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Future developments with 'Tomudex' (raltitrexed)

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The efficacy and tolerability of raltitrexed ('Tomudex', formerly ZD1694) as a single agent for the treatment of advanced colorectal cancer has been established in a large clinical trial programme. It is now possible to move the drug forward into the treatment of earlier stages of colorectal cancer. In addition, its mode of action lends itself to combination with other agents, not only 5-fluorouracil, but also oxaliplatin and irinotecan for the treatment of advanced disease. Preclinical and early clinical data also suggest that raltitrexed may show activity in a range of other tumour types. Studies evaluating these potential clinical applications of raltitrexed are either planned or already under way.

Keywords: Adjuvant therapy, advanced cancer, colorectal cancer, combination therapy, 5-fluorouracil, raltitrexed, 'Tomudex'

Introduction

Raltitrexed ('Tomudex', formerly ZD1694) is now available in a number of countries for the first-line treatment of advanced colorectal cancer. It is the product of a rapid clinical development programme [1] and its efficacy and safety have been observed in large international studies and are reviewed in detail within this supplement [2,3]. Speculation on the potential clinical value of raltitrexed in combination therapy, in the adjuvant setting and for use in other tumour types has prompted the initiation of further studies designed to determine whether the novel, direct mode of action of raltitrexed may have wider clinical applications. These potential applications are discussed here, and some of the clinical studies planned or already under way are briefly described. Raltitrexed is not approved for combination use or in any cancers other than colorectal.

Combination therapy for advanced colorectal cancer

With 5-fluorouracil

The general principle in selecting combinations of cytotoxic agents is to achieve maximal toxicity to the cancer cells with minimal toxicity to normal tissue. Raltitrexed and 5-fluorouracil have proved effective as single agents in the treatment of advanced colorectal cancer [1,4–6] although their modes of action are somewhat different (Fig. 1). They both inhibit thymidylate synthase. Raltitrexed inhibits the enzyme directly, and this inhibition is enhanced by metabolism of the drug within the cells to polyglutamate forms which are more potent inhibitors of the enzyme than the parent drug and are retained within the cells. In contrast, 5-fluorouracil acts indirectly, being metabolized to 5-fluorodeoxyuridine monophosphate which acts as a false substrate for thymidylate synthase [7]. Other metabolites of 5-fluorouracil are incorporated into RNA so that, unlike raltitrexed which has specific action, 5-fluorouracil affects both DNA and RNA synthesis. Therefore, the combination of raltitrexed and 5-fluorouracil may produce a more complete blockade of the enzyme than either agent alone.

Evidence from preclinical studies supports this use of combination therapy. Raltitrexed has been shown to increase the incorporation of fluorouracil phosphate into RNA if administered after 5-fluorouracil [8]. Research with the human colorectal cancer cell lines HT 29 and HCT 8 has shown that 5-fluorouracil and raltitrexed, applied simultaneously for 24 h, had significant synergistic interactions in both cell lines (Table 1). When 5-fluorouracil was applied for 1 h before a 24-h incubation with raltitrexed, strong antagonism was seen for high doses of 5-fluorouracil and low doses of raltitrexed, whereas low doses of 5-fluorouracil and high doses of raltitrexed proved synergistic. Reversing the schedules (24-h raltitrexed followed by 1-h 5-fluorouracil) gave synergistic interactions for all drug ratios [9].

Table 1. Cytotoxic activity of 5-fluorouracil (5-FU), methotrexate and raltitrexed in 5-fluorouracil-sensitive and -resistant and raltitrexed-sensitive and -resistant cell lines, expressed as the resistance factor (median inhibitory concentration in resistant cell line divided by that in the corresponding wild-type cell line)

	Treatment			
Cell line	5-FU, 1 h	5-FU, 24 h	Raltitrexed, 24 h	Methotrexate
HCT 8 RT	0.99	1.0	3.0	2.8
HT 29	–	–	–	–
HT 29 RT	1.9	1.5	3.2	3.0
HT 29 R1	3.5	2.0	1.3	–
HT 29 R24	11.5	5.3	3.3	–
HM2	–	–	–	–
HM2 R1	3.6	2.5	2.0	–
HM2 R24	5.2	5.8	11.0	–

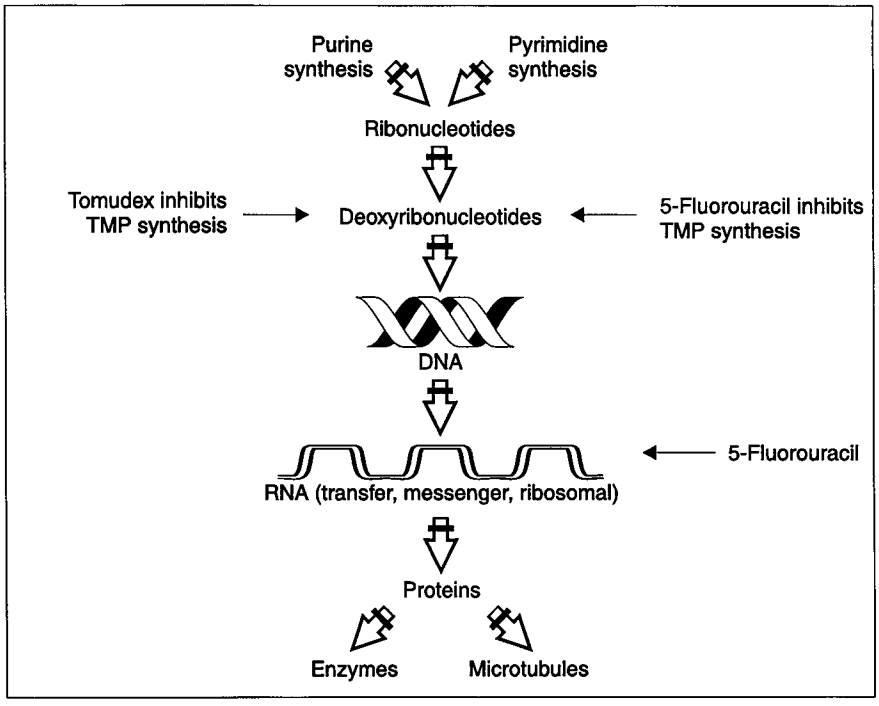

Fig. 1. Sites of action of raltitrexed ('Tomudex') and 5-fluorouracil. TMP, thymidine monophosphate.

Schwartz *et al.* [10] reported results from a phase I study in which 12 patients with advanced colorectal cancer were treated with escalating doses of raltitrexed up to 2.0 mg/m^2 over 15 min followed, within 24 h, by a 900 mg/m^2 bolus of 5-fluorouracil; this therapy was applied every 21 days [10]. The combination was well tolerated with no dose-limiting toxicity. Two patients previously treated with 5-fluorouracil showed a partial response and the disease became stable in six. These early results are encouraging, and further dose escalations are planned.

Raltitrexed and 5-fluorouracil differ in their toxicity profiles. Raltitrexed is associated with a significantly lower incidence of severe leucopenia and mucositis but a higher incidence of anaemia and raised liver transaminases than 5-fluorouracil. However, the myelosuppressive effects of 5-fluorouracil can be reduced by giving the drug as a continuous infusion rather than a bolus [11]. Therefore combining raltitrexed with 5-fluorouracil given by continuous infusion may maximize the effectiveness while minimizing toxicity, since higher doses of 5-fluorouracil can be given using this approach than using bolus administration. Accordingly, an exploratory study is under way to define the optimal dose for such a combination regimen in patients with advanced colorectal cancer, administering raltitrexed by a short infusion once every 3 weeks and 5-fluorouracil by 24-h infusion once every 7 days. Several dose levels of this dose-finding study have been completed without any major toxicity. The dosing schedule is shown in Table 2.

Table 2. Treatment protocol for raltitrexed in combination with 5-fluorouracil (5-FU) in phase I study

Treatment dose	Raltitrexed (mg/m^2 per day)	5-FU (mg/m^2 per day)
1	2.6	1200
2	2.6	1600
3	2.6	2000
4	2.6	2400
5	3.0	2000
6	3.0	2400

Ralitrexed was administered as a 15-min infusion on days 8 and 29. 5-Fluorouracil was administered as a 24-h infusion on days 1, 8, 15, 22 and 29. The cycles were repeated starting on day 35.

With platinum compounds

Platinum-containing compounds have long been established as cytotoxic chemotherapy for certain solid tumours. They act by causing damage to DNA, interfering with transcription and replication. Cisplatin is the longest-established drug in this class, but its use is limited by severe toxic effects (notably nausea and vomiting, nephrotoxicity, myelosuppression, neurotoxicity and ototoxicity). Carboplatin, a second-generation derivative, is associated with less severe nausea and vomiting and less nephrotoxicity, neurotoxicity and ototoxicity, but is more myelosuppressive than cisplatin.

Oxaliplatin is a third-generation platinum compound which has not been associated with nephrotoxicity and which causes minimal myelosuppression [12]. Dose-

Table 3. Dose escalation for raltitrexed in combination with oxaliplatin

Dose level	Oxaliplatin (mg/m²)	Raltitrexed (mg/m²)
–I	85	2
I	85	2.5
II	110	2.5
III	110	3
IV	130	3

Table 4. Dose escalation for raltitrexed in combination with CPT-11

Dose level	CPT-11 (mg/m²)	Raltitrexed (mg/m²)
–I	175	2
I	175	2.6
II	200	2.6
III	250	2.6
IV	250	3
V	300	3
VI	350	3

limiting toxicity has consisted mostly of nausea or vomiting, diarrhoea and cumulative peripheral sensitive neuropathy [13]. The activity of oxaliplatin as a single drug in advanced colorectal cancer is low (about 10%). Patients resistant to 5-fluorouracil alone have been reported to show a clinical response when treated with oxaliplatin in combination with 5-fluorouracil and leucovorin [14,15]. Synergistic activity of oxaliplatin with 5-fluorouracil has also been demonstrated in transplantable tumour models [16].

Oxaliplatin and raltitrexed act by different mechanisms, with oxaliplatin damaging DNA and raltitrexed preventing DNA synthesis and repair. Results of animal studies indicate that raltitrexed in combination with oxaliplatin may have less cytotoxic potentiation than oxaliplatin and 5-fluorouracil [17]. Therefore, combination therapy may enhance the effectiveness of both compounds. The different toxicity profiles of oxaliplatin and raltitrexed also support the concept of combination therapy. A dose-escalation study is under way at present to test the potential of this combination therapy in patients with various forms of advanced cancer (Table 3).

With topoisomerase inhibitors

For a cell to grow or divide it must copy its DNA, either to produce an RNA template for protein synthesis (transcription) or to form more DNA for the daughter cells (replication). In both cases, the double helix structure must be unwound and the DNA strands separated to expose a short single-stranded section which can act as a template. This poses topological problems, as unwinding one section of DNA places torsional (twisting) strain on the neighbouring sections. This strain must be relieved periodically if DNA transcription and replication are to continue, which is the function of topoisomerase I. This enzyme bonds covalently to DNA, placing a transient single-strand break in the backbone, so allowing the broken ends to rotate and release the torsional strain, and then re-ligates the fracture and moves on to the next section. Inhibitors of topoisomerase I prevent the religation step and leave the enzyme covalently bound to DNA at a single-strand break [18,19]. Without religation and release of the enzyme, further DNA unwinding cannot occur, both transcription and replication stop, and cell growth ceases.

Numerous topoisomerase I inhibitors have been synthesized and have reached various stages of development; these include CPT-11 (irinotecan), topotecan, GI 147211, 9-aminocamptothecin and DX 8951 [11]. Of these, CPT-11 has demonstrated activity in phase II trials in colorectal cancer, with response rates of 15–32% in previously untreated patients as well as in 5-fluorouracil-resistant cancers [19–21]. As CPT-11 and raltitrexed have both demonstrated activity against colorectal cancer, and are known to act by quite distinct molecular mechanisms, there is a possibility that combination treatment would act synergistically. The dose-limiting toxicities for CPT-11 in phase II trials were diarrhoea and neutropenia. Nausea/vomiting is another frequent adverse event, while mucositis is rare [20]. By contrast, the major toxicities for raltitrexed treatment in phase II trials were diarrhoea, asthenia and flu-like symptoms, while nausea/vomiting was rarely severe. Severe leucopenia was also rare [22].

Thus, CPT-11 and raltitrexed differ in their safety profiles and in their mechanisms of action. Therefore, a combination of the two drugs may offer increased efficacy without increased toxicity. The cytotoxic interaction between raltitrexed and the active metabolite of CPT-11, SN 38, has been evaluated in 5-fluorouracil-sensitive (HT 29 and HCT 8) and 5-fluorouracil-resistant (HT 29R1 and HT 29R4) cell lines [20]. When raltitrexed was given simultaneously for 24 h with SN 38, a synergistic cytotoxic interaction was reported [23]. Aschele *et al.* [24] showed that sequential rather than simultaneous administration produced synergistic activity whether either raltitrexed or CPT-11 was given first [24]. In this study, however, the magnitude of the potentiation was greater when SN 38 was given first and higher relative doses of raltitrexed (10:1 ratio) were used. A dose-escalation study is under way at present to investigate the optimal dose and safety profile of raltitrexed + CPT-11 in patients with advanced colorectal cancer. The dosing schedule is shown in Table 4. Several dose levels of this combination have been administered without any major toxicities.

Adjuvant therapy

Raltitrexed as adjuvant therapy

It is generally accepted that patients with Dukes' stage C colon cancer benefit from adjuvant chemotherapy. Until recently a combination of 5-fluorouracil and levamisole administered for 1 year was considered the standard treatment for colon cancer. However, the results of a recently published study have demonstrated the effectiveness of 5-fluorouracil + leucovorin as an adjuvant treatment for Dukes' stage C colon cancer [25]. The authors [25] presented a pooled analysis of three trials ($n = 1493$) in which patients were treated for 6 months with 5-fluorouracil at 370–400 mg/m^2 + leucovorin at 200 mg/m^2 daily for 5 days, every 28 days (six cycles). Three-year disease-free survival and overall survival data from these patients were compared with those of untreated controls. After a median follow-up period of 37 months, the 3-year disease-free survival of the treated patients was 71% compared with 62% for untreated controls ($P < 0.0001$). The overall survival after 3 years was 83 and 78%, respectively ($P < 0.03$). Moreover, three large randomized studies have shown that 5-fluorouracil + leucovorin for 6 months is at least as effective as 5-fluorouracil + levamisole for 1 year [26–28].

These results on the activity and administration of raltitrexed support the use of raltitrexed as adjuvant therapy for colorectal cancer. A large pan-European trial for adjuvant treatment of colon cancer (Pan-European Trial on Adjuvant Colon Cancer; PETACC) is imminent, comparing raltitrexed with a range of bolus 5-fluorouracil + leucovorin regimens (Mayo).

Raltitrexed and radiotherapy as combined adjuvant therapy in rectal cancer

Early-stage colon cancer can frequently be cured by surgical resection, with cure rates of 90% reported for cancer of Dukes' stage A or B1 [5]. However, rectal cancer is not as readily cured by surgery, because the close confines of the pelvic bones prevent the surgeon obtaining an adequate tumour-free margin around the cancer site [29]. As a result, local recurrence of rectal cancer is common, reaching 25% in patients with Dukes' stage B carcinoma, and 50% in patients with stage C disease [29].

Radiotherapy is often prescribed in an attempt to reduce the risk of recurrence [30] and the use of preoperative radiotherapy may also improve survival [31]. The use of chemotherapy alone (5-fluorouracil + semustine) as adjuvant therapy has proved ineffective in reducing local control or increasing survival [29]. However, the administration of postoperative 5-fluorouracil in combination with radiotherapy resulted in a 15% survival advantage as well as a lower incidence of metastases and of local recurrence [29]. The optimal schedule for chemoradiotherapy for operable rectal cancer is not known, however. In Europe, there is a clear tendency towards preoperative radiotherapy combined with postoperative chemotherapy and also with preoperative chemotherapy [32].

Table 5. Dose escalation levels for raltitrexed and radiotherapy as combined adjuvant therapy

Dose level	Raltitrexed (mg/m^2)
I	2.0
II	2.6
III	3.0

No escalation of radiotherapy dose; the patients are given 50.4 Gy in 28 fractions, with treatment given five times per week.

If adjuvant postoperative radiotherapy is to be prescribed concurrently with postoperative raltitrexed, the optimal dose of raltitrexed must be determined. A dose-finding study is under way at present to determine the optimal dose of raltitrexed used in combination with a standard radiotherapy course (50.4 Gy in a total of 28 fractions at 1.8 Gy per fraction, administered five times per week) in the adjuvant setting for Dukes' stage B or C rectal cancer (Table 5). The study has presently reached the second dosage level.

Raltitrexed in other tumours

Results of a phase II study evaluating raltitrexed in a range of solid tumours have indicated encouraging activity at a number of sites, particularly in breast and pancreatic cancer [33]. These data support earlier preclinical observations in cultured cell lines, including murine leukaemia and human lymphoblastoid, cervix and breast cancer cell lines and also ovarian, lung, gastric, bladder and breast xenografts [34].

Clinical studies are now under way to further examine the potential of raltitrexed in different tumours. The drug will be evaluated in combination with radiotherapy in lung, head and neck and rectal cancer (described above). To date, 23 patients with head and neck cancer have been entered into a study for treatment with raltitrexed as monotherapy (3 mg/m^2 once every 3 weeks) with or without radiotherapy. Other monotherapy studies include the use of raltitrexed in prostate cancer, sarcoma, pancreatic cancer and paediatric solid tumours and acute leukaemias. Raltitrexed is also currently being evaluated in combination with doxorubicin, paclitaxel, cisplatin and several other cytotoxic drugs in phase I trials.

Conclusions

Raltitrexed is a novel cytotoxic agent which has demonstrated efficacy in advanced colorectal cancer and appears to be better tolerated than current 5-fluorouracil-based regimens. Its mode of action offers potential synergy with

other agents acting via other molecular mechanisms. Trials are under way at present to investigate the use of raltitrexed in combination with CPT-11 (a topoisomerase inhibitor), oxaliplatin (a third-generation platinum compound) and 5-fluourouracil. Raltitrexed may also prove to be useful as a component of combined pre- or postoperative adjuvant chemo- and radiotherapy for rectal cancer, and this possibility is currently being assessed. Its potential for use in other cancers including breast, pancreatic, lung, head and neck and prostate cancers and paediatric solid tumours and leukaemias is also under investigation. Raltitrexed may, therefore, significantly expand the options available to the oncologist treating colorectal and other advanced cancers, although at present it is licensed only as a single agent in advanced colorectal cancer.

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