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Introduction

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Colorectal cancer is the second most common cancer in the Western world and is a major cause of cancer deaths. Although a proportion of patients are diagnosed early, approximately half of all patients with colorectal cancer will eventually develop advanced disease [1]. Cytotoxic chemotherapy and/or best supportive care are the only treatment options in most of these cases.

Chemotherapy for colorectal cancer began in the late 1950s when 5-fluorouracil was introduced. Treatment with bolus 5-fluorouracil alone affords an 11% objective response rate according to a recent meta-analysis, while a range of 10–20% is commonly seen in trials, but modulation of the action of 5-fluorouracil by co-administration with leucovorin or methotrexate doubles this response rate [2,3]. 5-Fluorouracil-based chemotherapy has been shown to prolong survival significantly compared with best supportive care [4–6]. Complex dosing schedules, requiring prolonged or frequent hospital visits, are often applied for this chemotherapy, adding to costs for health-care providers and possibly to the stress and inconvenience experienced by patients [2].

Raltitrexed ('Tomudex', formerly ZD1694) is a promising new, effective and convenient single agent for the palliative treatment of advanced colorectal cancer. Raltitrexed is the result of a collaborative research programme between Zeneca Pharmaceuticals and the Institute of Cancer Research, Royal Marsden Hospital, Surrey, United Kingdom. The rapid and extensive clinical development of raltitrexed encompasses the initiation of preclinical and pharmacological studies in 1991 through to the publication of the final results from three major phase III studies in 1996–1997 (Fig. 1) [7–9]. Efficacy and safety data from more than 1500 patients are now included in the clinical database. Such a large trial database is unusual for a new cytotoxic agent and allows clear conclusions to be drawn about the relative advantages and disadvantages of raltitrexed and its impact on patient well-being.

To be considered a treatment advance, a drug should offer benefits in terms of efficacy and tolerability compared to established therapies; nevertheless, a drug judged to be comparable by these criteria may also be a useful addition to the therapeutic armamentarium against this disease, particularly if it offers advantages to the patient in terms of convenience.

The first consideration is efficacy. If key efficacy criteria in colorectal cancer therapy (palliative benefits, response rates, time to progression and survival) are considered, raltitrexed and modulated 5-fluorouracil are comparable. The shortfall in time to progression in two of the three studies may be partly accentuated by the timing and frequency of patient assessment (the earlier and more frequent visits by patients in the raltitrexed groups enabled an earlier recording of progression to take place). However, when other criteria are considered, raltitrexed performs similarly to 5-fluorouracil + leucovorin both in the comparative studies cited and in other reported phase III studies. Moreover, these results were obtained comparing the optimum modulation of 5-fluorouracil (developed, refined and matured over 40 years of experimental and clinical studies) to a single-dose schedule of raltitrexed developed and tested clinically since 1991. One can therefore expect further advances in treatment with raltitrexed.

A further consideration is tolerability. Subjective toxicities (those that are apparent to the patient) are the most relevant in the palliative setting. Of these, mucositis is of most concern, followed by diarrhoea and then asthenia. Mucositis was reported significantly more frequently with 5-fluorouracil + leucovorin compared with raltitrexed, and diarrhoea was also somewhat more common with 5-fluorouracil + leucovorin. 5-Fluorouracil was associated with a lower incidence of clinically relevant asthenia compared with raltitrexed.

Assessment of quality of life in large trials is always very difficult. However, the data on raltitrexed, particularly from the third phase III trial, indicate that this drug has a lower incidence of World Health Organization (WHO) grade 3 and 4 toxicity than 5-fluorouracil + leucovorin in early cycles. This was reflected in an improved quality of life for the patients and a requirement for fewer dosage modifications during these early treatment cycles.

The final consideration is convenience. Phase I and pharmacokinetic studies established the optimum dosing schedule for raltitrexed as 3 mg/m^2, conveniently administered as a single intravenous infusion once every 3 weeks [10]. It is certainly advantageous for the patients to receive a single infusion once every 3 weeks rather than the 5 days every 4 weeks required with the 5-fluorouracil + leucovorin regimen. Thus, in terms of convenience to both patients and health-care providers, raltitrexed offers a more favourable administration schedule than 5-fluorouracil.

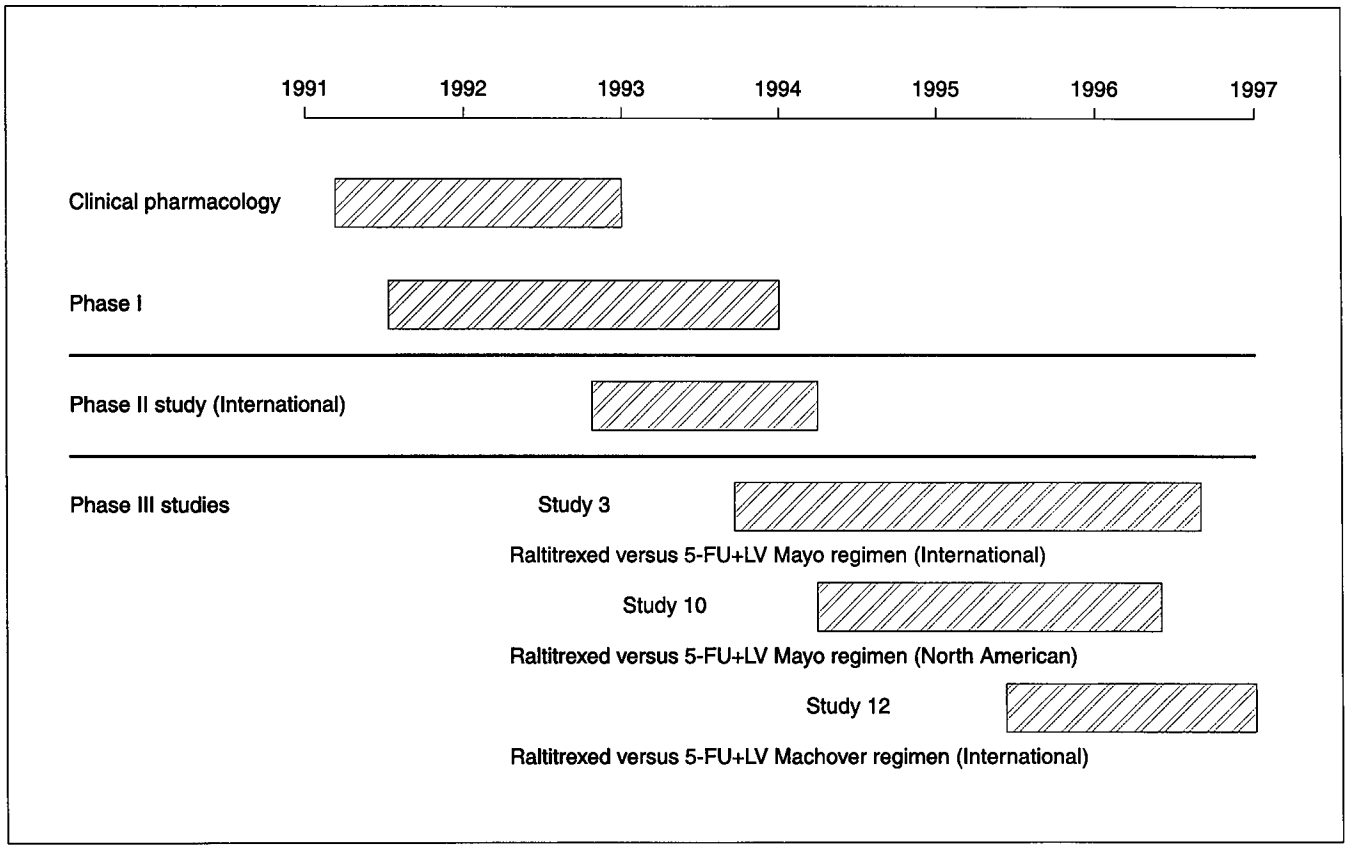

Fig. 1. The clinical development of raltitrexed. 5-FU + LV, 5-fluorouracil + leucovorin.

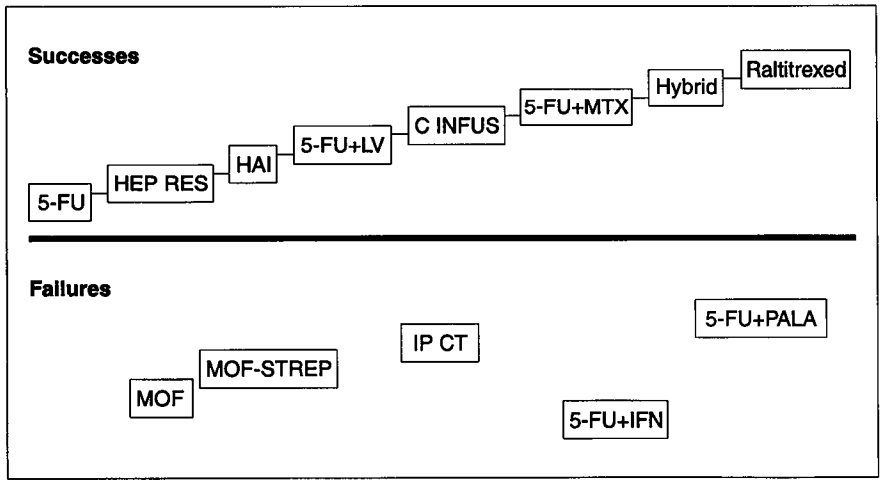

Fig. 2. Successes and failures among novel treatments for advanced colorectal cancer. 5-FU, 5-fluorouracil; HEP RES, hepatic resection; HAI, hepatic arterial infusion; LV, leucovorin; C INFUS, continuous infusion; MTX, methotrexate; MOF, semustine + vincristine + 5-fluorouracil; STREP, streptozocin; IP CT, intraperitoneal chemotherapy; IFN, interferon.

The development of raltitrexed is presently a modest but important advance in the treatment of colorectal cancer. It has a novel mode of action, inhibiting thymidylate synthase directly and specifically, without requiring modulation by a second agent. The safety profile of raltitrexed is acceptable, predictable, manageable and consistent. Raltitrexed represents the first new cytotoxic agent to show activity in advanced colorectal cancer for almost 40 years. It is a promising addition to a list of therapies which have been evaluated with varying degrees of success in this field (Fig. 2). The encouraging results obtained so far seem likely to lead to further new options

for the treatment of this common condition. Studies are under way to evaluate raltitrexed in combination therapy with 5-fluorouracil and other new agents, such as oxaliplatin and camptothecins. It is hoped that raltitrexed will also prove effective in other tumour types.

'Tomudex' is a trademark, the property of Zeneca Pharmaceuticals.

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