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Stop Flow in abdominal and pelvic cancer relapses

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1. ABSTRACT

To determinate MTD, DLT and safe doses for phase II study, a dose finding study with Mitomicyn and Adriamycin Stop-Flow administration was carried out. A phase II study focused on resectability of pelvic colorectal relapses is in progress. From November 1995, 84 pts, 52 male and 32 female (94 treatments), with advanced not resectable abdominal (14 pts) or pelvic (70 pts) relapses, and resistant to previous systemic chemotherapy, were enrolled in the study. 46 pts entered the phase I-early phase II study, while subsequently 38 pts were recruited in ongoing phase II study. Safe dose were: MMC 20 mg/mq and ADM 75 mg/mq. The phase II study focused on colorectal relapses registered very promising responses: 90% pain control, 1 pCR and 26 PR / 63 (OR 43%), 8 NC (13%) 9/27 responder patients (33%) obtained a complete resectability of colorectal relapses. Stop-Flow is a safe and feasible technique very useful as a palliation treatment.

2. INTRODUCTION

Cells that are exposed to severe hypoxia, whether chronic or acute, may be unable to adapt to the external pH, undergoing changes in cell physiology which alter the cell membrane's capacity to transport, activate and metabolize many cancer-fighting drugs. Hypoxia of a target tissue causes:

- An increase in permeability
- A decrease in osmotic pressure
- An increase in the concentration of antiblastic drugs both in intra and extracellular spaces. *In vitro*, many drugs have proven to have a more damaging effect on hypoxic cells under conditions of acidosis and/or glucose deficiency, due to several mechanisms. Oxygen deficiency can be considered a selective point of attack of drugs whose chemical and physical properties require a reductive type of activation

Table 1. Patient characteristics (Phase I – Early Phase II)

Number of patients		84	
Number of treatments		94	
Mean age		57 (range: 36-70)	
Males		52	
Females		32	
Performance Status			
0		20	
1		34	
2		30	
Abdominal stop-flow		Pelvic stop-flow (Phase I and Phase I-II)	
Total	14	Total	70
Stomach	5	Colon-sigma	22
Pancreas	6	Rectum	44
Colon	2	Ovaries	2
Mesothelioma	1	Vulva	1
		Uterus	1

(hypoxia induces chemical reactions of endocellular reduction) in order to become electrophilic molecules capable of strong covalent bonds which induce critical conditions for cell survival. These drugs are known as bioreductive alkylating agents

Teicher formulated a classification of three categories of drugs with different oxygenation conditions on the basis of their toxicity (1)

- Drugs that are preferentially active under hypoxic conditions (mitomycin, adriamycin, metronidazole)
- Drugs That Are Active Under Normal Conditions Of Oxygenation (Bleomycin, Procarbazine, Striptonogrine, Actinomycin D, Vincristine)
- Drugs whose action is independent of oxygen concentration (nitrosoureas, 5 fluorouracile, methotrexate, cisplatino)

Mitomycin-C (MMC) may be considered the prototype of bioreductive alkylating agents. The bioactivtion of mitomycin in an alkylating agent occurs in the tumor cell with a reaction that requires an aerobic state and an NADPH-producing enzymatic system. Research in this area has shown MMC to be more toxic against hypoxic cells, with a cell killing potential, at relatively elevated concentrations of the drug, approximately 10 times than displayed against normally oxygenated cells. Under hypoxic conditions even adriamycin (ADM) may be considered a bioreductive alkylating agent, whereas an oxygen-dependant mechanism may be present with normal oxygenation. Teicher demonstrated that adriamycin is more toxic in hypoxic cells at all the levels of concentration tested. Like mitomycin, ADM, at the highest tested concentration, showed a cell killing potential against hypoxic cells 10 times than against normally oxygenated cells. Stop-flow technique could provide an opportunity to exploit the advantages of local/regional therapy in anatomical districts artificially created with the use of arterio-venous catheters that are capable of selectively isolating, according to the site of the tumor, the pelvic, abdominal or thoracic vascular compartment involved (2,3,4,5,6,7).

3. MATERIALS AND METHODS

The phase I dose-finding study was designed to test the use of MMC and ADM in a number of different disease. A total of thirty-nine patients affected with various disorders and who, by standard criteria, were considered no longer treatable by conventional means, were recruited. Their general performance was poor. In the phase I study, fourteen patients were treated with abdominal stop-flow (Table 1) and twenty-five with pelvic perfusion. In the phase I-II study, pelvic recurrences due to colorectal cancer obviously predominated. At the beginning of the study, the clinical target for the phase II study had not yet been established. The initial responses extrapolated from the phase I study prompted us to consider pelvic relapses caused by colorectal and gynecological tumors. The latter became the object of a separate, ongoing study (8,9,10). Stop-flow treatment of pelvic recurrences of colorectal cancer was chosen as the primary target. The study, part of a national project now in its conclusive phase, already appears to herald new proposals. At the same time, it is well known that pelvic recurrences which are operable or can be made operable by the use of adjuvant treatment have a decidedly better prognosis (11,12,13,14,15). In fact, the phase II study is not directed solely at controlling pain and assessing therapeutic response in terms of international criteria (RECIST), but also has among its goals a re-examination of the indication for surgical resectability after stop-flow. Thirty-one patients were enrolled in the phase II study and received a safe dose of 20 mg/m^2 of MMC and 75 mg/m^2 of ADM. All patients gave their informed written consent. University of Cagliari Ethical Committee approval, was received in 1997.

4. RESULTS

A clear-cut pharmacokinetic advantage for perfused tissues was observed both for MMC and doxorubin (DOXO) or epirubicin (EPI) DOXO and MMC local concentrations resulted, respectively, 5-26 (10 and 15 for EPI) and 6-48 higher than those measured in peripheral plasma in spite of elevated interindividual variabilities. The drug percentage eliminated in the ultra filtrate was 7.7% (MMC) and 0.9% (DOXO) The plasmatic drug AUC0-24 were similar to those observed with iv bolus of equivalent drug doses (8,9,10,16).

In conclusion the minimal systemic and local toxicities and the clinical results observed in these patients suggest that this is a suitable system for local deliver of high drug doses in the treatments of recurrent unresectable pelvic cancers, which are poorly responsive to conventional clinical protocols. The endo-arterial administration directly into the local vasculature produces high pelvic-systemic concentration gradients during the stop-flow perfusion. The technique merits further evaluation.

In one case, the balloon catheter burst. The effects were negligible and the ballon fragments were all retrieved. In 4 other cases the ultrafiltration procedure lasted longer than the 60 minutes anticipated, with no appreciable effect on medullary toxicity (16).

Table 2. Pain control in pelvic stop-flow (70 patients)

Pain Control	Assessable Patients (58 patients)	Response Duration (days)	Mean Response duration (days)
Excellent	48	32-660 +	110
Good	4	32- 320 +	80
Absent	6	-	-

Excellent=no pain; Good=dose reduction≥50% of painkilling drugs

Table 3. Pelvic stop-flow: preliminary assessment of clinical response

Response evaluation	N.	Gynecological cancer	Colon-sigma-rectum cancer	Response duration (months)
Total no. of patients	70	4	66	
Assessable patients	67	4	63	
CRp	1		1	26
PR	28	2	26	3 -36 (median 12)
NC	8		8	5 -16+
PD	9	2	24	

CRp: Complete pathologic responses , PR: Partial responses, NC: No change, PD: Progressive disease

Non-hematological toxicity was displayed principally by an increase in transaminase, nausea, vomit and mucositis. Grade IV toxicity only appeared at the third dosage level. With regard to complications, 1 patients had a reversible deep venous thrombosis, 1 had an acute tubular necrosis that was resolved after 20 days, 1 had a paraparesis that cleared in 4 days and 3 had pain due to ileopsoas necrosis that lasted 4-12 days (16).

The maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) observed at the second dosage level (WHO grade IV leucopoenia) made it necessary to try an intermediate dose level with 20 mg/m^2 of MMC and 75 mg/m^2 of ADM. As it turned out, this dosage, tested on 22 patients, was the one subsequently used in the phase II study.

The third level dosage was found to be overly toxic, as demonstrated by the thrombocytopenia recorded. While individual responses varied considerably, the pharmacokinetic benefits of the method were evident. Local concentrations of MMC and ADM were, respectively, 5 to 26 and 6 to 48 times higher than those found in the peripheral blood (16).

In 12 out of 14 patients, evaluation of the results of abdominal stop-flow failed to provide any significant data in terms of clinical response. Moreover, the technique proved difficult to carry out because it entailed anchoring the balloons in the subdiaphragmatic site. The fact that most of the toxic effects were concentrated in the patients receiving abdominal treatment convinced us to suspend clinical investigation for this group. Instead, all our attention became focused on the pelvic stop-flow technique, which was certainly easier to reproduce. Furthermore, patients in the pelvic group experienced more effective and longer-lasting pain control than those undergoing abdominal stop-flow. Indeed, the positive results among the pelvic group were sufficient to justify a much larger phase II study.

In ten patient, a second cycle was followed and results similar to those of the first one were registered. Pain remission was observed in 52 patients; no severe toxicities were observed with this kind of treatment (Table 2)

The preliminary data show a very promising response rate: 1 CRp + 26 PR of the 63 total assessable colorectal relapses with a response duration range of 3-36 and a median of 12 months (Table 3) At the moment a critical point is represented by the refuse of a part of patients and surgeons to practice a resection surgery.

5. DISCUSSION

Many tumors, as they grow, remain confined for long periods within organs or anatomical districts not amenable to radical surgical resection or effective radiation therapy even at the moment of diagnosis. The final objectives of locally or regionally administered chemotherapy are clear: to increase the therapeutic effectiveness of drugs whose beneficial action has already been established and to nullify or reduce the toxicity of substances which, administered intravenously, appear to be active only at doses difficult to tolerate. If, in addition to these advantages, by using the local approach we could also provide a microenvironment independently capable of enhancing the lethal effect on malignant cells, we would have the necessary condition the best possible therapeutic results of modern oncology. At present, our efforts are directed towards the realization of this technically feasible goal by means of hypoxic antiblastic district perfusion in extracorporeal circulation (stop-flow), with the following advantages (5,6,7):

- Use of elevated drug dosages that would otherwise not be possible
- Reduction of systemic side effects
- Enhancement of the therapeutic action of bioreductive drugs in association with hypoxia, otherwise unattainable
- Creation of an artificial pelvic target, totally isolated from other anatomical districts with the use of arteriovenous catheters and pneumatic cuffs

The preliminary data produced by the pharmacokinetic study were extremely positive. The concentrations of ADM and MMC were much higher within the vascular circuit created with the stop-flow technique in the peripheral blood. In the early part of the

phase Il study, the findings regarding haematological and non-haematological toxicity, correlated with dose-finding, made it possible to establish a "safe dose," which allowed the study to continue. Preliminary findings with regard to therapeutic response in the abdominal stop-flow group were of scant significance compared to those obtained in the pelvic stop-flow group, both on account of the limited number of patients treated and the less effective and less durable control of pain in the former. Furthermore, abdominal stop-flow was difficult to implement because it entailed anchoring the balloons in the subdiaphragmatic site, dangerously dose to the area of maximum heart ejection (8,9,10). It should also be kept in mind that with an increase in the number of patients studied, the heightened difficulty in positioning the balloon catheters could correspond to a greater risk of embolism. By contrast, the clinical responses obtained in colorectal and gynaecological pelvic recurrences seem promising (3,4,5,6,7,10). In particular, pelvic recurrences of colorectal disease, due to their frequency, may constitute a useful clinical target for assessing the capacity that this therapeutic procedure has in rendering recurrences resectable. Of considerable importance, is too the significant reduction in pain among patients in the pelvic group, with a consequent improvement in their quality of life. The results thus far achieved certainly justify further study on a larger scale. The findings to date, infact, refer to preliminary results in a national multicenter study still underway, with recruitment nearly completed. With regard to stop-flow treatment of pelvic recurrences from gynaecological tumours, the results obtained, while referring to an extremely limited number of cases, may represent the starting point for stimulating new clinical research (4). If the administration of these drugs under conditions of hypoxia were to have the effect of rendering pelvic recurrences which are no longer responsive to standardized treatment operable, the therapeutic implications for this alternative to radiation and chemo-radiation therapy would indeed be impressive (11,12,13,14,15,17,18,19). Problems regarding the ideal staging system for pelvic recurrences of colorectal disease, however, must still be resolved (20,21,22). Therefore, pelvic stop-flow represents an intriguing method of treating pelvic recurrences from colorectal and gynaecological tumours. The technique is easy to reproduce but at the same time is amenable to improvement. The clinical responses obtained thus far suggest that the use of stop-flow chemotherapy may lead to an increase in the rate of radical resections, possibly in association with radiotherapy. The results of a more extensive study now underway will serve to verify such hypotheses.

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