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Introduction

Raltitrexed (Tomudex™) in Combination Treatment for Colorectal Cancer: New Perspectives

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In recent years, significant advances have been achieved in the treatment of colorectal cancer, including the use of adjuvant chemotherapy following surgery in patients with colon cancer and the use of palliative chemotherapy for metastatic disease. Further potential for improvements in outcome for patients with colorectal cancer is provided by the introduction of new agents in combined treatment modalities. Although some of these new agents, such as raltitrexed, oxaliplatin and irinotecan, are active in colorectal cancer, single-agent therapy as first-line treatment has failed to demonstrate a substantial increase in survival. However, preclinical studies have indicated that combination treatments have the potential benefit of enhanced response rates. One such agent, raltitrexed, is currently under investigation in combination with 5-FU (bolus and infusional), oxaliplatin, cisplatin, irinotecan and anthracyclines, principally in patients with advanced colorectal cancer, but also in patients with other tumours. Similarly, combinations of adjuvant or neo-adjuvant radiotherapy and chemotherapy are being investigated and can offer a benefit in the treatment of rectal, oesophageal, pancreatic and gastric cancer. Promise for the future, therefore, appears to lie in combined treatment modalities which are expected to provide superior alternatives to current standard treatments. © **1999 Elsevier Science Ltd. All rights reserved.**

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SIGNIFICANT ADVANCES in the treatment of colorectal cancer have been made in recent years. Among the most striking developments is the use of adjuvant chemotherapy following surgery in patients with colon cancer [1, 2]. The value of chemotherapy as palliative treatment for metastatic disease has also been established [3]. Moreover, randomised trials of chemotherapy against best supportive care have provided strong justification for the use of chemotherapy in the management of advanced colorectal cancer [4]. It has also been shown that asymptomatic patients with advanced colorectal cancer live significantly longer, and have a better quality of life, when chemotherapy is started immediately at diagnosis compared with patients who are treated at the occurrence of symptoms [5]. Exciting new possibilities have been brought forth by the introduction of new agents with activity against colorectal cancer, including raltitrexed (Tomudex™), oxaliplatin and irinotecan.

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Standard adjuvant treatment for colon cancer is 5-fluorouracil (5-FU) plus leucovorin for 6 months. This combination has clearly demonstrated clinical benefit in Dukes' stage C disease, as shown by a reduction in the recurrence rate and a 12–15% improvement in median overall survival [1, 6]. Ongoing studies are addressing a number of clinical issues that have yet to be resolved, including the potential benefit of 5-FU in Dukes' stage B disease and the identification of patient subgroups at high risk of recurrence. The role of new agents in adjuvant treatment is also under investigation. For example, the ongoing Pan-European Trial of Adjuvant Colorectal Cancer (PETACC-1 trial) is comparing raltitrexed with 5-FU plus leucovorin.

For more than 30 years, 5-FU has been the only available treatment for metastatic colorectal cancer. At present, standard first-line therapy is 5-FU plus leucovorin, administered by bolus or continuous infusion. This regimen has a 16–40% response rate which translates into a modest increase in survival [7]. Raltitrexed, a specific thymidylate synthase inhibitor, is now regarded as an alternative first-line therapy

following the demonstration of efficacy, tolerability and quality of life benefits comparable with 5-FU plus leucovorin [8, 9]. Oxaliplatin, a new platinum derivative, has shown modest but definite antitumour activity in patients with refractory advanced colorectal cancer [10]. The combination of oxaliplatin and 5-FU seems to be more active than 5-FU [11]. The topoisomerase inhibitor, irinotecan, is associated with increased survival, a longer time to progression and an improved quality of life in patients resistant to 5-FU, but it is currently reserved as second-line therapy [12–14]. In first-line treatment of advanced colorectal cancer an alternating schedule with irinotecan and 5-FU/leucovorin shows a response rate of 30% [15]. Combination studies of 5-FU plus irinotecan are ongoing.

Although many drugs are known to be active in colorectal cancer, single-agent therapy as first-line treatment has failed to demonstrate a substantial increase in survival. Preclinical studies have shown that the activity of raltitrexed is enhanced when it is co-administered with other cytotoxic agents [16] and with radiotherapy [17]. Similarly, oxaliplatin and irinotecan have demonstrated synergistic activity with a number of other compounds [18]. These observations have prompted an extensive evaluation of combination treatments with the potential benefit of enhanced response rates. Raltitrexed is currently under investigation in combination with 5-FU (bolus and infusional), oxaliplatin, cisplatin, irinotecan and anthracyclines (doxorubicin, epirubicin), principally in advanced colorectal cancer but also in other tumours. In the future, it may be possible to maximise cytotoxicity by the combination of three agents. Further studies are required to define the most effective combinations and administration schedules.

Combined treatment modalities, including adjuvant or neo-adjuvant radiotherapy plus chemotherapy, are also being evaluated and appear to offer potential in the treatment of rectal, oesophageal, pancreatic and gastric cancer. In particular, the way forward in rectal cancer appears to be a combination of radiotherapy and chemotherapy (chemoradiation), although an optimum schedule has not yet been internationally agreed [19, 20].

In conclusion, the need for more active treatment regimens in advanced colorectal cancer remains a challenge. Colorectal cancer still accounts for around 10% of all cancer deaths, even though significant developments have led to a decline in mortality rates over the past 20 years [21]. Promise for the future lies in combined treatment modalities which are expected to provide superior alternatives to current standard treatments. The full potential of new agents and therapeutic approaches has yet to be explored, but it is hoped that these advancements will lead to an improved outcome for patients with colorectal cancer.

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