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REVIEW

Chronic Anemia Due to Mitomycin C Is Drug Dose-Dependent, Normocytic, Progressive, Related to Erythropoietin Levels and Quantitatively Predictable: Implications for Radiochemotherapy

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Summary

Mitomycin C (MC) is used as therapy against solid tumors, also combined with other chemotherapeutic agents or radiotherapy. It may cause acute, subacute, or chronic anemia capable of modifying the results of chemo- and radiotherapy. Erythropoietin may be lowered by cancer itself or because of chemoradiotherapy. There are few studies investigating the relationship between erythropoietin and chronic anemia.

We prospectively analyzed the chronic anemia and erythropoietin in 38 patients with solid cancer. Patients were 40 to 82 years of age. MC was randomly given every 3 weeks as a single drug at 10 or 20 mg/m^2. When myelotoxicity occurred the next therapy cycle was delayed until recovery. RBC indices, hemolysis, erythropoietin, liver and kidney function were studied. MC cycles were 136 (3.6 ± 1.4 per pt), 32 being delayed because of myelotoxicity.

Hematocrit, hemoglobin and RBC were inversely related to the cumulative dose (r = 0.70 to 0.86; p 0.03 to 0.01) of MC. Other tests remained stable. Anemia occurred almost twofold earlier in the 20 mg/m^2 group (p=0.049). Basal erythropoietin, already lower than in age and sex watched 81 non cancerous subjects (p<0.001), decreased during MC therapy (p<0.01). For each given MC mg/m^2 a 0.0372 Hb mg/dl reduction occurred.

Chronic anemia due to MC is accompanied by erythropoietin reduction. These results can help in designing chemoradiotherapy.

***Key words*: Anemia, chemoradiotherapy, erythropoietin, mitomycin C.**

INTRODUCTION

The antibiotic mitomycin C was and is largely used as a chemotherapeutic agent against a large variety of solid tumors [1,2]. This drug may be given with or after radiotherapy and the caused anemia reduces the radiotherapy efficacy [3,4]. However mitomycin C, a non cell-cycle specific drug, may exert greater cytotoxicity under hypoxic than aerated conditions. This problem is complex [5-8] and outside the scope of the present clinical research.

Mitomycin C has been used in combination with cisplatin [9], a drug that itself causes anemia [10,11] associated with an erythropoietin deficiency related to kidney damage [12]. In our experience the relationship between anemia and reduced kidney function has not been appreciated [9].

Anemia associated with mitomycin C may be caused by the rare acute hemolytic-uremic syndrome [13-15] or more commonly by chronic myelosuppression [16-18]. Some information on this chronic type of anemia can be deduced from older studies [16-18]. However knowledge of the phenomenon may be relevant in relation to multidrug chemotherapy regimens and associated radiotherapy.

Thus, we prospectively analyzed the effects of two different doses of mitomycin C on some aspects of erythropoiesis, possible hemolysis, and erythropoietin levels.

PATIENTS AND METHODS

Forty-one consecutive patients (*Table 1*) were enrolled in the study. Three was excluded just before randomization because of refusal (2 subjects) or CNS-TIA (Central Nervous System Transitory Ischemic Attack) (1 subject). Therefore, 38 patients were treated with mitomycin C and all remained assessable for toxicity and therapy response.

After the approval by the Local Ethical Committee, the patients' informed written consent was obtained according to current Italian regulations. Exclusion criteria were the presence of: any type of acute disease, asthma, untreated or unstable diabetes or blood hypertension, heart infarction, cerebral stroke, metastasis, abnormal liver and/or kidney function and recent deep vein thrombosis. Patients were also excluded if they had had previous therapy with mitomycin C, bleomycin, alkylating agents and cisplatin over the last 6 months, and radiotherapy on the lung or mediastinum at any time.

Current respiratory function tests had to be normal, and no myelotoxicity above grade II was allowed. Finally the measurable disease had to be in progression.

All patients had a Karnofsky performance status (KPS) of 80% and no one had a bodyweight loss greater than 5% over the last 6 months .

Hemoglobin values and erythropoietin were available in controls, i.e. 81 non-smoking subjects without cancer including bleeding patients with iron deficiency anemia because of benign condition, and in 53 untreated cancer patients. All these control subjects had normal kidney and liver function, and were balanced for sex, age and KPS in comparison with mitomycin C patients.

Mitomycin C powder was dissolved in distilled water as recommended by Kyowa Hakko Ltd (Japan) and push i.v. was

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TABLE 1 - *Baseline evaluation of characteristics of patients treated with mitomycin C (treated with either 10 mg/m² or 20 mg/m² Group I, Group II, respectively).*

		N°	%	Group I	Group II
Patients		38		17	19
Male/Female		18/20	47.4/52.6	17	21
Age (years) range		40-82		40-82	41-80
Mean		62		62	62
Median		62		62	61
Previously treated pts:	with chemotherapy*	25	65.8	25	65.8
	with radiotherapy	6	15.8	3	3
Site of primary cancer					
Breast adenocarcinoma		12	34.2	6	6
Non small cell lung cancer		12	31.6	5	7
Gastrointestinal adenocarcinoma		11	26.3	6	5
Bladder transitional cell carcinoma		1	2.6	/	1
Soft tissue sarcoma		2	5.3	1	/

* not including mitomycin C; see methods

given over about 60 s, immediately after an i.v. injection of 40 mg methylprednisolone. Two different mitomycin C dose levels were randomly administered, 10 or 20 mg/m² (lower or higher dose group) every 3 weeks. No dose reduction was planned; instead chemotherapy was delayed until recovery from toxic effects in the event of granulocytes below 2,500 μl and/or of platelets below 100,000 μl.

Therapy was continued if tolerated and only if steady state, partial or complete remission was obtained, the disease being restaged repeatedly before each next odd cycle.

Blood sampling was obtained between 8.00 - 9.30 a.m. in overnight fasting patients. The following tests were repeated before each next mitomycin C cycle: full blood count and reticulocytes (automatic counting by ADVIA 120 Bayer), erythropoietin, serum iron, transferrin, ferritin, albumin and haptoglobin, total and conjugated bilirubin, lactic dehydrogenase, gammaglutamyltranspeptidase, alkaline phosphatase, alanine and ornithine transaminase, uric acid, urea, creatinine, Na, K, Cl, Mg, Ca, direct and indirect Coombs tests. Twenty-four hour urine collection for creatinine clearance, Hb loss and RBC Addis test were available.

We used an immunoassay-chemiluminescent method to detect erythropoietin (by Unicel DXI 800, Beckman Coulter) and CA125 (by ADVIA Centaur, Bayer) [19,20].

Also, Vitamin B12 and RBC folate were available, at basal time and after the fourth mitomycin C administration. The same "basal" tests were available in all control subjects.

RBC data were expressed as the percent variation from basal pre-treatment levels (Student t-test for paired data). Differences in the mean as a function of dosage were analyzed by one-way analysis of variance (ANOVA). ANOVA and paired t test were conducted to compare the mean changes before and after treatment. A P value 0.05 was considered statistically significant. A regression model was performed to identify a relationship between RBC and erythropoietin and mitomycin C. Furthermore, to assess the correlation between Hb and erythropoietin, Spearman rank correlation coefficient was used in control subjects and non-bleeding cancer patients. Wilcoxon signed-rank test was used to determine if this difference was significant.

For patients who required a delay in chemotherapy, the frequency of delays was analyzed using Fisher's exact test.

RESULTS

We administered 136 mitomycin C cycles, averaging 3.58 ± 1.37 (mean ± SD; median 3.50) per patient. Thirty-two cycles were delayed (24%) because of neutropenia and/or thrombocytopenia in 21 out of 38 patients (55%). Among these 21 patients, the median total delay was 14 days, with a median per patient and per cycle of 7 days.

In all patients, the hematocrit and Hb underwent a progressive and significant reduction in relation to the number of chemotherapy cycles and cumulative mitomycin C dose.

In the higher mitomycin C dose group, a significant reduction of hematocrit was seen even after the first cycle (-6%, p=0.032), whereas in the lower mitomycin C dose group a significant drop (-6.0%; p=0.004) was observed only after the second cycle (-7.1%). After four cycles the observed 13.7% reduction in the lower dose group was lower ($p<0.05$) than the 28.1% in the higher dose group.

Hb behaved similarly to the hematocrit. The Hb reduction after the first mitomycin C cycle was already appreciable in the higher dose than in the lower dose group (6.00% vs 4.80%). However, there were no differences in hematocrit and Hb between the two dose groups, when mitomycin C reached the same dosage. The cumulative mitomycin C dose was responsible for the hematocrit and Hb reduction independently of dose. Because of this, the results from both groups were considered together for data analysis.

Indexes of red blood cells (MCV, MCH and MCHC) did not vary over basal values during chemotherapy (p = 0.89-0.08). Reticulocytes, as counted weekly during the first cycle together with full blood count, decreased to -300% ($p<0.001$) at the eighth day. On the eighth day serum iron rose by 86.25% ($p<0.001$) and then increased from 75.1 to 86.5% ($p<0.01$) within the next few days after every subsequent drug administration. Hb and hematocrit were practically unchanged at those times. Subsequently, the reticulocytes remained between 150 and 200% lower in comparison with basal values ($p<0.01$). However, in the morning before the next drug administration, iron metabolism was already restored to basal levels, with no statistically appreciable variations (data not shown).

In the patient groups erythropoietin was basally lower than in controls of the same age and sex (*Figure 1*). Erythropoietin dropped at every mitomycin C cycle (*Figure 2*), and the reduction was significant ($p<0.01$; each patient was a control of himself). However with the cumulative mitomycin C dose at the level of 80 mg/m² and with Hb= 8.9, the erythropoietin increased from 5.4 to the 9.3 U/L ($P<0.002$). The highly significant ($R^2=0.9971$) correlation between Hb levels and mitomycin C levels is depicted in *Figure 3*.

Kidney function (including the 24-h urinary collection crea-

tinine clearance), Mg, Na, Cl, K, Ca and liver function tests, transferrin, ferritin, albumin, haptoglobin, LDH and Coombs tests, Vitamin B12 and RBC folate, and urinary loss of Hb and red blood cells all remained unchanged at every cycle measurement.

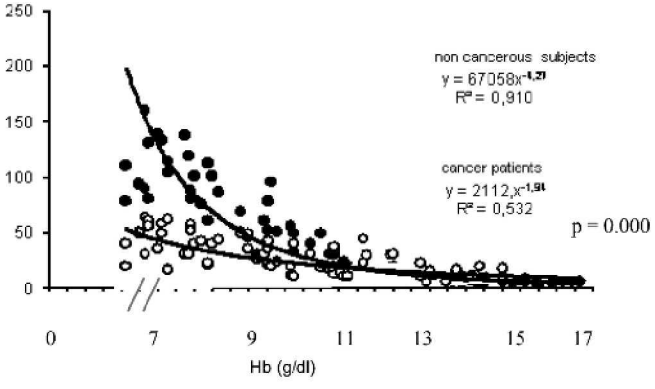

FIGURE 1 - Relationship between baseline Hb (g/dl) and erythropoietin (U/L) in 81 noncancer subjects with normal Hb or with various degrees of iron deficiency anemia (black spots) and 38 non-bleeding cancer patients (white spots) treated with mitomycin C. The difference between the two groups is highly significant.

DISCUSSION

Mitomycin C is used in cancer chemotherapy, against large a variety of adenocarcinomas and squamous cell tumors including non-small cell lung cancer (NSCLC) [1,2,9]. However, the drug is toxic to bone marrow function and anemia may occur. Since mitomycin C is mostly used in combination with other drugs, its true role in anemia remains unknown.

There are a few quantitative studies which focus on chronic anemia. Kenis and Strykmans [16] found a contraction of iron metabolism and a reduction of reticulocytes in 50 patients 14 days after mitomycin C administration. In 5 cases the bone marrow erythroblast incorporation of tritiated thymidine was found to be reduced [16]. A greater than 3 g/dl decrease in Hb in 3 (11%) out of 26 women with breast cancer treated with 20 mg/m^2 mitomycin C every 6 weeks for two cycles, followed by a maintenance dose of 15-20 mg/m^2 every 4 to 6 weeks, was described [17].

Koons *et al* [21] used a regimen based on 20 mg/m^2 mitomycin C every 4 weeks for two cycles, followed by a maintenance dose every 4 to 6 weeks. In the presence of leukopoenia or thrombocytopenia, mitomycin C was either reduced or postponed. With this unfixed dose schedule, 28 patients were treated for two cycles and one-third of them experienced a 30% or greater decrease in hematocrit [21].

In patients with NSCLC, mitomycin C 10 mg/m^2 at 3-week intervals in combination with cyclophosphamide and cisplatin caused a grade 2 drop of Hb in 26 out of 200 cycles and a grade 3 drop in 4 cycles [9]. These investigations were not intended to identify the possible mitomycin C dose-related anemia, and did not provide information on the type of anemia. Hemolysis and urinary RBC loss were searched for and excluded in our previous experience [9].

The type and grade of anemia secondary to mitomycin C should be taken into consideration also when combined with radiation therapy or with other drugs which are toxic to erythropoiesis. The Hb level during radiotherapy is positively and significantly associated with both local control and survival in several types of cancer [5], such as cervical cancer [22,23], bladder carcinoma [24] and head and neck tumors [25]. Even a small reduction of the Hb concentration is detrimental to the effectiveness of radiotherapy against laryngeal cancer [26].

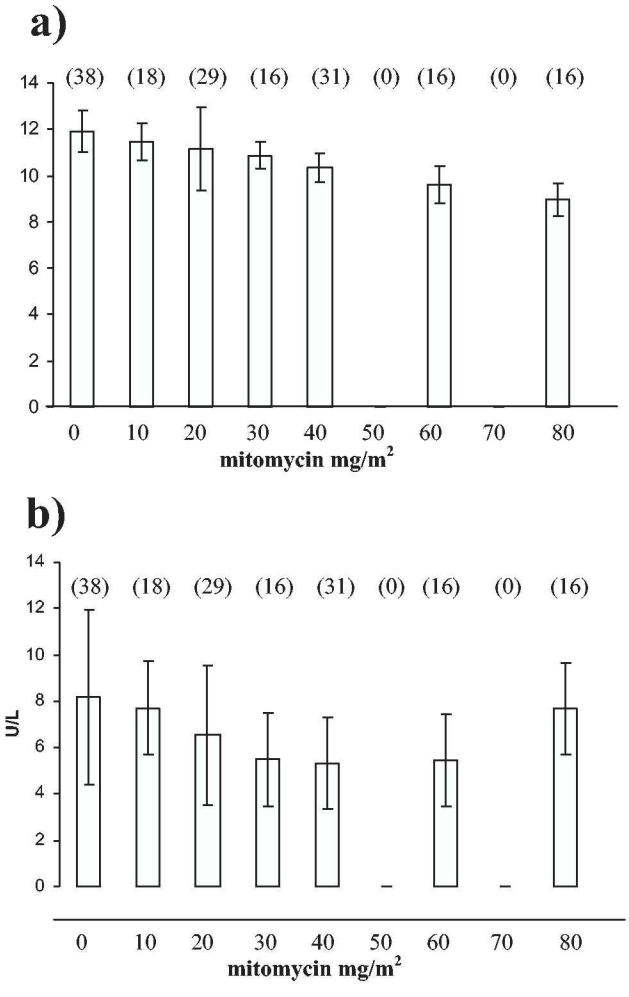

FIGURE 2 - Hb (a) and erythropoietin (b) in high dose plus low dose patients during mitomycin C therapy (in parenthesis number of patients). Doses of mitomycin C are cumulative. The difference is statistically significant ($p<0.001$).

We prospectively studied the magnitude and type of anemia during therapy with mitomycin C randomly given at two dose levels, 10 and 20 mg/m^2 every 3 weeks. Anemia was progressive during mitomycin C therapy and related to the cumulative drug dose ($p<0.03$ to 0.04). MCH, MCV and MCHC indices remained practically unchanged as were erythrocyte folic acid and vitamin B12.

After 80 mg/m^2 of mitomycin C were administered, hematocrit, Hb and RBC were reduced by 20%. Thus anemia due to mitomycin C may be predictable; for each unit of areal density (mg/m^2) of mitomycin C a drop of 0.00372 mg/dl of Hb can be predicted. (*Figure 3*).

The basal circulating erythropoietin, that was already lower than the expected basal Hb concentration in control subjects, progressively reduced ($p<0.01$) during therapy. Erythropoietin slowly continued to reduce until Hb was down to 8.9 g/dl, and then it showed a statistically significant increase.

Possible accompanying toxicity was investigated because hemolytic uremic syndrome may be induced by mitomycin C. This kind of anemia is usually acute or subacute, clinically relevant,

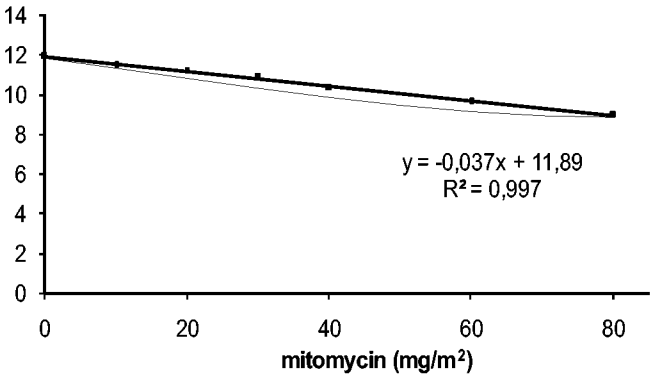

FIGURE 3 - Correlation between Hb levels and mitomycin C cumulative dose.

and mainly but not exclusively observed in patients with gastrointestinal mucinous adenocarcinomas [13-15]. In our patients the anemia developed slowly, was relatively mild in magnitude, chronic, related to the administrated mitomycin C, predictable in terms of Hb g/dl versus each administered mg/m^2 of mitomycin C. The erythropoietin contemporaneously underwent a statistically valid reduction. The 11 patients with gastrointestinal adenocarcinomas were also analyzed separately, and no differences in the blood counts were observed during mitomycin C therapy in comparison with the remaining 27 patients.

The described impairment of renal function and hemolysis related to mitomycin C [13-15] were never observed in our patients, and Hb and RBC urinary loss did not increase during therapy as we had previously observed [9]. Haptoglobin and either total or conjugated bilirubin, as well as BUN, creatinine, creatinine clearance with 24 h urine collection and liver function tests remained practically unchanged during mitomycin C therapy. The Coombs tests never became positive. Obviously, we cannot rule out mild hemolysis and/or some urinary loss of RBCs in days when the tests were not performed. However, serum iron, total iron binding capacity (TIBC), percentage of transferrin saturation and plasma ferritin showed no appreciable variations during therapy, as measured 21 days after each mitomycin C dose. Therefore, urinary iron loss was improbable, also because anemia was consistently normocytic.

Anemia might be caused also by reduced absorption or deprivation of folic acid. However, in our patients MCH and MCV did not increase, and erythrocyte folic acid and vitamin B12 did not decrease.

The possible role of mitomycin C in reducing endogenous erythropoietin was investigated by comparing erythropoietin levels in 81 controls and in 38 cancer patients, who experienced a mild significant reduction of erythropoietin ($p<0.01$). Thus, erythropoietin did not increase in response to anemic hypoxia, at least until the Hb decreased to 8.9 g/dl.

Because 32 cycles were delayed due to leukopenia or thrombocytopenia, the hematocrit, Hb and RBC had time to recover. The exact magnitude of anemia due to hypothetical undelayed cycles of mitomycin C remains underestimated.

In a cancer patient responsive to mitomycin C, in which numerous cycles of therapy may be administered, anemia would require planned erythropoietin treatment. This would become more relevant when mitomycin C is used in combination with radiotherapy or other drugs, which can themselves depress the erythropoiesis.

One of the key issues for the radiotherapist is the importance of hypoxia due to the radiotherapy response. A bioreductive drug like mitomycin C could be useful from the perspective of the radiation biologist to obtain increased local control and possibly increased overall survival, when combined with radiotherapy because of its characteristic of activity on hypoxic cells. So, while mitomycin C administered prior to radiotherapy induces anemia which is detrimental to radiotherapy, the use of mitomycin C during radiotherapy not only provides a combined killing effect but also induces greater cytotoxicity on hypoxic cells [27,28]. The relevance of having a drug capable of killing the hypoxic cell is confirmed by tiparazamine, (a bioreductive anticancer drug toxic against hypoxic cells and a well studied compound, tested in many trials) which has enhanced some standard regimens [29]. The erythropoietin administration appears to be feasible and usually well tolerated [30,31], but at the same time, does not explain why erythropoietin administered to correct anemia and Hb, does not seem to be therapeutically beneficial [32,33] and may have a negative influence on outcome as opposed to radiotherapy alone [34]. So, despite the theoretical advantage, the effect seems unrelated to erythropoietin administration when the intent is to correct anemia in radiotherapy.

We may conclude that anemia due to mitomycin C is essentially normocytic, related to and dose dependent for the two dose levels that we investigated, regularly progressive and predictable. The erythropoietin, basally lower than in control subjects, continued to decrease with therapy.

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