Phase I Study of Hepatic Arterial Degradable Starch Microspheres and Mitomycin¹

William D. Ensminger,² John W. Gyves, Philip Stetson, and Suzette Walker-Andrews

Departments of Internal Medicine [W. D. E., J. W. G., S. W-A.] and Pharmacology [W. D. E., P. S.], Upjohn Center for Clinical Pharmacology, University of Michigan Medical Center, Ann Arbor, Michigan 48109

ABSTRACT

Intraarterial administration of 40-μm degradable starch microspheres (DSM) in a drug solution can temporarily retard flow of the drug-blood column through the arteriolar-capillary bed and lead to increased local drug deposition. Premonitory to Phase II-III efficacy studies applying this concept to regional therapy, it was necessary to determine the DSM dose to use. Patients with hepatic cancers were treated with varying doses of DSM with mitomycin C coadministered into the hepatic artery to define a dose of DSM which produces acceptable toxicity with maximal hepatic drug deposition as determined by a reduction in systemic mitomycin C exposure. Comparison of six patients receiving 6 ml of DSM (6 × 10⁶ particles/ml) with ten patients receiving 15 ml showed a lower incidence and decreased severity of acute toxicity in terms of nausea/vomiting (16% versus 50%) and right upper quadrant hepatic pain (none versus 40%) with 6 ml of DSM. Reduction in systemic mitomycin C exposure evaluated by decrements in the area under the concentration curve in peripheral blood with time due to DSM was similar in both groups. Another seven patients were treated with escalating doses of DSM concurrently with 5 mg of mitomycin C. Although all seven patients tolerated 6 ml of DSM, higher doses (9 ml, 12 ml, 15 ml) led to incremental patient drop-out due to severe, acute right upper quadrant pain with only two patients able to receive 15 ml of DSM. In these patients, 6 ml of DSM appeared nearly equivalent to higher doses in terms of systemic exposure to mitomycin C. Eleven additional patients were evaluated for tolerance to repeated 6-ml dosing of DSM. Four patients had epigastric pain correlating with flow to the stomach demonstrated by nuclide angiography. The seven patients with no pain and no flow to stomach were treated with good tolerance for three-plus courses. Thus, 6 ml of DSM appear to be appropriate for Phase II-III studies.

INTRODUCTION

The primary aim of regional drug delivery in cancer therapy is to generate greater drug exposure in a major tumor-bearing region with decreased systemic exposure in an attempt to utilize dose-response effects to favorably alter the therapeutic index of treatment. The pharmacokinetic principles defining the elements in selective exposure with regional chemotherapy have recently been reviewed (2, 4). For intraarterial therapy, in particular, the increase in concentration at the target site is an inverse function of regional arterial blood flow. Thus manipulations which produce a reduction in regional blood flow can potentially improve regional drug exposure. Intraarterial injection of DSM² has been used as a means to produce transient arteriolar-capillary block with decreased regional blood flow (3, 6, 9). The effects of such blockade on the pharmacokinetics of coadministered hepatic arterial carmustine and mitomycin C have been investigated (3, 6). It has been demonstrated that systemic exposure can be reduced for carmustine and mitomycin C by coadministration intraarterially with DSM due to greater hepatic drug deposition. Other clinical investigations examining the deposition of intraarterially administered radiolabeled albumin particles (of similar size to the DSM) have demonstrated that tumors in the liver are generally hypervascular relative to normal liver (5). These results suggest that concurrent intraarterial administration of a suspension of DSM in a concentrated drug solution might lead to the deposition of more drug in tumor relative to normal liver parenchyma and thereby generate improved therapeutic effect.

The purpose of the current Phase I study was the definition of the dose of DSM which, when given with mitomycin C into the hepatic artery of patients with liver cancers, would produce the maximum enhancement of mitomycin C deposition within the limits of acceptable patient tolerance. The determination of this dose was necessary prior to the conduct of activity-seeking Phase II-III studies.

MATERIALS AND METHODS

DSM (Spherex, Pharmacia, Uppsaia, Sweden) are specially formulated cross-linked starch spheres 40 ± 5 μm in diameter. The degree of cross-linkage is highest in the outer shell, so that the spherical shape is maintained until the final stage of dissolution. The microspheres are degraded by serum amylase and become progressively smaller in size with a t½ for complete dissolution between 15 and 30 min in vitro (in normal serum). The spheres are stable in a dry state and can be stored at room temperature. The concentration of the clinically formulated DSM suspension is 6 million microspheres/ml (90 mg/ml). DSM were provided by the manufacturer.

Thirty-four patients with incurable cancer in the liver (colorectal, 27; biliary, 2; pancreatic, 1; carcinoid, 1; hepatocellular, 1; gastric, 1; unknown primary, 1) took part in these studies after giving consent according to Department of Health and Human Services guidelines. There were 21 males and 13 females who had a median age of 54 yr (range, 33 to 74 yr). All patients had failed prior systemic chemotherapeutic or hepatic arterial therapy with FUDR. A silicone rubber (Silastic) catheter was placed surgically (28 subjects) or a percutaneous catheter was placed fluoroscopically (6 subjects) into the hepatic artery so as to directly infuse the entire liver as documented by radionuclide angiography (10). In all instances the injectate, consisting of the dose of mitomycin C alone or with the indicated dose of DSM, was made up to a volume of 15 ml and administered over 1 min by steady hand injection using a 20-ml syringe.

Toxicological evaluation consisted of monitoring patients at time of

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² To whom requests for reprints should be addressed.

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treatment for acute symptomatology followed posttreatment by a weekly clinical evaluation which included complete blood counts and liver-derived serum enzyme determinations (glutamate-oxalate transaminase and alkaline phosphatase). Pharmacokinetic evaluation consisted of determination of the area under the concentration curve for systemic mitomycin C exposure for the first h after injection of the various mixtures. Peripheral venous blood samples were obtained at 0, 1, 2, 4, 6, 8, 10, 15, 20, 30, 45, and 60 min after injection, and the plasma was analyzed for mitomycin C using a sensitive high-performance liquid chromatography assay (6). Although this was not an efficacy study, patients had physical examinations and nuclear or computerized tomography liver scans before therapy and 6 to 8 wk after treatment. Standard response criteria were used for evaluation in the 25 patients having measurable disease.

Determination of the appropriate dosage of DSM was carried out in three separate studies. The first (nonrandomized) study compared the toxicological effects of mitomycin C at 10 mg/m² in two groups of patients, one (six subjects) receiving 6 ml of DSM with mitomycin C and another (ten subjects) receiving 15 ml of DSM with mitomycin C. A second study in seven additional patients examined the relative systemic exposures generated by escalating doses of concurrent DSM given with a set dose, 5 mg, of mitomycin C. On separate, successive days, patients received mitomycin C with increasing doses of microspheres starting at a zero control dose and going up by 3-ml increments as far as acute toxicity would permit or to a maximum single daily dose of 15 ml of DSM. At the end of the DSM escalation, patients were retreated with 5 mg of mitomycin C alone as a control for potential changes in mitomycin C pharmacokinetics induced by the repeated DSM treatments. The course of sequentially increased doses was completed in 7 to 10 days, during which time patients remained hospitalized in the Clinical Research Unit.

After determining that 6 ml of DSM appeared to be an appropriate Phase II dose, a third confirmatory study was initiated to evaluate tolerance to multiple courses of DSM (6 ml) with mitomycin C (15 mg/m²) given every 6 wk. Prior to initiation of treatment with mitomycin C plus DSM, 11 additional patients received a test dose of DSM given admixed with labeled ⁹⁹mTc-MAA to ascertain whether there was extrahepatic flow to the stomach or duodenum, as previously described (10), and to ascertain whether there was significant discomfort with DSM alone. Four patients were excluded and did not receive mitomycin C due to transient (10 min), severe, epigastric pain (correlating with marked flow to the stomach and/or intestine) on the DSM-⁹⁹mTc-MAA test dose (10). The seven patients having no flow to the stomach had no acute pain and subsequently received the repeated doses of DSM and mitomycin C.

RESULTS

The toxicity displayed in the group receiving 6 ml of DSM versus that in the group receiving 15 ml of DSM with mitomycin C is presented in Table 1. Nausea/vomiting and acute pain in the epigastrium or liver area were transient in all patients and ap

<table>
<thead>
<tr>
<th>ml injected</th>
<th>No. of patients</th>
<th>Nausea/vomiting</th>
<th>Acute pain</th>
<th>Increased liver enzymes</th>
<th>Myelosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>6</td>
<td>1 (16%), mild</td>
<td>2 (33%), mild</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>5 (50%), moderate</td>
<td>4 (40%), moderate</td>
<td>4 (40%), moderate</td>
<td>2 (20%), transient</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>to severe</th>
<th>to severe</th>
<th>to severe</th>
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</thead>
<tbody>
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<td></td>
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</tbody>
</table>
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Table 2
Systemic mitomycin exposure [(area under concentration – time curve extrapolated to infinity for mitomycin C plus DSM)/(area under concentration – time curve for mitomycin C alone)] in patients receiving either 6 ml or 15 ml of microspheres

<table>
<thead>
<tr>
<th>Group receiving</th>
<th>6 ml (36 million)</th>
<th>15 ml (90 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.48</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>0.66</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>0.67</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>0.68</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>0.73</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>0.82</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>0.83</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>0.69</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>0.70</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>0.83</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

0.67 ± 0.11⁶
0.59 ± 0.16

a No statistical difference in groups by the Wilcoxon 2-sample rank sum test (1).
b Mean ± SD for given group.

Table 3
Systemic mitomycin exposure [(area under concentration – time curve extrapolated to infinity for mitomycin C plus DSM)/(area under concentration – time curve for mitomycin C alone)] relative to dose of microspheres in individual patients each receiving graded doses to tolerance

<table>
<thead>
<tr>
<th>Microsphere dose (ml)</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.65</td>
<td>0.59</td>
<td>0.62</td>
<td>0.61</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>0.78</td>
<td>0.75</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>0.76</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.68</td>
<td>0.59</td>
<td>0.46</td>
<td>0.43</td>
<td>0.34</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>0.88</td>
<td>0.92</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.95</td>
<td>0.89</td>
<td>0.96</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.93</td>
<td>0.74</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.67 ± 0.17⁶
0.74 ± 0.12
0.74 ± 0.17
0.69 ± 0.21
0.40 ± 0.08

a No statistical difference in ratios at 6 ml and 9 ml by Wilcoxon 2-sample rank sum test (1).
b Mean ± SD of ratios at indicated dosage.

DISCUSSION

The development of a reliable implanted drug delivery system consisting of a surgically implanted silicone rubber hepatic arterial catheter connected to a s.c.-placed pump or port has generated a large pool (literally thousands) of patients for hepatic arterial therapies. Since FUDR rarely produces complete regressions and often fails in time, additional effective therapies are necessary.

The recent demonstration that many human hepatic tumors entrap approximately 3-fold more radiolabeled microspheres than are entrapped by a similar volume of normal hepatic tissue provides a further impetus for the development of microsphere-based therapies able to utilize such selective differences (5). Due to tumor hypervascularity, DSM should lodge selectively in tumors and mimic the distribution pattern seen by radionuclide tomographic angiography with Tc-MAA. Depending directly upon the number of microspheres injected relative to the number of precapillary arterioles in the vascular bed infused, flow reduction should occur in a graded manner. At sufficiently high doses (15 ml), approximating 90 million DSM, hepatic arterial blood flow can be totally blocked in about 25% of patients (3). By 30 min after hepatic arterial injection, the DSM are completely lysed by serum amylase, and flow resumes through the hepatic arterial tree as ascertained by contrast angiograms. In the remaining 75% of patients, hepatic arterial flow decreases by 80%, and arterial-venous shunting occurs (3). Based upon pharmacokinetic considerations, as hepatic arterial flow is reduced, the regional exposure advantage of a hepatic arterial drug infusion should increase (2).

In order to determine the most "appropriate dose" of DSM, there are several considerations. As the number of DSM injected is progressively increased, there should come a point where all 40-μm precapillary arterioles that can be blocked are embolized. Further increases in dosage above a certain level may be counterproductive. In particular, as the dose of DSM injected is increased, progressive extrahepatic shunting, primarily to the lungs, may occur (10). The average amount of DSM shunted to the lungs is 15% with 36 million DSM (6 ml) and rises progressively to 27% when 90 million (15 ml) DSM are injected. Thus at a larger dose of DSM, a higher fraction of coadministered drug could flow systemically because of increased arterial-venous shunting. Shunting would tend to work against the desired effect of increasing the proportion of precapillary arterioles that are

leukopenia with a white blood count nadir of 3,000/μl occurring only on the first of three courses. One patient with very advanced and widely metastatic colorectal cancer had a platelet nadir of 67,000/μl on a second course, but no leukopenia. None of these patients had a worsening of hepatic function with repeated treatment either clinically or by enzyme determinations.

Although this was not a Phase II study evaluating antitumor activity, there were nine patients who appeared to have a partial response among 25 evaluable patients in the entire group receiving DSM with mitomycin C. In the subgroup receiving repeated doses of 6 ml of DSM, all of whom had failed prior hepatic arterial FUDR, there were two patients with partial responses (hepatoma, carcinoid tumor), four patients with stable disease (colorectal cancer, three; carcinoid tumor, one), and two patients with progressive disease (colorectal cancer).
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embolized by more DSM. The data comparing 6 ml versus 9 ml, 12 ml, and 15 ml of DSM indicate that 6 ml achieves a substantial fraction of the reduction achievable with the higher doses (Tables 2 and 3; Chart 1).

Dose-dependent toxicity with DSM is perhaps the most important aspect in dosage selection for Phase II efficacy trials. The tolerance to 6 ml in terms of the acute side effects of nausea, vomiting, and pain is quite acceptable with a low incidence and mildness when it occurs. Larger doses do not appear sufficiently well tolerated. The 6-ml dose also appears suitable for repeated administration for at least three doses in terms of lack of demonstrable cumulative or new toxicity. Thus, from a toxicological vantage point, 6 ml of DSM appear to be uniformly well tolerated and, thus, an appropriate dose to use with mitomycin C in Phase II efficacy studies. The activity detected in this Phase I study with nine of 25 evaluable patients responding is suggestive of significant therapeutic potential and forms the stimulus for undertaking Phase II activity-seeking studies.

Although it is apparent that the addition of DSM to mitomycin C can generate new dose-limiting acute toxicities, one at present can only speculate as to whether there are significant therapeutic effects. Inasmuch as mitomycin C appears to be preferentially activated to cytotoxic metabolites in hypoxic tumor cells (8), the generation of ischemia in a liver tumor (which is fed by the hepatic artery) through blockage of flow with DSM could be advantageous. The approximately 30% reduction in systemic mitomycin C exposure seen when DSM are given with hepatic arterial mitomycin C should be additive to the hepatic extraction seen with mitomycin C alone which averages 22% (7). Whether doubling the hepatic deposition of mitomycin C and generating a hypoxic environment is meaningful clinically can only be determined in activity-seeking Phase II-III studies.

Certainly definition of an improved therapeutic effect when DSM are used adjunctly with a chemotherapeutic agent, such as mitomycin C, which already has a modicum of activity, will require a randomized Phase III trial of hepatic arterial drug alone versus drug plus DSM. Nonetheless the investigations to date have provided guidance as to an appropriate DSM dose as well as the necessary precautions (e.g., a pretreatment nuclide scan with a test dose of DSM alone) suitable for such larger trials. It is likely that the DSM and other chemoembolic agents will prove useful in the experimental therapeutics of regional cancers that are shown by nuclide angiography to be hypervascular.

REFERENCES

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