Prevention of irinotecan plus 5-fluorouracil/leucovorin-induced diarrhoea by oral administration of neomycin plus bacitracin in first-line treatment of advanced colorectal cancer

Irinotecan (CPT-11) plus 5-fluorouracil/leucovorin (5-FU/LV) regimen is at present employed as first-line chemotherapy for advanced colorectal cancer (CRC). Its clinical use is associated with an elevated incidence of diarrhoea (~60–70%). Diarrhoea is the dose-limiting toxicity of this regimen and sometimes represents a serious adverse event [1]. Recently, the role of the intestinal bacterial microflora in the etiopathogenesis of the CPT-11-induced intestinal toxicity has been discovered. The active metabolite of CPT-11, SN38, is generated from CPT-11 by sieric carboxylesterase, and subsequently conjugated to SN38-G by hepatic UDP-glucuronyltransferase. SN38-G is the inactive metabolite of CPT-11 and is excreted into the small intestine, from which it is eliminated in the faeces [2].

Some studies have pointed out the ability of intestinal bacterial β-glucuronidases to transform SN38-G into SN38, causing direct damage to the intestinal mucosa [3]. In recent years, several authors have investigated the possibility that inhibition of the intestinal bacterial microflora with antibiotic therapy may decrease the CPT-11 intestinal toxicity [4]. After such consideration, we started a study to evaluate the role of therapy with neomycin plus bacitracin at a dose of 1000 mg t.i.d. during CPT-11 plus 5-FU/LV chemotherapy (Saltz regimen).

Thirty-two patients with metastatic CRC were evaluated between March 2000 and July 2002. Only 15 of these patients experienced diarrhoea after the first cycle of chemotherapy and were enrolled in the study. They were treated in the first cycle of chemotherapy with loperamide 4 mg followed by 2 mg every 2 h, for a period of 12 h after the last stool; from the second cycle of chemotherapy onward, they were treated with an association of neomycin 25000 IU plus bacitracin 2500 IU (bimixin) at a dose of 1000 mg t.i.d. (days 2–5 and 16–19 of each cycle, during chemotherapy). In all 15 patients, we observed complete resolution of diarrhoea from the second until the fourth chemotherapy cycle. Only two patients experienced grade 1 diarrhoea in the fifth chemotherapy cycle, and only five in the last cycle, two grade 1 and three grade 2.

At the end of each cycle of chemotherapy, the patients completed a questionnaire on chemotherapy tolerability. All patients treated with neomycin tolerated chemotherapy much better than a control group of 15 patients treated without antibiotic therapy. Our research indicates that in combined treatment with CPT-11 plus FU/LV it is possible to reduce the incidence and severity of diarrhoea by cotreatment with oral neomycin plus bacitracin.

In contrast to previous experience of antibiotic therapy in the prevention of CPT-11-related diarrhoea [5], we used neomycin associated with bacitracin in these patients, a more common antibiotic combination used in clinical practice. However, the lower intestinal toxicity of CPT-11 in the Saltz regimen (CPT-11 180 mg/m²) compared with CPT-11 monotherapy (CPT-11 350 mg/m²) may explain the better control of the CPT-11-induced diarrhoea obtained in our patients, making this an interesting finding. Furthermore, this study constitutes a greater awareness of the role of the bacterial β-glucuronidase in CPT-11-induced diarrhoea.

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References


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