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Case Report

Early diagnosis of colon cancer after 2-clorodeoxyadenosine administration

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SUMMARY

Purine analogues such as 2-chlorodeoxyadenosine (2-CdA) are specific inhibitors of the cell cycle. We present a patient with chronic lymphoblastic leukemia who received 2-CdA and two months later was diagnosed with de novo colon adenocarcinoma Dukes stage I. The patient was treated surgically and is still living on with satisfactory laboratory tests.

If we do accept that the diagnosis of colon cancer in our patient was not a simple coincidence and, having in mind that hematological malignancies often coexist with other malignancies, we could consider, with reservations, that our case report is a potential model explaining the in vivo action of nucleoside analogues such 2-CdA in oncogenesis and apoptosis in bowel epithelium.

Key words: chronic lymphocytic leukemia, 2-chlorodeoxyadenosine (2-CdA), colon cancer, apoptosis, colonoscopy.

INTRODUCTION

Purine analogues fludarabine and 2-chlorodeoxyadenosine (2-CdA) are specific inhibitors of the cell cycle and require DNA synthesis in order to express their effect; induction of cell death through the apoptosis mechanism.[1,2] In addition to this, chronic diseases,[3] genetic susceptibility and instability may play a role in the carcinogenesis phenomenon.[4,5] Those purine analogues gain access to the cell via a specific nucleoside transporter (NST) protein.[6] The cytoxic effect of 2-CdA requires the intracellular accumulation of 2-CdA nucleosides.

In vitro studies have demonstrated that NST expression on chronic lymphoblastic leukemia (CLL) lymphocytes is low and in vitro exposure to the analogues increases both the level of NST expression and the % cells in S-phase. In addition, exposure to the analogues downregulates bcl-2 protein expression and increases apoptosis.[7,8] It is widely accepted that the bcl-2 expression plays a major role in inhibiting the apoptosis mechanism.[9,10]Although there are strong indications about the role of 2-CdA in regulating bcl-2 it is not yet proved that bcl-2 expression can be an in vitro determinant of the responsiveness in chemotherapy or a catalyte in further prognosis of such malignancies.[11]

We present herein a patient with CLL who received 2-CdA due to CLL transformation in prolymphoblastic leukemia and 2 months later was diagnosed with de novo colon adenocarcinoma.

CASE REPORT

A 72 year-old patient with CLL was admitted in our hospital because of lower gastrointestinal bleeding. The patient was a smoker for the last forty years, no alcohol abuser and the last 10 years was on diuretics due to systolic hypertension. The patient underwent cholecystectomy 30 years ago because of chololithiasis and for the last 10 years he was diagnosed with colon diverticula.

The diagnosis of CLL stage III was made 2 years ago and the patient was started on chlorambucil and methylprednizolone. Two months before this last admission the patient was diagnosed with prolymphocytic leukemia (PL) with 40% bone marrow infiltration and he was started on chemotherapy with 2-chlorodeoxyadenosine (2-CdA)

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achieving complete remission. Symptomatically, at the same time a colonoscopy had been performed because of abdominal pain and diverticulitis of the descending colon was diagnosed. During admission the patient was pale and hypotensive, and the digital examination of rectum revealed loss of red blood.

Laboratory examination revealed hemoglobin 7.2g/dl, white blood cells at 12.600/mm^3, platelets at 160.000/mm^3 while biochemical profile revealed elevated lactate dehydrogenase and hyperouricemia. Colonoscopy revealed a small bleeding mass in the transverse colon which proved Dukes stage I adenocarcinoma. The patient was treated surgically and is still living on with satisfactory laboratory tests.

DISCUSSION

The early detection of a colonic neoplasia in the patient after 2-CdA administration is implying a potential etiological relationship between this unusual phenomenon of early detection of bowel neoplasia shortly after 2-CdA administration. The possibility that an in situ bowel neoplasia or a dysplastic lesion pre-existing colon adenocarcinoma cannot be excluded. It is widely accepted that endoscopy has its own limitations but the fact that in this patient no abnormality was diagnosed by experienced endoscopist two months before this episode of bleeding should not be ignored. Natural history of colon adenocarcinoma includes several parameters such as precancerous or dysplastic lesions, inherited factors and various aspects on cell immunology such as defense and repair mechanisms.[12]

Considering the above speculations it could be possible that various anti-neoplastic agents may differentiate, usually accelerate oncogenesis procedures of the gastrointestinal tract stem cells.[13]

In vitro experiments have stated that the nucleoside analogues down-regulate the expression of the bcl-2 promoter and, consequently, decrease the final total amount of the oncogenic bcl-2 protein by increasing apoptosis. However, this statement has not yet been proved in the everyday clinical practice and the update state of the art is only that the bcl-2 oncogenic protein expression plays a capital role in inhibiting the apoptosis mechanism.[1]

If we do accept that the diagnosis of colon cancer in our patient 2 months after 2-CdA administration was not a simple coincidence and, having in mind that hematological malignancies often coexist with other malignancies, we could consider, with reservations that our case report is a model explaining the possible in vivo action of nucleoside analogues and mainly this of 2-CdA. This hypothetical in vivo mechanism could have as center theory the contribution of nucleoside analogues and nucleoside transporters in increasing or in not down-regulating the apoptosis of the bowel epithelium. This hypothetical regulation in bowel epithelium apoptosis may have characteristics different than those of the apoptosis regulation in the haemopoietic system.[1] The starting point is that of the dramatically different way of functioning, apoptosing and the different life-time of those two cell types; haemopoietic and colonic. It should be also stressed here that according to the previous hypothesis an important statement is illustrated; the fact that patients with hematologic malignancies are in much more increased risk compared to the general population to be diagnosed with a second or even third neoplasia. This happens either as a consequence of the prolonged immunosuppresion, inactivation of the repairing mechanisms of apoptosis or as a result of the various anti-neoplastic agents used for several tissues but with unknown impact on other tissues of the same patient. Consequently, chemotherapy favors sometimes repair of some tissue disturbing repair mechanisms of other tissues. Various experimental models have been proposed for prevention[14,15] or induction of carcinogenesis.[16,17] We strongly believe that the way the nucleoside analogues interfere and regulate the apoptosis in a dysplastic or in situ cancerous bowel epithelium still remains a critical question to answer. Patient developed de novo colon cancer 2 months after PL therapy probably attributed to the 2-CdA action in bowel epithelium. The gap from administering the nucleoside analogue till the first manifestation of the bowel neoplasia must also undergo a lot of discussion and criticism.

However, the precious contribution of the nucleoside analogues in haematologic malignancies should be further studied for the better understanding of the mechanisms of oncogenesis and apoptosis in other tissue malignancies, as may happen in the bowel of the reported patient.

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