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FROM THE DEPARTMENTS OF SURGERY AT UNIVERSITY HOSPITAL, UMEÅ, MALMÖ GENERAL HOSPITAL, MALMÖ, KAROLINSKA PHARMACY, KAROLINSKA INSTITUTE, STOCKHOLM, SAHLGRENSKA HOSPITAL, GOTHENBURG, SWEDEN, UNIVERSITY OF ALABAMA, BIRMINGHAM, UNIVERSITY OF CALIFORNIA, SAN DIEGO, USA, AND ULLEVÅL HOSPITAL, OSLO, NORWAY.

PHARMACOKINETICS OF INTRA-ARTERIAL MITOMYCIN C WITH OR WITHOUT DEGRADABLE STARCH MICROSPHERES (DSM) IN THE TREATMENT OF NON-RESECTABLE LIVER CANCER

M. ANDERSSON, K. F. ARONSEN, C. BALCH, L. DOMELLÖF, S. EKSBORG, L. O. HAFSTRÖM, S. B. HOWELL, R. KÅRESEN, J. MIDANDER and H. TEDER

Abstract

The effects of degradable starch microspheres (DSM) on mitomycin C pharmacokinetics and bone marrow toxicity were studied in a phase II multicenter study. Sixty-three patients with non-resectable primary or secondary liver cancer were randomized to receive either i.a. mitomycin C 15 mg/m^2 first, followed 5 weeks later by mitomycin C 15 mg/m^2 plus DSM 360 mg administered into the hepatic artery (group I) or the same treatments in the opposite sequence (group II). In 36 out of 47 patients who received at least 2 treatments, peripheral venous blood samples were analyzed for mitomycin C pharmacokinetics on a minimum of 2 paired courses. In all patients, the area under the concentration time curve (AUC) was significantly lower when the drug was co-administrated with DSM, but the terminal half-life ($t_{1/2}$) of mitomycin C was unchanged. In group I the addition of DSM resulted in a significantly lowered AUC, but not in group II. The discrepancy between the 2 groups is probably due to differences in DSM-induced intra-hepatic shunting. The addition of DSM resulted in significantly higher platelet nadir values, but unchanged white blood cell count nadir value. In conclusion, DSM reduce the systemic exposure of mitomycin C and seem to lessen the haematologic toxicity judged from a less pronounced decrease in platelets.

Key words: Liver cancer, chemotherapy, intra-arterial, degradable starch microspheres.

Primary and secondary liver cancer have an extremely poor outcome (1, 2), and it has been estimated that more than 200 000 persons in the USA yearly will die from or with liver metastases (3). Ligation of the hepatic artery or hepatic dearterialization has been tried for several years in order to impair the nutritional blood flow to the liver tumors. Transient reduction of the tumor burden has been observed, but no significantly increased survival (4, 5). Systemic cytostatic treatment in locally advanced liver cancer is of limited value, with remission rates of only about 20% (6–8). Hepatic intra-arterial cancer chemotherapy has the potential advantage of achieving a very high target drug concentration in the tumor, and can produce a substantial pharmacologic advantage when appropriate agents are used (9). By combining reduction in arterial blood flow with hepatic intra-arterial cytostatic treatment target drug exposure may be prolonged, tumor drug uptake increased, and systemic drug exposure decreased (10).

Intra-arterially administered degradable starch microspheres (DSM) have been shown to reduce arterial blood flow for 15–30 min after the infusion (11). The present multicenter study was designed to analyze the effects of DSM administered via the hepatic artery, on the pharmacokinetics of co-administered mitomycin C in patients with locally advanced primary or secondary liver cancer. The possible protective effects of DSM on mitomycin C-induced bone marrow toxicity were also studied.

Material and Methods

Patient selection. Sixty-one patients with histologically proven primary or secondary liver cancer were randomized in the multicenter study. Inclusion criteria were positive cancer histopathology, non-resectable tumor, and disease limited to or mainly limited to the liver. Exclusion criteria were portal hypertension, portal vein or hepatic artery occlusion demonstrated at angiography, previous treatment with BCNU or mitomycin C and performance score less than 70 on the Karnofsky scale. The study has been accepted by the ethical committees at the participating hospitals. Thirteen patients were excluded since they received only one treatment and one patient due to im-

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Table 1

Patient characteristics

Primary tumor site	Toxicological study	Pharmacokinetic study
Colon-rectum	32	23
Liver	4	4
Various sites*	11	9
Total	47	36

*Breast, lung, pancreas, unknown.

Table 2

Median pharmacokinetic parameters in both treamtent groups. Figures within parentheses show 95% confidence interval from the median

	Mitomycin C (Gr 1: 1st infusion Gr 2: 2nd infusion)	Mitomycin C+DSM (Gr 1: 2nd infusion Gr 2: 1st infusion)	
AUC nmol·min·ml^{-1}	139 (101–161)	102 (80–134)	p=0.004
$t_{1/2}$ min	38 (32–49)	36 (29–53)	p=0.41

paired function of the vascular access port. Forty-seven patients received at least 2 treatments. Peripheral venous blood sampling for mitomycin C analysis and pharmacokinetic evaluation was performed in 36 of these patients.

The mean age of the patients (25 males and 22 females) was 60 years (range 37–78). The primary site of the tumor was predominantly colorectal (Table 1).

Treatment schedule. The patients were randomized to treatment with either mitomycin C, 15 mg/m^2 (group I), or mitomycin C (same dose) plus 360 mg DSM (group II) as first treatment. A cross-over treatment was given 5 weeks later. The degradable starch microspheres (Spherex) were kindly supplied by Pharmacia AB, Uppsala, Sweden. DSM and mitomycin C were thoroughly mixed before administration. The treatment was administered via a catheter, introduced into the proper hepatic artery under fluoroscopic control. In a few cases the intra-arterial infusion was given via a subcutaneous vascular access port (Port-A-Cath). The infusion time was 4 min and the infusion volume 30 ml. After the first 2 treatments a clinical evaluation was performed, and in the absence of progressive disease or pronounced toxicity, the dose of mitomycin C was increased to 25 mg/m^2 and the patient was treated with an additional pair of courses.

Blood sampling. Blood (5 ml) was sampled from a peripheral vein 2, 4, 8, 16, 32 min and 1, 2, 4 and 6 h from the end of infusion. The blood was collected in glass tubes containing 250 IU heparin, and immediately centrifuged for 10 min at 4000 rpm. The plasma fraction was removed and stored at −80°C until analysis of mitomycin C.

In addition, blood was sampled before treatment and on days 14, 21, 28 and 35 after the treatment for analysis of white blood cell and platelets and on days 1, 5 and 7 for analysis of bilirubin, ASAT, ALAT, alkaline phosphate counts and creatinine. The change in percentages in these parameters was calculated with the use of the pretreatment and the maximal increased/decreased values.

Table 3

Median AUC, $t_{1/2}$, delta AUC and delta $t_{1/2}$ in the treatment groups (first treatment underlined). Figures within parentheses show 95% confidence interval from the median

	Group I	Group II
AUC mitomycin C nmol·min·ml^{-1}	<u>136</u> (110–166)	134 (109–162)
AUC mitomycin C+DSM nmol·min·ml^{-1}	91 (70–108)	<u>127</u> (98–152)
delta AUC* nmol·min·ml^{-1}	46 (20–71)	15 (−18–46)
$t_{1/2}$ mitomycin C min	<u>45</u> (33–58)	38 (32–48)
$t_{1/2}$ mitomycin C+DSM min	40 (25–72)	<u>44</u> (35–59)
delta $t_{1/2}$** min	7 (−12–21)	−5 (−19–4)

* Delta AUC = AUC mitomycin C−AUC mitomycin C+DSM.
** Delta $t_{1/2}$ = $t_{1/2}$ mitomycin C−$t_{1/2}$ mitomycin C+DSM.

Mitomycin C assay. Mitomycin C was assayed using a modification of the technique reported by denHartigh et al. (12) and Hu & Howell (13). Briefly, mitomycin C was

Table 4

Median haematologic nadir values in the treatment groups. Figures within parentheses show 95% confidence interval from the median

	Mitomycin C	Mitomycin C+DSM	
WBC ($x10^3/mm^3$)	4.7 (4.1–5.2)	5.0 (4.5–5.4)	p=0.28
Platelets ($x10^3/mm^3$)	144 (129–164)	155 (145–187)	p=0.005
Percentage decrease in platelet count	70 (59–117)	55 (33–66)	p=0.004

Table 5

Median maximal values of bilirubin, ALAT, ASAT, alkaline phosphates and creatinine. Figures within parentheses show 95% confidence interval from the median

	Mitomycin C	Mitomycin C+DSM	
Bilirubin (μmol/l)	12 (10–14)	14 (13–16)	p=0.06
ALAT (μkal/l)	0.49 (0.41–0.64)	0.61 (0.48–0.79)	p=0.20
ASAT (μkat/l)	0.76 (0.67–0.90)	1.00 (0.87–1.20)	p=0.08
Alk. phosphat. (μkat/l)	5.5 (4.8–8.6)	7.3 (4.7–9.4)	p=0.12
Creatinine (μmol/l)	88 (80–90)	88 (80–96)	p=0.72

measured by reverse phase high pressure liquid chromatography following saturation of the sample with sodium chloride in extraction into chloroform: isopropylalcohol. Porfiromycin was used as internal standard, and baseline separation was obtained between the mitomycin and porfiromycin peaks and all the other peaks in the chromatogram. The limit of sensitivity was 1 ng/ml, and recovery was 76.1±5.7% (SD), with a coefficient of variation of 2.5%.

Pharmacokinetic evaluation. The AUC (area under the concentration time curve) was calculated by the trapezoidal rule. The terminal half-life ($t_{1/2}$) of mitomycin C (M) was obtained from a standard pharmacokinetic model procedure, using the Gauss-Newton-Harley algorithm. The AUC ratio was calculated as AUC_{M+DSM}/AUC_M.

Statistical procedures. The Wilcoxon's matched-pairs signed-ranks test were used for the comparison of 2 related samples. Two independent samples were compared with the Mann-Whitney U-test. The χ^2-test and the Mann-Whitney U-test were used for comparison of the AUC ratio in the 2 groups. A p-value less than 0.05 was considered statistically significant.

Results

Overall, of the 61 patients randomized 25 (13 from group I and 12 from group II) were excluded from the pharmacokinetic study and 14 patients from the toxicologic evaluation because of rapidly progressive disease or incomplete blood sampling. No essential difference was found with regard to primary tumor site between the excluded and the analyzed patients. The pharmacokinetic and toxicologic evaluations were performed after the first 2 treatments.

Seventeen patients were randomized to receive mitomycin C alone (group I) and 19 patients to receive mitomycin C plus DSM (group II) as the first treatment. The median values of the pharmacokinetic parameters for both groups are shown in Table 2 and for each group in Table 3. Median AUC after mitomycin C was significantly lower with DSM than without when all patients (p=0.004) and group I (p=0.002) were considered, but not when group II alone was considered. The median $t_{1/2}$ of mitomycin C did not seem to be influenced by the addition of DSM. The AUC ratio (AUC_{M+DSM}/AUC_M) was less than 1 in 27 patients (15 in group I and 12 in group II), and more than 1 in 9 patients (2 in group I and 7 in group II). No significant difference with regard to AUC ratio was found between the 2 groups.

The median decrease in platelet count was significantly lower and the median platelet nadir value significantly higher when DSM were added to the treatment, but the median white blood cell count was unchanged (Table 4).

Although some patients experienced slight pain after administration of the DSM, the microspheres did not induce any significant hepatic toxicity. The maximal posttreatment values of bilirubin, ALAT, ASAT, alkaline phosphatases and creatinine were not significantly different after mitomycin C plus DSM as compared to mitomycin C alone (Table 5). Out of 47 patients, one complete and 6 partial responses were observed.

Discussion

The small but significant reduction in the decrease in platelets in percentages, and the higher platelet nadir values when DSM were added, indicate that DSM, to some extent, protect the bone marrow against mitomycin C-induced marrow toxicity. This protection, however, was not sufficient to result in a higher nadir white blood cell count.

Studies on primary human tumor samples often demonstrate that the tumors are resistant to drug concentrations attainable in the plasma, but are frequently sensitive to drug concentrations 2 times higher (14). Consequently a treatment strategy which increases the tumor drug concentration might significantly improve the clinical results. The combination of DSM and cytostatic agents exemplifies such a strategy. The microspheres transiently occlude or reduce the hepatic arterial blood flow at the arteriolar level for about 15 to 30 min before DSM are degraded by serum amylase. The blood flow reduction should result in a prolonged drug exposure time and higher tumor and liver drug concentrations. Mitomycin C was chosen as a suitable anticancer drug because of its previously proven effect against liver cancer (15), and its pharmacokinetic characteristics (13).

The lower systemic drug exposure (measured as the reduction of median AUC) when DSM were added to the treatment was found to average 27%. This is consistent with earlier studies reporting reductions of 30–35% (10, 16). However, in the present study, only patients randomized to receive mitomycin C alone as the first treatment (group I), showed a significant decrease in AUC when DSM were added. The reason for this is difficult to explain. Previous investigations, in which DSM have been administrated into the hepatic artery, have demonstrated intrahepatic arterio-venous shunting (17, 18). This phenomenon, which appears to be related to the dose of DSM (18), may reduce the occlusion effect of the microspheres. It has also been claimed that DSM open up or increase the blood flow in arterio-venous shunts (17). An altered shunting effect may hypothetically be explained by vascular damage induced by a prolonged mitomycin C exposure.

For practical reasons, a fixed dose of DSM was chosen. We decided a low dose of DSM (360 mg, 6 ml) based upon early studies (11). In a phase I study, this dose was found to cause little shunting to the lungs (15%) in comparison to larger doses of 9–15 ml of DSM (16).

Finally, it has been reported that the activation of mitomycin C is increased under anaerobic conditions (19). Whether this fact, in combination with the pharmacokinetic advantages of DSM as an adjunct to mitomycin C, is sufficient to improve the therapeutic effect has to be defined by further studies.

Request for reprints: Dr Magnus Andersson, Dept of Surgery, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden.

REFERENCES

1. Bengmark S, Hafström LO. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer 1969; 23: 198–202.
2. Jaffe BM, Donegan WL, Watson F, Spratt JS. Factors influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet 1968; 127: 1–11.
3. Domellöf L. Natural history of liver cancer: Ann Chir 1986; 75 (Suppl 200): 19–21.
4. Almersjö O, Bengmark S, Rudenstam CM, Hafström LO, Nilsson LAV. Evaluation of hepatic dearterialization in primary and secondary cancer of the liver. Am J Surg 1972; 124: 5–10.
5. Nilsson LAV. Therapeutic hepatic artery ligation in patients with secondary liver tumors. Rev Surg 1966; 23: 374–6.
6. Bedikian AY. Regional and systemic chemotherapy for advanced colorectal cancer. Dis Col Rec 1983; 26: 327–32.
7. Huberman MS. Comparison of systemic chemotherapy with hepatic arterial infusion in metastatic colorectal carcinoma. Semin Oncol 1983; 10: 238–48.
8. Lee YTN. Systemic and regional treatment of primary carcinoma of the liver. Cancer Treat Rev 1977; 4: 195–212.
9. Ensminger WD, Gyves JW. Regional cancer chemotherapy. Cancer Treat Rep 1984; 68: 101–15.
10. Gyves JW, Ensminger WD, VanHarken D, Niederhuber J, Stetson P, Walker S. Improved regional selectivity of hepatic arterial mitomycin by starch microspheres. Clin Pharmacol Ther 1983; 34: 259–65.
11. Lindberg B, Lote K, Teder H. Biodegradable starch microspheres—a new medical tool. In: Davis SS, Illum L, McVie JG, Tomlinson E, eds. Microspheres and drug therapy. Amsterdam: Elsevier, 1984: 153–88.
12. denHartigh J, vanOort WJ, McVie G, Bocken MCYM, Pinedo HM. A sensitive method for analysis of mitomycin C in clinical pharmacology studies. Proc Am Assoc Cancer Res 1981; 22: 179.
13. Hu E, Howell SB. Pharmacokinetics of intra-arterial mitomycin C in humans. Cancer Res 1983; 43: 4474–7.
14. Hamburger AW, Salmon SE. Primary bioassay of human tumor stem cells. Science 1977; 197: 461–3.
15. Crooke ST, Bradner WT. Mitomycin C: a review. Cancer Treat Rev 1976; 3: 121–39.
16. Ensminger WD, Gyves JW, Stetson P, Walker-Andrews S. Phase I study of hepatic arterial degradable starch microspheres and mitomycin. Cancer Res 1985; 45: 4464–7.
17. Starkhammar H, Håkansson L, Morales O, Svedberg J. Effect of microspheres in intra-arterial chemotherapy. A study of arterio-venous shunting and passage of a labelled marker. Med Oncol Tumor Pharmacother 1988; 4: 87–96.
18. Ziessman HA, Thrall JH, Gyves JW, et al. Quantitative hepatic arterial perfusion scintigraphy and starch microspheres in cancer chemotherapy. J Nucl Med 1983; 24: 871–5.
19. Nomura F, Ohnishi K, Koen H, et al. Effects of hypoxia and phenobarbital treatment on the metabolism of mitomycin C in experimental animals. Hepatology 1985; 5: 1190–3.