Towards immunotherapy for pancreatic cancer

Editor,—McKenzie and Apostolopoulos’ recent article on immunotherapy for pancreatic carcinoma (Gut 1999;44:767–769) gave an excellent overview. We agree that the poor prognosis of this disease makes it imperative that new agents and novel therapeutic strategies are investigated. However, although this paper discusses classical immunotherapy (where immune competent cells are stimulated to attack pancreatic cancer cells directly), the induction of antibodies directed against growth factors by immunisation (where the immunogen stimulates the immune system to inhibit the growth of tumour cells indirectly) is not mentioned. We are currently undertaking a phase II clinical trial for inoperable pancreatic cancer using one such immunogen, Gastrimmune, which induces neutralising antibodies against the antigen gastrin-17 and more recently has been shown to inhibit the growth of human pancreatic carcinoma cell lines. Gastrimmune is also undergoing a phase II trial for gastric cancer at the University Department of Surgery, Nottingham, UK.

Gastrin has been shown to be a growth factor in a variety of malignancies including colorectal, gastric, and pancreatic cancers in both in vitro and in vivo studies; precursor forms such as progastrin and glycine extended gastrin also have a trophic effect. More recently the autocrine/paracrine pathway, in which tumour cells produce and respond to gastrin, has been shown to be increasingly important. In vitro and in vivo studies have also shown the trophic effect of gastrin and the inhibitory effect of both gastrin receptor antagonists and anti-gastrin antibodies, and further studies have confirmed gastrin expression in human pancreatic cancer cell lines and resection specimens. Thus, there is good evidence to suggest that immunisation against gastrin may be beneficial in the prevention of pancreatic cancer.

We have shown that Gastrimmune induced antibodies inhibit the growth of human pancreatic cancer cell lines, and they have previously been shown to inhibit the growth of gastric, colon, and hepatocellular cancer cell lines in vitro and in vivo. Over 150 patients have now received Gastrimmune in several trials. The side effect profile has been extremely good and the early efficacy data in colorectal cancer has been encouraging; phase III studies are currently being designed for both pancreatic and colorectal cancer.

Pancratic cancer has an appalling prognosis. New molecular insights provide encouragement that novel therapeutic strategies may improve outcomes. Against this background, the immunisation of patients with solid tumours in humans, as we are experienced in rejecting grafts and with tumour grafts using antibody and complement. For murine tumours, we have not been able to cause rejection of human MUC1+ tumours in mice by using large amounts of monoclonal antibodies and additional complement, under circumstances which lead to rapid destruction of lymphoid cells.

However, total pessimism now seems unwarranted. Firstly, murine antibodies to leukaemia and leukaemia have been found to be particularly useful in the treatment of these diseases. The antibodies need to be “armed”, especially with isotypes, and using antibodies to CD19 and CD20 “I labelled antibodies have been shown to have a direct effect on cell surface molecules which are another exception. A well known antibody, Her2/neu, reacts with molecules present in 20–30% of pancreatic cancer. Her2/neu molecules have a growth factor function and if they can be blocked on the cell surface, this may be only shown by a clinical trial. There may also be problems with antibodies obtaining access to tumours not expressing the appropriate molecules as they de-differentiate. However, these are problems of any cellular or humoral immune response, and are no longer regarded as being peculiar to antibodies. Nevertheless, it is appropriate to consider special antibodies and growth factors to be part of immunotherapy for pancreatic cancer.

Finally, the colon cancer trial in which patients with Duke’s C disease had improved prognoses after receiving 171A antibody, is of interest, although it still to be established whether the specific or non-specific nature of the antibody was responsible for the improvement, or whether phase III trials are now in progress to assess this. It is easier to treat disease by immunotherapy if treatment starts at an early stage. Unfortunately, early diagnosis of pancreatic cancer remains difficult—how can a disease with a relatively low frequency be diagnosed in the absence of symptoms? When the symptoms finally appear it may already be too late for immunotherapy.

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Reply

Editor,—Brett and Caplin have highlighted that our paper was biased towards cellular immunotherapy. We specifically excluded references to antibodies, but welcome the opportunity to mention these in the context of immunotherapy of pancreatic cancer. In the early 1980s, murine monoclonal antibodies offered great hope for the diagnosis and cure of cancer, but by the end of the decade, the outlook was pessimistic. Used alone, murine monoclonal antibodies had little effect, mostly because of the occurrence of HAMA (human anti-mouse response) which proved by the use of such antibodies in the treatment of lymphomas; they are particularly sensitive to irradiation and because the patients were immunosuppressed by the disease, they made little HAMA and therefore could be treated successfully. Antibodies that do not act primarily via their Fc piece by activating complement but have a direct effect on cell surface molecules are another exception. A well known antibody, Her2/neu, reacts with molecules present in 20–30% of pancreatic cancer. Her2/neu molecules have a growth factor function and if they can be blocked on the cell surface, this may be only shown by a clinical trial. There may also be problems with antibodies obtaining access to tumours not expressing the appropriate molecules as they de-differentiate. However, these are problems of any cellular or humoral immune response, and are no longer regarded as being peculiar to antibodies. Nevertheless, it is appropriate to consider special antibodies and growth factors to be part of immunotherapy for pancreatic cancer.

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Ring-like elevations in the large bowel: endoscopic signs to distinguish the artefact from true neoplastic lesions

Editor,—We read with great interest the article by Martin et al (Gut 1999;45:147) on normal histological findings in small depressed lesions of the large bowel. They described three patients with 7–8 mm depressed lesions, similar to small flat or depressed neoplastic lesions, during sigmoidoscopy (two cases) and total colonscopy (one case). Specimens taken by extensive biopsy or removed by endoscopic mucosectomy were histologically normal with no evidence of neoplasia. Two weeks later, colonoscopy with chromoscopy in one patient failed to locate the lesion. In contrast to true flat adenomas characterised by rough, red, depressed mucosa and an irregular outline, the lesions had normal central mucosa and a regular circular elevation. The authors therefore concluded that flat lesions with a regular circular shape and normal central mucosa are likely to be of little significance, and recommended diagnostic cold biopsy in these cases.

Despite their claim of the first report of normal histological findings in small depressed lesions, we had described similar lesions as ring-like elevations.1 Histological assessment of biopsy and endoscopic mucosectomy specimens of the elevations revealed slight oedema within and around the lesion, similar to that seen in the ascending colon and rectum, requiring frequent aspiration, we suspect that their lesions are also pseudolesions caused by suction of the mucosa into a colonic polyp forming ring-like elevations.1 Although they mentioned that suction had not been applied to the mucosa, experienced endoscopists usually aspirate retained fluid unconsciously during colonoscopy. Although histological findings of their lesions showed normal mucosa, we suspect that slight oedema was probably present within the lamina propria of their ring-like lesions. We believe their lesions are the same as ring-like elevations.

Some diminutive polyps disappear during maximal colonscopic insufflation. This phenomenon is invariably associated with hyperplastic polyps, but not with adenomas.2 Dye-spraying techniques readily visualise the innumerable fine grooves, the so-called in-nominate grooves, which remain visible in non-neoplastic lesions and in normal colonic mucosa, but not in neoplastic lesions.2 Because ring-like elevations usually disappear after vigorous air insufflation and the innominate grooves are always visualised in the elevations, the disappearing phenomenon and the presence of innominate grooves in the lesions serve to differentiate this artefact from true neoplastic lesions.3 With these endoscopic signs, we can avoid biopsy or removal, and thus the cost of pathological examinations.

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Reply

Editor,—We value the comments made by Matsushita et al and are grateful to them for bringing to our attention their earlier letter which reports ring-like elevations of the colon associated with the colonscopic saucation. Gastroint Endosc 1997;46:196.


Liver biopsy under ultrasound control: implications for training

Editor,—As a gastroenterologist/hepatologist, I appreciate the analysis provided by Shah et al (Gut 1999;48:628–629) about having to surrender liver biopsy samples to radiologists as a result of reduced training opportunities. The desire of an overwhelming number of gastroenterologists to become proficient in ultrasound techniques1 should send a loud and clear message to the relevant regulatory training bodies. Once ultrasound has been introduced into gastrointestinal training programmes in the United Kingdom, such as in Europe or the USA, the questions raised by Shah et al would have been partially solved, albeit indirectly.

The purpose of ultrasound guidance in liver biopsy is threefold: (i) to target the liver, (ii) to avoid the gall bladder.1 In this day and age, it would be unthinkable to perform a blind liver biopsy on a patient who has a discrete liver lesion. However, when it comes to diffuse or generalised disease, “X marks the spot” or ultrasound assisted technique should suffice. Although the liver is a large and superficial organ, targeting it, even for diffuse or generalised disease, should not be left completely to chance. In the ultrasound assisted technique, the procedural aspect of liver biopsy is essentially blind subsequent to the initial ultrasound to mark the spot. Therefore becoming proficient in this technique would prevent loss of expertise in the blind approach, and yet the medicolegal position remains sound.

Inadvertent biopsy of the gall bladder can be easily missed by allowing the patient to have a light breakfast, as the gall bladder becomes contracted following a meal.1 However, the more cautious would prefer patients to fast, in case they develop a complication requiring operative intervention.

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Reply

Editor,—Dr Chuah makes some valuable points about the problems of training in gastroenterology in relation to ultrasound. One of the key messages of our survey was to differentiate the “X marks the spot” ultrasound technique from the real time ultrasound guided method, which is in standard use within our hospitals. Using this technique, the needle is continuously visualised throughout its time within the liver and therefore there is minimal risk of biopsy of gall bladder or intrahepatic vessels. We consider this to be the best technique to use but it is the most difficult method in which to become proficient. Most training schemes for specialist registrars in gastroenterology will have difficulty in accommodating the additional time required to learn this technique.

S SHAH
JF MAYBERRY

BOOK REVIEW


A comprehensive study of vitamin D, this book starts with a brief consideration of the evolutionary aspects of vitamin D and the essential role of photosynthesis of the vitamin in the conservation of calcium in aquatic and land animals. Cutaneous synthesis is the principal source of vitamin D for most healthy people but dietary intake becomes increasingly important in the very young and the elderly. Adequate intakes (formerly called recommended daily allowances) for all age groups, and for pregnant or lactating women, are provided and the central question of how to define vitamin D deficiency is revisited; based on serum parathyroid hormone responses to vitamin D supplementation, a threshold level of intake of 20 ng/ml (50 nmol/l) is suggested.

Vitamin D deficiency is a common side effect of hepatic and gastrointestinal diseases and often results in bone disease; gastroenterologists should, therefore, have some knowledge of the causes, consequences, and treatment of vitamin D related bone disorders. It also has a wide range of actions which are unrelated to its effects on calcium metabolism; receptors for its active metabolite, 1,25-dihydroxyvitamin D, are found in many places including the stomach, thymus, immune system, gonads, and some cancer cells. The antiproliferative and prodifferentiation effects of vitamin D have already been exploited in the development of treatment for psoriasis and other skin disorders and the exciting potential applications of vitamin D in some malignant diseases are discussed towards the end of the book.

Since the pivotal research in the 1960s on the metabolism of vitamin D there has been intense research activity in a number of related areas, including the synthesis and metabolism of vitamin D metabolites and analogues, the molecular biology of the vitamin D receptor, and the mechanisms by which 1,25-dihydroxyvitamin D affects the renal, intestinal, and skeletal transport of calcium. These aspects are covered in considerable detail and occupy about one half of the book; there is also a detailed chapter on the methodology for assays of vitamin D, although the authors do not discuss the usefulness of these assays in clinical practice. The latter part of the book is devoted to clinical issues—for example, rickets and osteomalacia, osteoporosis, inherited defects of vitamin D metabolism, and the pathophysiology of hypercalcaemia associated with the extrarenal production of 1,25-dihydroxyvitamin D, which occurs in conditions such as sarcoidosis and lymphoproliferative disorders. There is also an interesting chapter on the epidemiology of cancer risk and vitamin D. Disappointingly, at least for the gastroenterologist, there is very little coverage of vitamin D deficiency associated with hepatic and gastrointestinal disorders.

The book is well produced and has many illustrations and diagrams; it provides an excellent and comprehensive account of the substantial advances occurring in this area. Furthermore, the chapters are well referenced, many containing over 100 references. This book is not for the gastroenterologist who wishes to extract information about the diagnosis and management of vitamin D deficiency in clinical practice, but will be highly valued by those with a close interest in following the fascinating progress of this hormone.

J E COM PSTON

CORRECTIONS

An error occurred in the keys to figures 4 and 5 of the paper by Yamaoka et al (Gut 1999;45:804–11). Gastritis should be represented by open circles and duodenal ulcer by closed circles. We apologise for any confusion this error may have caused.

The authors of Nardone et al (Gut 1999;44:789–90) have conceded an error. Figure 3(B) was an inverted image of figure 3(A) at a different magnification. The correct figure is published below. The authors regret any confusion this may have caused.