

LETTER TO THE EDITOR

Systemic Reaction to Leucovorin in a Child With Lymphoblastic Lymphoma Suggestive of Hypersensitivity

To the Editor: Leucovorin is used as rescue agent after high dose methotrexate or to enhance efficacy of 5-Fluorouracil. A 16-year-old male with Stage III T cell lymphoblastic lymphoma achieved complete remission following induction on BFM-90 protocol [1]. He received first course of high dose methotrexate 5 g/m² with leucovorin rescue which was uneventful. Following the second dose of high dose methotrexate, he was given leucovorin intravenously at doses of 30 mg/m² at hour 42 and 15 mg/m² each at hours 48 and 54. There was no reaction with first dose of leucovorin. Immediately after second dose, patient developed chills and rigors, followed by erythematous rash over face, neck and upper limbs along with a temperature spike of 38.8°C; the patient responded to anti-histaminics. Following the third dose of leucovorin, there was a generalized erythematous rash that blanched on pressure; the patient also had vomiting, dizziness and hypotension but no bronchospasm. Dopamine, anti-histaminics and hydrocortisone were started. The erythematous rash subsided over 24 hr but hypotension persisted for 42 hr. His serum creatinine increased from 0.9 mg/dl at baseline to 1.5 mg/dl on day 4. Hydration and alkalinization were continued following which serum creatinine levels returned to normal on day 7 from the start of methotrexate infusion.

In view of a single febrile episode after second dose and hypotension, the possibility of sepsis was considered and intravenous antibiotics were administered. Blood culture and chest radiograph were normal. Serum procalcitonin level, a marker of sepsis [2], was 2.1 ng/ml (<0.5: localized infection, ≥0.5–2: possible systemic infection; ≥2–10: systemic infection likely unless other causes are known; ≥10: exclusively due to severe sepsis). Serum IgE levels were 711 IU/ml (normal: 0.0–158 IU/ml). Thus, a final diagnosis of systemic reaction to leucovorin suggestive of hypersensitivity was made. Further chemotherapy was continued as per protocol but all high doses of methotrexate requiring leucovorin rescue were omitted.

Hypersensitivity reactions to leucovorin have been previously reported in patients receiving treatment for colorectal cancer [3,4]. Our patient received high dose methotrexate with ondansetron 48 hr before the occurrence of adverse reaction and no other concomitant medications were in use except intravenous fluids. The presence of

near normal procalcitonin level, sterile blood culture and absence of any focus of infection ruled out sepsis as a cause of the above episode. Typically hypotension in anaphylaxis is of short duration although it may be occasionally prolonged [5]. Allergy to folic acid is well known with presence of elevated folate specific antibodies [6,7]; however, leucovorin hypersensitivity is rare. Our report emphasizes that leucovorin hypersensitivity can be observed in children and provides awareness of this possible serious reaction to an otherwise innocuous antidote.

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REFERENCES

1. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell Lymphoblastic Lymphoma: A BFM Group report. *Blood* 2000;95:416–421.
2. Uzzan B, Cohen R, Nicolas P, et al. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis. *Crit Care Med* 2007;35:679.
3. Benchalal M, Yahchouchy-Chouillard E, Fouere S, et al. Anaphylactic shock secondary to intravenous administration of folinic acid: A first report. *Ann Oncol* 2002;13:480–481.
4. Benoit R, Grobost O, Chalmet P, et al. Anaphylactoid shock due to folinic acid during treatment of metastatic colorectal cancer. *Gastroenterol Clin Biol* 2000;24:1241–1242.
5. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78:76–83.
6. Woodliff HJ, Davis RE. Allergy to folic acid. *Med J Aust* 1966; 1:351–352.
7. Dykewicz MS, Nicholas A, Sun W, et al. In vitro demonstration of IgE antibody to folate-albumin in anaphylaxis from folic acid. *J Allergy Clin Immunol* 2000;106:386–389.

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