BIODEGRADABLE STARCH MICROSPHERES (SPHEREX), A CLINICALLY USEFUL MEDICAL DEVICE FOR COMBINED INTRA-ARTERIAL CHEMOTHERAPEUTIC TREATMENT OF PRIMARY AND METASTATIC CANCERS OF THE LIVER: THE POTENTIAL CLINICAL VALUE FOR SPHEREX IN REGIONALIZED IMMUNOTHERAPY, HYPERThERMIA AND RADIATION PROTECTION

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ABSTRACT:

Spherex is a medical device which produces controlled occlusion of arterial vessels for a half life of 15', governed by serum amylase digestion. The purposes of this study were to determine the feasibility and toxicity of the use of Spherex with standard chemotherapeutic agents for the treatment of unresectable cancers of the liver.

Twenty two patients with advanced cancer involving the liver were treated with hepatic arterial (HA) chemotherapy mixed with 900mg of 45\mu biodegradable starch microspheres (Spherex-Pharmacia) in a phase II study of Spherex combined with standard chemotherapy. Thirteen patients were treated repeatedly via permanent HA catheters placed operatively using subcutaneous ports whereas 9 patients received their treatments through percutaneously femoral placed HA catheters.

Seven patients of 22 treated clearly showed regression of liver metastases with 4 showing improvement in quality of life. All but one patient studied had >50% tumor liver replacement. Twelve colorectal patients received 5FU 600mg/m^2 day 1 and mitomycin, 10mg/m^2 day 3 in 28 day cycles. Adriamycin, 30mg/m^2, was used to treat one breast cancer patient; and 2 hepatoma patients with a significant partial remission of 9 months in the patient with breast cancer. Five patients received BCNU 100-200mg; 3 with melanoma with one dramatic response that lasted 7 months; one epidermoid carcinoma responded to 2 courses of BCNU and one of thiotepa with dramatic regression and clinical improvement and is still alive at 10 months. One patient, a systemic FAM failure, has responded to 5FU/mito and 5FU alone x 3 courses. Eight patients had one course, 3:2, 3:3, 4:5, 1:5, 1:7, 1:8, 1:14 of Spherex/chemotherapy.

Mild hematologic toxicity was present in only one patient and only 1 of 22 patients had a complication with duodenitis from improper catheter placement. Transient pain in liver and nausea and vomiting were the major toxicities seen.

From our Phase II study, we feel that Spherex chemotherapy can be repeatedly administered via the HA as a convenient palliative approach.
to liver metastatic or primary disease. The advantages of Spherex HA occlusion combined with chemotherapy relate to the fact that 85-95% of the blood supply to metastatic carcinoma of the liver is of HA origin and Spherex achieves a tumor ischemia combined with an increase in chemotherapy concentration to the HA bed with minimal systemic toxicity.

This study demonstrates the safety and convenience of Spherex/chemotherapy combinations, but the therapeutic advantages of Spherex over other forms of hepatic arterial occlusion or chemotherapy can only be inferred unless a larger controlled or comparative study is undertaken.

Spherex occlusion has also been used experimentally in Sweden to produce transient ischemia of bowel and peripheral limbs to protect target organs from radiation injury during the occlusive period. Hyperthermia to liver metastasis can be regionally enhanced during Spherex administration and this approach deserves study.

INTRODUCTION

We now have a new approach to the treatment of liver metastases or primary hepato/biliary tumors with hepatic arterial administration of starch microspheres synthesized by Pharmacia, Uppsala, Sweden. Spherex is the clinical formulation of 45±5 diameter microspheres with a clinical half life of 15 minutes, governed by serum amylase degradability.

Spherex is a medical device for passively increasing local chemotherapy concentration as well as producing transient repeatable intra-tumoral ischemia. Data suggests that Spherex can provide a 3 to 11 fold increase in local chemotherapy concentration within the hepatic arterial tumor bed as amylase digests the starch releasing the occlusion and making the drug locally available (Arfors et al., 1979 a,b; Lindell et al, 1977 a,b,1978). The action of Spherex can provide an ischemic and a drug, radionucleide or monoclonal antibody localizing modality for the treatment of liver tumors.

The new and developing technology of arterial catheter placement to regional areas or via direct surgical placement, with ready access via catheters attached to subcutaneous ports, permits this technique to be of value not only in the treatment of hepatic metastases or primary hepatoma, but it will also allow for treatment in other regional areas as well, i.e., the kidney or tumors localized to the pelvic area or limbs.

Starch microspheres, unique in that they are made to be biodegradable, consist of cross-linked potato starch specially designed to become temporarily trapped at the arteriolar level. The starch undergoes digestion from the normal concentration of endohydrolases (amylase) in the serum.

Because the degree of cross-linking is greatest in the outer shell of the microspheres, the spheres maintain their shape for a considerable time during digestion. For clinical administration microspheres are provided in 1 ml normal saline (0.9%) in a concentration of 60 mg/ml.

As of March, 1985, 17 patients have received Spherex in 2 dose titration studies; 20 patients have been looked at in a blood flow