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Acknowledgements—We gratefully acknowledge the technical assistance of Ms. Eva Mauch. This work was supported by the Deutsche Forschungsgemeinschaft (DFG).

Eur J Cancer, Vol. 28A, No. 8/9, pp. 1437–1441, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Comparison of Intra-arterial Versus Intravenous 5-Fluorouracil Administration on Epidermal Squamous Cell Carcinoma in Sheep

Garry J. Harker and Frederick O. Stephens

Clinical evidence that intra-arterial chemotherapy is more effective in regressing head and neck cancers than equivalent intravenous doses is lacking. Intra-arterial versus intravenous 5-fluorouracil infusion was compared in a naturally occurring, auricular epidermal squamous cell cancer in sheep. Of 18 lesions infused intra-arterially and of 18 infused intravenously with the same dose, 39 and 11%, respectively responded objectively (over 50% regression); mean (S.E.) tumour volume reduction was 37(23) and 18(22)%, respectively. There was a statistically significant difference in the mean tumour response and in numbers of tumours regressing by at least 40% of tumour volume (50% of intra-arterial treated tumours compared with 11% of intravenous treated lesions) after the 16 day total infusion time in favour of intra-arterial treatment. Technically, the intra-arterial route in this model was an improvement on previous small animal models. These findings lend support to the need for continuing clinical study of intra-arterial infusion.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1437–1441, 1992.

INTRODUCTION

THE STATE of the art concerning the theory, development, application and criticism regarding the intra-arterial chemotherapeutic technique in the treatment of cancer, has been reviewed comprehensively [1–4]. In spite of vast clinical experience, appropriate experimental and clinical trials have not been conducted in the management of head and neck carcinoma, in contrast with hepatic cancer [5–8], to confirm the principle that intra-arterial drug administration results in higher regional tumour drug concentrations and regression rates than are attainable by systemic drug delivery [1, 9]. This is primarily due to the fact that relatively small patient numbers are managed in diverse units where the required clinical and surgical expertise are available. On this basis, multi-institutional trials, enabling standardisation of therapeutic regimens, have been difficult to establish. Several investigators have sought further information from experimental small animal models, however, most series have had drawbacks for both biological and technical reasons [10–12]. This report documents the suitability of sheep epidermal squamous cell carcinoma in the head and neck region (Fig. 1) as a model for the study of intra-arterial 5-fluorouracil (5-FU) administration.

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Revised 27 Feb. 1992; accepted 28 Feb. 1992.

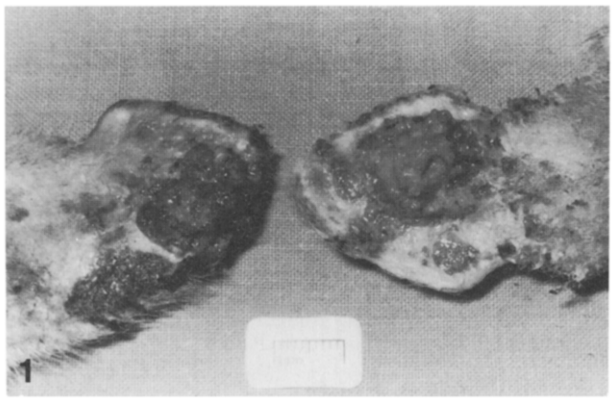

Fig. 1. Typical early auricular squamous cell carcinoma in the sheep.

MATERIALS AND METHODS

Animals

36 merino ewes bearing auricular epidermal squamous cell carcinoma were obtained from the central and western NSW regions in Australia. The animals were randomised to either an intra-arterial or intravenous treatment group. Sheep were fed *ad lib.* and housed under cover in standard enclosures prior to, and during, the study.

Vessel catheterisation

For intra-arterial 5-FU infusion a 19 gauge Deseret intracath (Deseret Medical Inc, Park David Company, Utah) was introduced, under general anaesthesia, into the external carotid artery on the tumour affected side. Access to this vessel was gained either by way of the superficial temporal or cranial thyroid artery. The catheter was brought to the midline position in the dorsum of the neck via a subcutaneous tunnel, and, through a separate skin incision, was connected to tubing from an I-Med constant infusion pump (Milton Trading Company, Oxfordshire). Injection of disulphine blue dye (ICI) via the catheter determined whether infused 5-FU would appropriately access the auricular tumour under consideration. This process was conducted on a weekly basis to ensure that the intra-arterial catheter position had not altered. For intravenous drug delivery, a similar catheter was positioned in the jugular vein of sheep bearing similar squamous tumours. All catheters, either intra-arterial or intravenous, were anchored to each animal's collar, thus preventing tension being placed directly on the skin entry site. Disruption of the infusion lines, due to animal movement, was prevented by a mechanism designed to continually take up excess tubing.

Drug administration

5-FU (7 mg/kg/24 h: Roche) was infused continuously, either intra-arterially or intravenously, in 1 l of normal saline daily. Heparin (5000 units/l) was added to prevent thrombosis at the catheterisation site. As there is a small, but direct arterial link between the major maxillary artery and the cerebral circulation in sheep, infusion of 5-FU was limited to 16 days. A preliminary study of the drug had indicated that after this period of time a small number of sheep may have developed unilateral cerebral symptoms when infused intra-arterially with 5-FU.

Tumour volume and biopsy

All tumours, being less than 25 cm^3 [13], were categorised as Stage II neoplasms according to the classification of Jun *et al.* [13]. Pre-therapy samples were taken under general anaesthesia for vessel cannulation. Following 5-FU infusion, sheep were killed by thiopentone injection, and the tumours measured and biopsied for follow-up assessment.

Response and statistical criteria

The objective response rate was determined as the summation of the complete and partial responses. A complete response represented the total regression of a tumour macroscopically, if not histologically. Partial response tumours were those which regressed by 50% or more following drug infusion. As therapy was conducted for a predetermined 16 day period, the comparative number of tumours showing a greater than 40% reduction in volume was also noted. Differences in proportions between groups were tested by the χ^2 test with application of the Yates correction for continuity. Comparative analysis of mean values was performed by a two-tailed *t*-test. A probability of less than 0.05 was considered to be significant.

RESULTS

Clinical response

The objective response rate for lesions infused intra-arterially was 39% (7 of 18 tumours) (Table 1); the mean tumour response being [mean(S.E.)] 37(23)% and ranging from an 80% regression to 10% progression. A typical partial regression to intra-arterial 5-FU administration is shown in Fig. 2. The response to equivalent dose intravenous therapy was poor, with an 11% objective response (2 of 18 lesions) (Table 1). The mean tumour volume reduction was 18(22)%, ranging from 60% regression to 20% progression. The difference in the mean tumour regression rates, comparing intra-arterial and intravenous treatment, was significant ($P < 0.05$) (Fig. 3). Similarly, analysis of the numbers of tumours exhibiting a greater than 40% reduction in volume, over the designated 16 days total infusion time, was significantly in favour of intra-arterial 5-FU infusion (9 of 18 lesions: 50%) compared with intravenous therapy (2 of 18 lesions: 11%) ($P < 0.05$) (Table 1).

Drug related toxicity

When 5-FU was infused intra-arterially there was no evidence of alopecia, stomatitis or mucositis. Low grade unilateral facial erythema was noted in three sheep. In one of these animals transient signs of mild neurotoxicity were observed 2 days before completion of the course of 5-FU. These symptoms resolved rapidly with cessation of therapy. This intra-arterial dosage did not produce symptoms associated with gastrointestinal (GIT) or bone marrow (BM) toxicity. All animals infused intravenously, with an equivalent dosage, experienced negligible systemic side effects. There was no evidence of buccal mucosa ulceration, skin irritation or alopecia. The GIT and BM tolerated 16 days

Table 1. Comparative response rates following either intra-arterial (IAI) or intravenous (IVI) 5-fluorouracil infusion

Mode of infusion	Objective response	>40% response	<40% response	Progressive disease
IAI*	7‡(39%)§	9(50%)	7	2
IVI†	2(11%)	2(11%)	10	6

*Intra-arterial infusion ($n = 18$), †Intravenous infusion ($n = 18$), ‡Number of responding tumours, §Percentage tumour response rate.

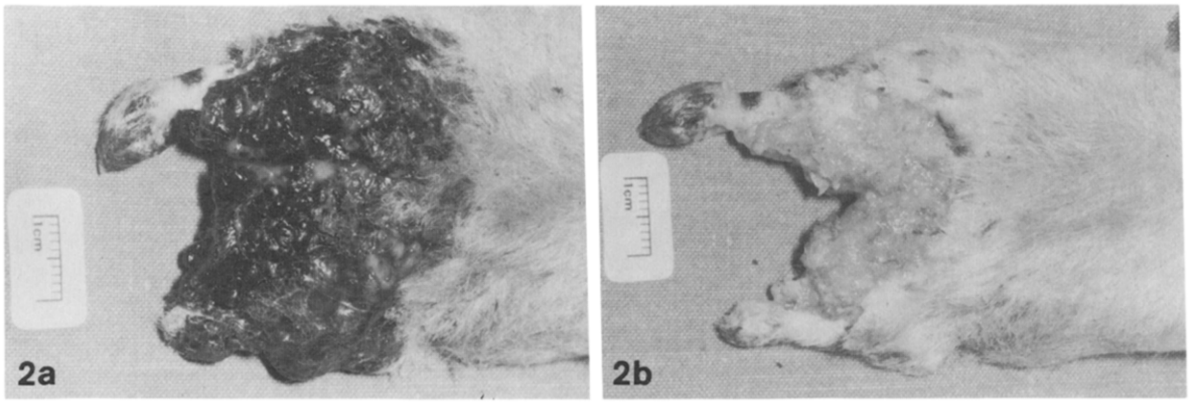

Fig. 2. A 6.1 cm³ moderately differentiated carcinoma (a) which regressed by 69% (b) during intra-arterial 5-FU infusion.

of 5-FU infusion therapy with no significant changes in these parameters in any animal.

Technical aspects

Technically, of the 18 intra-arterial infusions conducted, only one exhibited a transient catheter blockage which was readily cleared with no ill effect. No catheters became dislodged from the arterial lumen, and there were no clinical obvious thrombotic, or air embolic episodes. Similarly, intravenous catheterisation presented no problems regarding catheter disruption or replacement.

DISCUSSION

The primary purpose of an experimental tumour is to serve as a model for human cancer—to provide information concerning both the biology of neoplasia, and techniques, agents and regimens which might improve the clinical process of cancer therapy. Whilst useful, experiments *in vitro* should not abstract so far from reality that relevance to the ultimate goals of therapeutic management is lost. Most tumours used in previous experimental intra-arterial chemotherapeutic trials were derived from transplantable tumour lines, by selecting subpopulations of tumour cells which outgrew in culture or by cloning the malignant cells *in vitro*. None were spontaneous tumours, all lesions being induced by artificial radiation, chemicals or viruses [11, 12, 14–16]. Where possible, fundamental evaluation of malignancy at all levels rests on studies of spontaneous cancers. The actiological, pathological and behavioural similarities of epidermal squamous cell carcinoma in sheep and man, living in a similar Australian environment, are remarkable [4, 17–20]. Moreover, lesions occur on the body surface, affording ease of access for clinical evaluation and biopsy.

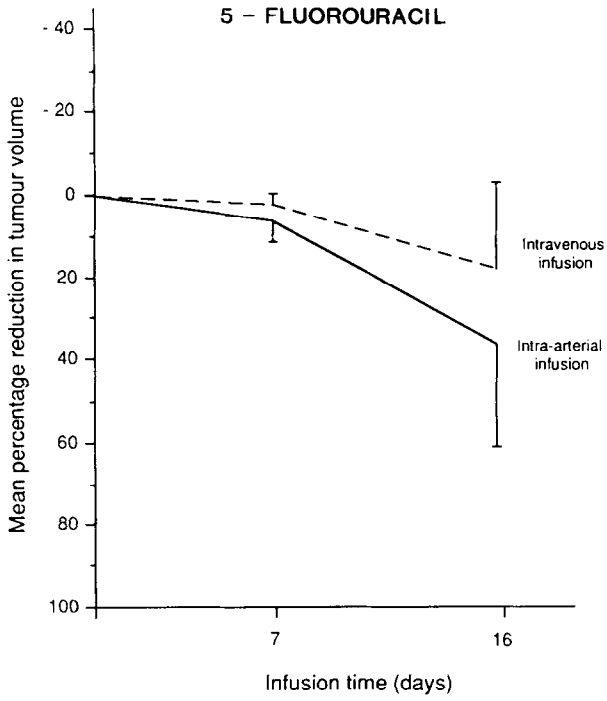

Fig. 3. Graph demonstrating the comparative mean tumour response (S.E.) following 16 days constant rate intra-arterial and intravenous 5-FU infusion (7 mg/kg/24 h; n = 18 for both groups).

The dose, route of administration and schedule for 5-FU, and the derivative fluorodeoxyuridine (FUDR), both structural analogues of the important DNA precursor thymine, have varied considerably. At the present time 5-FU and FUDR are the agents most useful in the treatment of gastrointestinal and hepatic neoplasms and 5-FU has recently been used as intravenous induction therapy for head and neck carcinoma, in combination with cisplatin [21]. 5-FU is also useful topically in the treatment of some malignant and premalignant skin diseases.

Based on pharmacokinetic measurements of 5-FU in the afferent and efferent hepatic blood flow, there is a 20–50% hepatic extraction of the drug during regional arterial delivery [2, 6]. FUDR has been assumed to have a therapeutic advantage over 5-FU, with a reported first pass hepatic uptake of 95%. Hepatic extraction of the fluoropyrimidines, therefore, results in higher drug concentrations in the liver, combined with low systemic levels, during intra-arterial infusion therapy [5–8]. It is of relevance that several randomised clinical and experimental studies have compared the efficacy of hepatic artery infusion of the fluoropyrimidines with systemic administration. Sorsam *et al.* [5] studied a transplantable rat liver tumour, the Navikoff hepatoma, inoculated into the livers of Sprague–Dawley rats. They concluded that intra-arterial chemotherapy with FUDR was superior to all other delivery techniques in terms of tumour response; the mean increase in the hepatic tumour size of rats infused intra-arterially was 0.195 (ratio of pre- and post-therapeutic tumour volumes) compared with 14.5 for rats infused systemically. Comparing continuous intra-arterial infusion with bolus intra-arterial delivery, the continuous mode was considered preferable. In a review of the data from recent

randomised clinical trials, Van de Velde *et al.* [6] highlighted the work of Sugarbaker, reporting a definite trend in favour of intra-arterial FUDR administration in terms of the response rate for secondary liver cancer. Niederhuber [7] compared continuous infusion of FUDR systemically and intra-arterially showing a significantly increased hepatic tumour response rate in the intra-arterially infused group. Kemeny *et al.* [8] determined that direct intrahepatic FUDR therapy, in patients with liver metastases from colorectal carcinoma, produced a significantly higher complete and partial response rate of 50% compared with 20% for systemic therapy ($P = 0.001$). After tumour progression, 60% of the systemic patients crossed over to hepatic artery therapy; 25% then had a partial response, and 33% a minor response or stabilisation of disease on intrahepatic therapy.

The response rate of head and neck squamous carcinoma to systemic 5-FU has been reported at 15% in recurrent lesions [22, 23]. More recently, the use of high dose 5-FU (1 gm/m^2/24 h) for 5 days produced a 72% response but with associated systemic toxicity [24]. Concerning intra-arterial administration Freckman treated 36 patients with 500 mg/24 h for 14 days with 33% responding to therapy [25]. With moderate dose intra-arterial 5-FU infusion (7–15 mg/kg/24 h), the objective response rate has been reported at 60% [26, 27]. Muggia and Wolf [9] documented a 5-FU response rate of 56% with intra-arterial treatment, noting that systemic drug administration response rates seldom exceed 20% with an equivalent dosage. However, there have been no reports of a randomised clinical study directly comparing intra-arterial with intravenous 5-FU induction therapy for squamous carcinoma in the head and neck region.

In the randomised study in the sheep model, there was a statistically significant difference in the mean tumour regression rate in favour of intra-arterial 5-FU therapy, compared with intravenous infusion. Similarly, a significantly greater number of intra-arterially treated tumours (50%) responded by at least a 40% reduction in tumour volume compared with 11% of lesions treated intravenously. Remembering that the total 5-FU infusion time was limited to a 16-day period, it is reasonable to assume that the difference in objective response rates may well have been significant if at least 3–4 weeks infusion time had been involved. This demonstrable enhancement in the tumour response to intra-arterial 5-FU administration in the head and neck region of the sheep highlights the two proposed advantages in the use of regional chemotherapy in appropriate clinical situations. The first, and most obvious, is that there is an associated increased concentration of the agent in the region of distribution of the infused artery [2, 28]. Secondly, it has been reported that total dose exposure of tumour cells to the anti-cancer agent is increased, with, in the case of the head and neck region, most of the agent returning via the draining venous system to the systemic circulation [2, 28]. Therefore, whilst systemic side effects would be virtually the same, regional side effects would be increased in association with the regional tumour response. Such a response pattern is seen in the sheep model, some animals in the intra-arterial group demonstrating mild, but clinically relevant signs of regional toxicity. The fact that 5-FU was delivered by continuous infusion, as opposed to bolus injection may well have been advantageous as this form of administration has been shown to produce a higher incidence of tumour regression without significant systemic toxicity [29, 30].

Technically, catheter insertion and fixation, as described in this report, was performed in such a way that sheep did not disrupt the infusion system, yet retained adequate comfort. Maintenance of intra-arterial infusion was not plagued, therefore, by catheter blockage (due to kinking of the line) or dislodgement problems implicated in small animal studies [11, 12]. The calibre of the sheep carotid artery branch vessels is such that cannulation of the superficial temporal or cranial thyroid artery is not difficult. The catheterised external carotid artery remained unobstructed, and was not ligated as is sometimes the case in the rat model [11].

In summary, this represents the first report whereby intra-arterial 5-FU administration has been achieved via the external carotid artery of a large animal, bearing a naturally occurring malignancy, in a manner analogous to the technique employed in the human condition. There was a significant difference in both the mean tumour response rate, and the numbers of carcinomas regressing by at least a 40% reduction in the tumour volume due to intra-arterial 5-FU infusion, compared with equivalent dose systemic delivery.

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Eur J Cancer, Vol. 28A, No. 8/9, pp. 1441–1446, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Expression of Glutathione-S-transferase-π in Human Tumours

Giuseppe Toffoli, Alessandra Viel, Loretta Tumiotto, Franca Giannini, Rachele Volpe, Michele Quaia and Mauro Boiocchi

Expression of glutathione-S-transferase-π (GST-π) gene was quantitatively analysed on various human tumours (renal cell, colorectal, head and neck, ovarian carcinomas, soft tissue sarcomas; non-Hodgkin lymphomas) and on the corresponding normal tissues when available (kidney, colorectum and head and neck). GST-π mRNA expression level was found to be significantly higher in tumours ($P<0.01$) than in the normal counterparts (mainly 7.3-, 3.5- and 3.0-fold in colorectal, head and neck, and renal carcinomas, respectively). Most tumours displayed a significant relationship between higher GST-π expression level and poor differentiation grade of tumour cells, thus suggesting a relationship between GST-π activity, neoplastic transformation and cellular differentiation grade. The high requirement of GST-π activity neoplastic cells displayed was not singularly related to cellular replication rate. Finally, GST-π gene expression levels were not affected by chemotherapeutic treatments.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1441–1446, 1992.

INTRODUCION

GLUTATHIONE-S-TRANSFERASE (GST) is a family of multifunctional enzymes which catalyse the nucleophilic addition of glutathione to a wide heterogeneous groups of compounds [1]. A variety of biological functions have been ascribed to this isozyme group, including intracellular binding and transport of lipophilic compounds such as bile products, steroid hormones, drugs and other xenobiotics [2]. By far the most studied function of GST enzymes is their role in cellular detoxification, primarily against oxygen-free radicals and peroxides, produced by cellular physiological processes and exogenous stimuli [1,3].

An anionic isozyme class of GST has attracted strong interest in the oncological field because of its ubiquitous and quantitatively high expression in chemically induced tumours [4, 5] and in cell lines transformed by transfected viral oncogenes [6]. The human isozyme of this class, GST-π, was found to be expressed in elevated amounts in most tumours belonging to almost all histological types [7–10]. These findings have suggested that the biological action of GST-π is of considerable importance to neoplastic cell survival. Moreover, the frequent quantitative increase of GST-π in drug-resistant cell lines, sometimes associated with the enhanced expression of the MDR1 gene product [6,11–13], seems to indicate a possible link between GST-π and the multidrug-resistant (MDR) phenotype.

To ascertain a possible functional association of GST-π overexpression with neoplastic transformation and/or cellular drug resistance, we studied a series of human tumours [renal cell, colorectum, head and neck, ovarian carcinomas, soft tissue sarcomas; non-Hodgkin malignant lymphomas (NHL)] and their corresponding normal tissues, when available (kidney, colorectum, head and neck).

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Revised 29 Jan. 1992; accepted 14 Feb. 1992.