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Clinical case

Gemcitabine-induced systemic capillary leak syndrome

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Summary

Systemic capillary leak syndrome (SCLS) is a rare disorder with a high mortality rate, characterized by rapidly developing edema, weight gain and hypotension, hemoconcentration and hypoproteinemia. This syndrome is caused by sudden, reversible capillary hyperpermeability with a rapid extravasation of plasma from the intravascular to the interstitial space. Even though SCLS has been suggested to be the pathogenic mechanism for the pulmonary toxicity of gemcitabine (GCB), a new deoxycytidine analogue with structural similarities to cytosine arabinoside, a direct correlation between GCB and SCLS has never been reported. We describe a case of repeated SCLS after GCB administration in a 51-year-old male with locally-advanced non-small-cell lung cancer treated with a combination of cisplatin and GCB. The detection of GCB-induced SCLS supports the hypothesis that SCLS could be the pathogenic way of GCB pulmonary toxicity. This finding can help to better understand and treat the potentially deadly GCB-related acute respiratory distress syndrome that is being recognized.

Key words capillary leak syndrome, chemotherapy, gemcitabine, pulmonary toxicity

Introduction

Systemic capillary leak syndrome (SCLS) is a rare disorder caused by a sudden, reversible capillary hyperpermeability with a rapid extravasation of plasma from the intravascular to the interstitial space. The most usual mechanisms inducing capillary leak relate to an increased size of the transcapillary transport passages by endothelial cell contraction. This results in a rapidly developing edema, hypotension and weight gain, hemoconcentration and possible renal shutdown.

This syndrome, described after snake bites [1] and in patients with sepsis [2, 3], is a well-known pathogenic way of toxicity for many drugs, including recombinant interleukin-2 [4] and Taxotere [5].

SCLS has also been suggested to be the pathogenic mechanism of the pulmonary toxicity of gemcitabine [6] (GCB), a new deoxycytidine with structural similarities to cytosine arabinoside, with confirmed antitumor activity in patients with non-small-cell lung cancer (NSCLC). Nevertheless, to our knowledge, a direct correlation between GCB administration and SCLS has never been reported.

We describe a case of repeated SCLS induced by GCB administration in an adult patient with locally-advanced NSCLC.

Case report

A 51-year-old male with stage IIIa non-small-cell lung cancer (NSCLC) was treated in our Institute with induction chemotherapy containing cisplatin (CDDP) plus gemcitabine (GCB).

Clinical and anamnestic findings revealed no signs of cough, swelling or dyspnea. Physical examination, cardiologic- and pulmonary-function evaluation were unremarkable.

The patient received CDDP 80 mg/m^2, administered as a one-hour infusion on day 1, and GCB 1250 mg/m^2 administered as a 30-min infusion on day 1 and 8, repeated every three weeks.

Treatment given on day 1 was preceded by desametasone 8 mg i.v. and granisetron 3 mg i.v. for the prophylaxis of nausea and vomiting; dexamethasone 4 mg i.v. was also given 12 hours after CDDP administration. The same anti-emetic treatment was repeated intravenously on day 2 and orally on days 3 and 4. Hydration with 3000 cc/day of saline and electrolytes supplementation was administered on a 48-hour infusion, starting 12 hours before treatment. The first treatment cycle was uneventful.

Two days after GCB administration on day 8 of the second cycle, the patient was admitted to our Institute with worsening dyspnea, diffuse swelling, weight gain and hypotension.

No alterations of blood count, serum electrolytes or renal function were registered. Despite albumin administration, the values of total protein hardly decreased during hospitalization (down to 6.3 g/l); proteinuria was excluded by urine examination.

Ventricular dysfunction, superior vena cava compression or thrombosis and lung infiltrates were excluded by echocardiography and thorax spiral CT scan. CT

scan also documented an evident disease response.

Intravenous administration of Furosemide and high-dose dexamethasone was promptly given, with complete symptom recovery within two days.

The third treatment cycle was given on time, with a 25% dose reduction of both CDDP and GCB.

The patient was readmitted to our institute 48 hours after day-8 GCB administration. He suffered again from severe dyspnea, diffuse swelling and hypotension. Blood examination showed pancytopenia (PLT. 34 × 10^9/l, WBC 2.0 × 10^9/l, Hb 7.8 g/dl), impaired renal function (serum urea 69 mg/dl, serum creatinine 1.5 mg/dl) and low total protein value with hypoalbuminemia (6.4 and 3.2 g/dl, respectively). A chest X-ray was consistent with bilateral interstitial edema and showed a stable lung-tumor disease

The patient received an intravenous administration of furosemide, high-dose dexamethasone and albumin, with a rapid and complete clinical recovery.

No other chemotherapy was given and the patient successfully underwent radical surgery.

Comments

This clinical report describes an enhancement of fluid filtration followed by a systemic capillary leak syndrome (SCLS) recurrently developed after gemcitabine (GCB) administration, strongly suggesting a strict correlation between symptoms and drug

The probable explanation of why SCLS did not occur after GCB administration on day 1 of each cycle could be the 4-day administration of 12 mg of dexamethasone given daily as a nausea and vomiting prophylaxis. As a matter of fact, when high-dose dexamethasone was given with furosemide and albumin to treat SCLS, the patient promptly recovered

Although there is no clear explanation why the patient did not have a SCLS after the first cycle, the delayed development of symptoms is consistent with reports on GCB-induced pulmonary toxicity [6].

Even though many drugs are known to induce SCLS, to our knowledge a correlation between SCLS and GCB has never been reported. The detection of GCB-induced SCLS is quite important, because this supports the hypothesis that SCLS could be the possible pathogenic way for the GCB-related acute respiratory distress syndrome (RDS) that is being recognized [6–8]. As observed in patients given an intermediate dose and high dose of ara-C, patients given GCB can also suffer a rare but life-threatening RDS· authors reporting these cases described some therapeutic effects from corticosteroids and diuretics and postulated a capillary leak phenomenon as the pathogenic mechanism of toxicity [6, 9].

Should patients develop SCLS during treatment with GCB, we recommend the administration of high-dose corticosteroid prophylaxis.

Any respiratory symptom should be promptly investigated in order to exclude lung toxicity that, if not recognized, could lead to death.

References

1 Nelson BK Snake envenomation Incidence, clinical presentation and management Med Toxicol Adverse Drug Exsp 1989, 4 17

2 Luce JM Pathogenesis and management of septic shock Chest 1987, 91 883

3 Parrillo JE, Parker MM, Natanson C et al. Septic shock in humans Advances in the understanding of pathogenesis, cardiovascular dysfunction and therapy Ann Intern Med 1990, 113 227

4 Chang AE, Rosenberg SA Overview of interleukin-2 as an immunotherapeutic agent Semin Surg Oncol 1989, 5 385

5 Semb KA, Aamdal S, Oian P Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment J Clin Oncol 1998, 16 (10) 3426-32

6 Pavlakis N, Bell DR, Millward MJ, Levi JA Fatal pulmonary toxicity resulting from treatment with gemcitabine Cancer 1997, 80 (2) 286-291

7 Brose MS, Cheng JM, Haller DG Incidence of pulmonary and non-hematologic toxicities related to gemcitabine Proc Am Soc Clin Oncol 2000, 19 196 (Abstr)

8 Tempero MA, Brand R Fatal pulmonary toxicity resulting from treatment with gemcitabine Cancer 1998, 82 (9) 1800-1

9 Vander Els NJ, Miller V Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy Chest 1998, 114 (6) 1779-81

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