combination endocrine therapies. The Danish Prostatic Cancer Group randomised 264 patients with either locally advanced or metastatic disease to either orchiectomy or goserelin, or goserelin with flutamide. A minor advantage was found with combination therapy in initial response rates but not in time to progression or overall survival. The median follow-up of these patients was 30 months [4]. The EORTC urological oncology group randomised 327 patients with metastatic prostatic cancer to orchiectomy or goserelin and flutamide. Time to progression was longer in the combination arm but there was no difference in overall survival. The median follow-up of these patients was 18 months [5]. The International Prostate Cancer Study Group trial of goserelin with or without flutamide found no advantage to combination therapy in an analysis of 571 patients with either localised or metastatic cancer followed for a median of 2 years [6]. The significance of these trials' conclusions is reduced when one considers the short follow-up, mixed patients populations and differences in treatment. A second EORTC study is investigating the benefit of cyproterone acetate given in combination with buserelin. The results of this study have been analysed and no advantage shown to combination therapy according to the trial organiser (J Klijn: personal communication). This latter study could be criticised because cyproterone acetate does have the theoretical disadvantage of inherent androgenicity [7]. This is obviously suboptimal in the context of the concept of anti-androgen treatment limiting the significance of the conclusion of this EORTC study.

The six major trials described above are amongst at least 10 investigations of combination endocrine therapy that are currently underway. These trials are the subject of a meta analysis whose results are eagerly awaited. In any analysis of the advantages of combination therapy, it should be noted that there are disadvantages to treatment with flutamide and these are expense and the 10–15% incidence of gastrointestinal complications. The added expense of treatment can be disregarded in our affluent European societies if the NCI's studies finding of a prolongation of life are confirmed. The gastrointestinal toxicity can usually be moderated by dosage reduction.

In addition to the therapeutic gain in terms of prolongation of remission and duration of life there is another advantage to the concomitant administration of anti-androgens and that is the avoidance of tumour flare. Without anti-androgens, GnRH analogues will cause tumour flare in between 1 and 40% of patients [8]. With co-administration of anti-androgens, this syndrome is virtually unknown [9].

Returning to the question posed by this editorial it would appear that there is no definitive conclusion as yet, as to the benefits of combination therapy in terms of prolonging the patient's life. Whilst awaiting a definitive conclusion, my own view is that we should continue to recommend combination therapy because of the significance of the NCI study's findings and because of the advantage of avoiding tumour flare.

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1. Labrie F, Dupont A, Belanger A, *et al.* New hormonal therapy in prostate cancer. Combined use of a pure anti-androgen and an LHRH agonist. *Horm Res* 1983, **18**, 18–27.
2. Redding TW, Schally AV. Investigation of the combination of the agonist D-Trp-6-LHRH and the antiandrogen flutamide in the treatment of Dunning R3327H prostate cancer model. *Prostate*, 1985, **6**, 219–232.
3. Crawford DE, Eisenberger MA, McLeod DG, A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989, **321**, 419–424.
4. Iversen P, Christensen MG, Friis E, *et al.* A phase III trial of zoladex and flutamide versus orchiectomy in the treatment of patients with advanced carcinoma of the prostate. *Cancer* 1990, **66**, 1058–1066.
5. Keuppens F, Denis L, Smith P, *et al.* Zoladex and flutamide versus bilateral orchiectomy. A randomized phase III EORTC 30853 study. *Cancer* 1990, **66**, 1045–1057.
6. Tyrell C, Altwein J, Klippel F, *et al.* A multicenter randomized trial comparing the luteinizing hormone-releasing hormone analogue goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. *J Urol* 1991, **146**, 1321–1326.
7. Poyet P, Labrie F. Comparison of the antiandrogenic/androgenic activities of flutamide, cyproterone acetate and megestrol acetate. *Mol Cell Endocrinol* 1985, **42**, 283–288.
8. Waxman JH, Man A, Tiptaft RC, *et al.* Importance of early tumour exacerbation in patients treated with long acting analogues of gonadotrophin releasing hormone for advanced prostatic cancer. *Br Med J* 1985, **291**, 1387–1388.
9. Waxman JH, Williams G, Sandow J, *et al.* The clinical and endocrine assessment of three different anti-androgen regimens combined with a very long acting gonadotrophin releasing hormone analogue in prostatic cancer. *Am J Clin Oncol* 1988, **11**, S152–155.

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Should Further Studies of Chemotherapy be Carried out in Pancreatic Cancer?

DEFEATISM AND nihilism are not prominent in the therapeutic vocabulary of surgical oncologists. Nevertheless, certain malignancies defy even the most aggressive intellects and resist all attempts to improve survival. Pancreatic cancer is a classical example. If resectable and localised the cancer should be removed, for after all, this is the only hope of cure. But what if it is irresectable, as in the majority of patients? Palliation by stents or surgical bypass is valuable but will not significantly improve survival. Intuitively, but with a degree of scepticism, one may seek a solution in cytotoxic chemotherapy. This can be used either as an adjuvant in patients who have undergone resection, or for the treatment of advanced and inoperable disease. Such therapy, however, can lead to intolerable cytotoxi-

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city for minimal (or nil) reward. There has been no shortage of chemotherapy studies but is it now time to temporarily abandon such approaches until more evidence of benefit is apparent? It should be remembered that even patients included in randomised clinical trials suffer from cytotoxicity! This article reviews the role of chemotherapy in pancreatic cancer and attempts a critique of the available evidence both for and against such an approach.

ADJUVANT TREATMENT

Adjuvant chemotherapy can be used following both resectional (or curative) surgery as well as following so called palliative surgery. The most frequently quoted study in this regard is that of the Gastrointestinal Tumour Study Group (GITSG) [1]. They compared surgical resection alone with surgical resection followed by postoperative fluorouracil (5-FU) combined with regional radiotherapy. The median survival of the 5-FU plus radiotherapy group was 20 months compared to that of 11 months in the untreated group. This translated to a 2-year actuarial survival of 43% vs. 18%. This study created much interest and attempts to reproduce the favourable results are being made. The U.K. Pancreatic Cancer Trials Group, for example, have reported results in 27 patients treated with a similar regime to the GITSG Group. The treatment was well tolerated, with no significant drug toxicity. At a median follow-up of 12 months, a 30% 2-year actuarial survival was achieved [2]. This regime of combined chemotherapy and radiotherapy in resectable disease is of continuing interest and deserves further investigation by means of larger randomised trials. Happily this regimen is associated with very little drug- or radiotherapy-induced toxicity.

Adjuvant therapy, however, following palliative surgery is a rather different matter. These patients have incurable disease and efforts are directed towards enhancing the poor survival figures. Response rates, if not translated into an improvement in survival, are hardly worth while. Moertel *et al.* [3] randomised 64 patients with pancreatic cancer to radiotherapy alone or radiotherapy with 5-FU by rapid injection over the first 3 days of radiotherapy. The combined therapy patients showed a survival advantage which was statistically significant (10.4 vs. 6.3 months). A subsequent study by the GITSG in 227 patients compared high dose radiotherapy (60 Gy) with radiotherapy and 5-FU. This resulted in an improved overall survival from 23 weeks to 40 weeks [4]. More recently Kahn *et al.* [5] reported the results of surgical bypass alone compared to synchronous chemotherapy and irradiation. This latter regime extended the mean survival time from 8.9 to 13.5 months but more importantly, resulted in pain relief in 80% of patients. Toxicity was minimal.

Many authors have concluded that these results do not justify the routine use of adjuvant therapy in irresectable pancreatic carcinoma (i.e. following bypass surgery) [6]. I would also subscribe to this opinion. A modest extension of survival is a high price to pay for potentially very serious side-effects associated with the burden of extra hospital visits and increased time away from home and natural environments. Patients should be considered for this form of treatment only within the confines of prospective randomised trials, and then after very careful discussion with the patients.

TREATMENT OF ADVANCED AND METASTATIC CARCINOMA

There is no effective systemic treatment for patients with advanced or metastatic pancreatic carcinoma. In addition, several studies have failed to show extra benefit from combination chemotherapy compared to single agents [7]. All single agents have comparable activity; specifically 5-FU, doxorubicin (and epirubicin) and mitomycin C [8]. Recently, interest has been directed towards epirubicin which has demonstrated remissions with acceptable toxicity. Topham *et al.* [9] randomised 69 unselected patients with locally advanced and metastatic carcinoma into either 5-FU, epirubicin and mitomycin C or epirubicin alone. There were no significant differences in survival in the two arms and toxicity in the combined group was markedly greater compared to epirubicin alone. Based on the results of this and other randomised studies one cannot recommend combination chemotherapy as standard treatment in this group of patients. A single agent may provide some palliation, but is unlikely to significantly prolong survival.

At one stage it was hoped that tamoxifen may have a role in advanced disease but unfortunately a recently reported randomised study of tamoxifen in unresectable adenocarcinoma failed to show any improvement either in remission rates or survival compared to placebo [10].

LOCOREGIONAL APPROACHES

Aigner *et al.* [11] have popularised the use of locoregional chemotherapy for non-resectable pancreatic carcinoma using intra-arterial infusion with mitomycin C, cisplatin and 5-FU. A recent study in 24 patients has been reported in which catheters were placed into the coeliac axis either angiographically or by surgical placement. Response rates were achieved in 77% of patients but only one complete response was noted. A median survival of 9 months was obtained. This is an interesting approach with minimal cytotoxicity but it does require sophisticated technology to place the catheter into the correct artery. Such treatment deserves further investigation but in the absence of phase III studies one cannot, at the present time, recommend it as a routine procedure.

CONCLUSIONS

The available evidence suggests that future studies should be directed to adjuvant chemotherapy following resectional ("curative") surgery. There is little objective survival improvement for chemotherapy when given to patients with irresectable or advanced metastatic disease. Hopefully more effective agents will be developed in the future which can be studied in randomised trials. In the meantime any chemotherapy delivered should be done with a certain degree of circumspection and only after full discussion of the implications with the individual patient. There is little evidence at present to suggest that survival will be improved with chemotherapy and palliation of symptoms can be achieved by less toxic means.

In conclusion the answer to the question posed by this article, i.e. "Should further studies of chemotherapy be carried out in pancreatic cancer?" must be equivocal. Until more effective regimens are available from phase I and II studies, chemotherapy trials should probably be restricted to adjuvant approaches following "curative" resection.

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1. The Gastrointestinal Tumour Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer* 1987, **59**, 2006–2010.
2. Neoptolemos JP. Adjuvant radio-chemotherapy following resection of pancreatic adeno-carcinoma. *Preliminary Results in Digestion* 1992, **3**, 127.
3. Moertel CG, Childs DS Jr, Reitemeier RJ, *et al.* Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet* ii, 865–867.
4. The Gastrointestinal Tumour Study Group. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil) and high dose radiation + 5-fluorouracil. *Cancer* 1981, **48**, 1705–1710.
5. Kahn PJ, Skornick Y, Inbar M, *et al.* Surgical palliation combined with synchronous therapy in pancreatic carcinoma. *Eur J Surg Oncol* 1990, **16**, 7–11.
6. Watanapa P, Williamson RCN. Surgical palliation for pancreatic cancer: developments during the past two decades. *Br J Surg* 1992, **79**, 8–20.
7. O'Connell MJ. Current status of chemotherapy for advanced pancreatic and gastric cancer. *J Clin Oncol* 1985, **3**, 1032.
8. Cullinan SA, Moertel CG, Fleming TR, *et al.* A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. *JAMA* 1985, **253**, 2061.
9. Topham C, Glees J, Rawson NSB. Randomised trial of epirubicin alone versus 5-fluorouracil, epirubicin and mitomycin C in locally advanced and metastatic carcinoma of the pancreas. *Br J Cancer* 1991, **64**, 179–181.
10. Bakkevold KE, Pettersen A, Arnesjo B, *et al.* Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and the papilla of Vater. *Br J Surg* 1990, **77**, 725–730.
11. Aigner KR, Muller H, Bassermann R. Intra-arterial chemotherapy with MMC, CDDP and 5-FU for non-resectable pancreatic cancer—a phase II study. *Reg Cancer Treat* 1990, **3**, 1–6.

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Papers

Multiple Drug Resistance in the Human Ovarian Carcinoma Cell Line OAW42-A

Alice Redmond, Elizabeth Moran and Martin Clynes

A new multidrug-resistant variant (OAW42-A) of a human ovarian carcinoma line has been selected by exposure to increasing concentrations of doxorubicin. The variant is resistant to doxorubicin, vincristine (but surprisingly not to colchicine), etoposide, tenoposide and also to cisplatin (a drug not usually involved in classical multidrug resistance), but not to 5-fluorouracil. Overexpression of P-glycoprotein in the resistant line was demonstrated by immunofluorescence and western blotting. Direct evidence for P-glycoprotein as a determinant of resistance was provided by transfection with a specific antisense oligonucleotide. Reversal was incomplete and this, along with the pattern of cross-resistance observed, suggests that additional mechanisms of resistance may also be involved. Substantial clonal variation in resistance exists within the cell line.
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INTRODUCTION

OVARIAN CARCINOMA in humans often responds well initially to combination chemotherapy, but unfortunately the cancer often reappears in a form which is resistant to a wide range of drugs.

Multiple drug resistance (MDR) in human cancer and in cancer cells *in vitro* has thus far been principally associated with overexpression of a membrane efflux glycoprotein (P-glycoprotein, P-170), [1–3], alterations in glutathione-related enzyme levels, [4, 5], or reduced or altered expression of a topoisomerase II enzyme [6]. Other mechanisms of MDR, for example, non-P-glycoprotein efflux-related proteins [7, 8], and alterations in cellular calcium levels [9] exist. Studies on tissue from ovarian carcinoma patients suggest that P-glycoprotein overexpresion and possibly also reduction in topoisomerase II activity may relate to acquired and intrinsic drug resistance in ovarian carcinomas *in vitro* [11–13].

Bradley *et al.* [14] selected a range of MDR variants of the human ovarian carcinoma cell line SKOV3 by growth in increasing concentrations of vinca alkaloids. All but one of 16 variants selected overexpressed P-glycoprotein. At lower resistance levels, *mdr*-1 mRNA and protein were overexpressed, whereas at intermediate levels *mdr*-1 gene amplification was also observed. In one of the most resistant variants, P-glycoprotein levels were much higher (relative to other variants) than would be expected from mRNA levels and gene copy number, indicating possible control at the post-translational level (e.g. increase in half-life of the protein). Different glycosylated forms of P-glycoprotein are known to exist [15] but the relevance of this form of post-translational modification to stability and half-life of P-glycoprotein is unknown. Bernard *et al.* [16] have also isolated by exposure to vincristine a variant of a human ovarian carcinoma line which overexpresses P-glycoprotein. Lau *et al.* [17] have described a variant of the human ovarian carcinoma cell line ES-2, selected by exposure to cyanomorpholino doxoru-

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