Novel Therapeutic Developments Other Than EGFR and VEGF Inhibition in Colorectal Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the current status of new cytotoxics that may provide new treatment paradigms for patients with colorectal cancer.
2. Explain these new agents’ mechanisms of action.
3. Discuss the current clinical development of these agents and how they might be integrated into the current armamentarium.

Abstract

Developments that may improve existing cytotoxic therapy for colorectal cancer (CRC) include alternatives to 5-fluorouracil (5-FU) such as the liposomal Thymidylate Synthase inhibitor OSI-7904L and the multitargeted antifolate pemetrexed. Studies have explored means of reformulating irinotecan, modulating its pharmacokinetics, and enhancing its activity by maximizing DNA damage through poly(ADP-ribose) polymerase inhibition. Cell cycle inhibitors may offer an alternative to combination with 5-FU. However, as standard regimens become more complex, so do the clinical trials needed to develop new agents, and the path to registration becomes ever more tortuous. It is therefore likely that several drugs with promise in CRC will not be developed for this indication. The Oncologist 2006;11:1018–1024

Cytotoxic Strategies

Three cytotoxic agents (namely, 5-fluorouracil [5-FU], oxaliplatin, and irinotecan) are of proven benefit in advanced colorectal cancer (ACRC) [1–9]. They have recently been joined by the vascular endothelial growth factor (VEGF) inhibitor bevacizumab and the epidermal growth factor receptor (EGFR) inhibitor cetuximab. In view of the expense and prolonged administration of these monoclonal antibodies, there is still interest in alternative cytotoxics, cell cycle inhibitors, and other strategies. These strategies aim to discover whether any of the three cytotoxic agents can be replaced or whether their activity can be augmented.

Replacement of 5-FU

5-FU is the fluoropyrimidine on which a sequence of advances in the treatment of ACRC has been based for decades. Oral fluoropyrimidines such as capecitabine and Uftoral (Merck Pharmaceuticals, West Drayton, U.K.) now offer a more patient-friendly alternative to i.v. bolus
or infusional 5-FU. In principle, there is scope for replacement of 5-FU by alternative antifolates or inhibitors of thymidylate synthase (TS).

**TS Inhibition**

OSI-7904L is a liposomal formulation of a TS inhibitor with good preclinical activity [10]. Monotherapy trials suggest activity in gastrointestinal tumors [11, 12]. Myelotoxicity, gastrointestinal toxicity, and rash are seen, but the drug is tolerable and there is no need for vitamin supplementation. A European Organization for Research and Treatment of Cancer phase I study now in progress in second-line ACRC patients combines OSI-7904L with oxaliplatin in an every-3-week schedule. Early experience suggests activity and only those toxicities expected with such a combination. It is unclear whether OSI-7904L will continue to be developed in CRC.

Potentially more significant is the progress being made with pemetrexed (Alimta®, Eli Lilly and Company Ltd., Basingstoke, U.K.), a multitargeted antifolate [13–18]. Pemetrexed targets multiple enzymes involved in folate metabolism, including TS, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminomidazole carboxamide formyl transferase. Phase II trials in first-line ACRC suggest single-agent pemetrexed achieves a response rate (RR) of 15%–20%, comparable with that found in the gastrointestinal tract. A temporary blockade of the drug transporter BCRP might improve the oral bioavailability of these agents [25]. Phase II studies with capsules containing a semisolid matrix formulation of irinotecan have started.

Several novel topoisomerase inhibitors are under investigation. Liposomal SN-38 obviates the need for activation by carboxylesterase and has completed phase I trials [29–34]. Edotecarin (J107088), a noncamptothecin inhibitor of topoisomerase 1, has high potency in vitro, and three phase I and five phase II studies have been completed [35–37]. Other edotecarin phase I and II studies and combination studies with other chemotherapeutics are now being completed, but the future of this drug is uncertain.

Several combined topoisomerase 1 and 2 inhibitors have been developed, but most have had additional toxicities without clear evidence of additional benefit over irinotecan in CRC. Symadex (C-1311) has DNA-binding properties and inhibits the catalytic activity of topoisomerase 2 [38]. It has shown excellent activity in vitro against CRC and has completed phase I trials in patients with advanced solid tumors, and a phase II monotherapy trial in CRC is planned.

There may be greater potential in altering the pharmacokinetics of irinotecan. Cyclosporin inhibits phosphoglycoprotein and multidrug resistance-associated protein 2 (MRP2) in biliary caniculi, thereby reducing biliary excretion of SN38G [39–43]. This effectively prolongs the half-life of irinotecan and may allow dose reduction. Phase II trials showed that this strategy reduced the incidence of diarrhea to 3% (from the expected 20%). In the United Kingdom, the PICCOLO...
(Panitumumab, Irinotecan, and Cyclosporin in COLOrectal cancer therapy) phase III trial currently in set-up will randomize second-line patients to irinotecan plus cyclosporin, standard irinotecan monotherapy, or irinotecan plus panitumumab, a fully humanized monoclonal antibody that inhibits EGFR.

Means of maximizing the DNA damage induced by irinotecan are also being pursued. Poly(ADP-ribose) polymerase 1 (PARP-1) is involved in the repair of breaks in DNA strands, and its inhibition has been shown to increase the DNA damage induced by alkylating agents, camptothecins, and ionizing radiation in tumor as well as normal cells [44, 45]. The PARP inhibitor AG041699 has been combined with temozolomide. The combination appears active and well tolerated and is now being investigated in a phase II trial in metastatic melanoma. A phase I study of a PARP inhibitor plus irinotecan is under consideration. This approach may be particularly helpful in tumors that are already defective in DNA repair mechanisms.

**Cell Cycle Agents**

It may also be possible to combine irinotecan with a cell cycle inhibitor as an alternative to 5-FU. Indisulam (E7070) is a novel sulfonamide with antiproliferative activity [46–51]. Cells are arrested in G1/S phase and undergo apoptosis. A phase II study of single-agent indisulam in 5-FU–resistant CRC showed a 70% rate of disease control. Myelotoxicity was dose limiting. A phase I study of indisulam combined with irinotecan demonstrated activity and was generally well tolerated, despite instances of myelotoxicity, rash, and injection-site reaction [51]. A phase II study of this combination in second-line ACRC closed early, and the future of this agent in CRC is unclear.

Kinesin spindle protein (KSP) inhibition is another means of arresting the cell cycle [52–54]. The KSP inhibitor SB715992, administered i.v. every 21 days, has been shown to induce mitotic arrest and apoptosis. Phase II trials of monotherapy are currently being conducted in ACRC.

CF101 is an oral A3 adenosine receptor (A3AR) agonist that downregulates protein kinase B/Akt– and NF-kappaB–related pathways [55–58]. Preclinical data show activity in CRC [59]. The drug, which is not itself cytotoxic, seems to have synergistic antiproliferative activity in combination with 5-FU, while also being myeloprotective. Phase I and II trials of CF101 in refractory CRC have shown that disease stabilization can be achieved with minimal toxicity. Combination trials with 5-FU and oxaliplatin/5-FU/leucovorin (FOLFOX) are planned and include use of the agent in nonrefractory disease [60].

**Other Novel Approaches**

**Apoptosis Induction**

Genasense® (G3139; Genta Incorporated, Berkeley Heights, NJ) is a phosphothioate antisense oligonucleotide against bcl-2 which induces apoptosis [61]. However, clinical trials in various tumors, including CRC (where Genasense® was combined with FOLFOX), have been disappointing, and the drug is not being pursued in this indication.

There may be more of a future for Telcyta (TLK286), a modified glutathione analogue that activates the stress response and induces apoptosis [62–65]. The prodrug is activated by glutathione-S-transferase P1-1, which is highly expressed in CRC, involved in resistance to cytotoxics, and correlated with poor prognosis. Trials of single-agent Telcyta in advanced CRC have shown significant antitumor activity with toxicity confined to grade 1/2 fatigue, anemia, and emesis. Combination studies with weekly and every-3-week chemotherapy schedules are planned.

Mapatumumab (HGS-ETR1) is a fully humanized monoclonal antibody to the TRAIL (Tumor necrosis factor-Related Apoptosis-Inducing Ligand) receptor-1 (or “death” receptor) which induces apoptosis in human cancer cell lines that express this receptor. It has antitumor activity against many tumor types, both as a single agent and in combination [66]. A phase II monotherapy trial of mapatumumab in ACRC is under way, and phase II combination trials with 5-FU, irinotecan, and oxaliplatin are planned.

**Proteasome Inhibition**

The proteasome inhibitor Bortezomib (Velcade®, PS-341; Janssen-Cilag Ltd., High Wycombe, U.K.) is proving valuable in the management of certain hematological malignancies, notably myeloma, and has encouraging preclinical and early clinical evidence of activity in solid tumors [67–70]. Phase I and II studies in CRC have included combination with 5-FU/LV, capecitabine, irinotecan, and FOLFOX [71, 72]. However, the phase II trial with irinotecan in irinotecan-refractory CRC was halted because of poor activity. Combination studies may continue in nonrefractory disease.

**Agents Targeted to the Microtubule**

While taxanes have proven disappointing in CRC, preclinical comparison with epothilones suggested the latter might be more active as stabilizers of the microtubule [73–77]. Unfortunately, this promise has not been fulfilled in phase II studies in patients with ACRC. The trial of single-agent ixabepilone (BMS-247550) was halted because of poor activity, and the trial of KOS-862 was halted because of...
cumulative toxicity in oxaliplatin-pretreated patients. However, ABT-751, an oral once-daily microtubule inhibitor, remains in phase I and II trials [78–80].

CEA Strategies and Immunotherapy

Labetuzumab (IMMU-100), a humanized immunoglobulin G1 monoclonal antibody directed against carcinoembryonic antigen (CEA) [81–85], causes inhibition of tumor cell proliferation in vitro by antibody-dependent cellular cytotoxicity. In vivo, synergy is seen with both 5-FU and irinotecan. Yttrium-labeled labetuzumab is now in clinical trials against CEA-expressing tumors [84, 85].

ALVAC CEA/B7 is a recombinant canary pox viral vaccine containing the full-length CEA gene plus a costimulator [86–89]. Phase I trials in advanced CRC have shown induction of immune responses and disease stabilization, with a good safety profile.

Oncovax is an active specific immunotherapy using autologous tumor cells and bacillus Calmette-Guerin vaccine [90]. A phase III trial following surgery (and in the absence of chemotherapy) showed that the vaccine significantly increased overall survival in stage II but not in stage III disease.

Oncophage represents an alternative immunotherapeutic strategy using autologous tumor cells to create a heat shock protein gp96–based vaccine [91, 92]. Phase II trials in CRC showed no toxicity and induction of immune responses but poor clinical activity. However, Oncophage is being fast-tracked by the U.S. Food and Drug Administration in renal cell carcinoma and melanoma.

The lack of success of Oncophage in CRC has not dampened interest in vaccines for this tumor. Trovax is an example of another product under development [93–95]. This is a novel vaccine that delivers the 5T4 tumor-associated antigen (which is widely distributed in several solid tumors, including CRC) in a pox virus vector. A phase II trial in advanced CRC showed the vaccine to be safe in combination with 5-FU. Immune response to the antigen was seen in 94% of cases, and the magnitude of this correlated with time to disease progression and overall survival. Trovax is under investigation in phase II trials as an adjuvant to resection of hepatic colorectal metastases and in combination with both IFL (irinotecan/bolus fluorouracil/LV) and FOLFOX in ACRC, and has shown immune responses with a good safety profile in these studies.

Discussion

Advances being made through growth factor–related therapies are reviewed elsewhere in this volume, as is the role of oral fluoropyrimidines such as capecitabine. This paper confines its interest to other areas of activity.

It remains possible that we will be able to provide antifolates better than 5-FU and that the efficacy of irinotecan can be enhanced and/or its toxicity reduced. However, studies of these approaches will have to compete for patients and for attention against trial programs aimed at optimizing the combination, dosing, and scheduling of the five agents now proven to have benefit in ACRC by phase III studies.

In combination with chemotherapy, there are intriguing suggestions that cell cycle agents may play a useful part, as may proteasome inhibition. However, developing appropriate registration strategies for these agents is likely to prove a major challenge. One possibility is to give novel agents a chance of proving their worth over a short period of treatment prior to use of standard first-line regimens. The setting would be in fit patients with good performance status and limited tumor volume but with disease that cannot become suitable for potentially curative resection. Such “window” trials would allow exploration of novel agents and correlative pharmacodynamic assays in a more appropriate population than very heavily pretreated ACRC patients.

One of the paradoxes of CRC is the failure of immunotherapy to have a significant impact on stage III and metastatic disease. However, even here, efforts to find a strategy that delivers antitumor, as well as immunological, activity are ongoing.

Disclosure of Potential Conflicts of Interest

The author indicates no potential conflicts of interest.

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