy, diarrhoea, mild myelosupression and mucositis, most of which are shared by both 5-FU and oxaliplatin. Our patient developed severe AIHA after the 12th cycle of FOLFOX-4, which is an uncommon complication after this regimen. Detailed immonologic tests were not performed to distinguish the offending drug in our case; however both oxaliplatin and fluoruracil were reported to cause acute AIHA in the literature. Oxaliplatin induced AIHA was reported to occur mostly after several cycles of treatment[1-6] and was suggested to have two mechanisms; i.e. both immune complex type and penicillin type (drug adsorbtion).[4] Platinum salts can act as haptens by binding to serum proteins and repeated exposure to these complexes can promote hypersensivity reactions.[3] Bolus[7] and protracted infusion of 5-FU had also resulted in AIHA, as well as UFT (uracil-tegafur) in one case.[8,9] Oxaliplatin and 5-FU are generally used in combination in colorectal cancer treatment and acute hemolysis should be kept in mind as a rare but potentially fatal complication in patients receiving FOLFOX regimens (FOLFOX-4, -6, -7). Prompt discontinuation of the drugs and treatment with corticosteroids and plasmapheresis in severe cases are essential. It is not rational to discontinue both of these two highly effective drugs in a patient who will continue to receive chemotherapy for colorectal cancer in the adjuvant or metastatic setting, therefore determination of the offending drug is crucial.

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