Progresses in the medical treatment of advanced colorectal cancer

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Abstract

In the last 2 decades, major progresses have been made in the management of patients with advanced colorectal cancer (ACC). The modulation of 5-fluorouracil (5-FU) by folinic acid (LV), followed by the introduction of irinotecan and oxaliplatin have significantly improved the outcome of these patients. New strategies consist of oral fluoropyrimidines, and of targeted agents to inhibit cancer signalisation.

Key words: advanced colorectal cancer, 5-fluorouracil, oxaliplatin, irinotecan, targeted therapy, cetuximab, bevacizumab.

Introduction

Chemotherapy of advanced colorectal cancer (ACC) has considerably evolved since the time bolus 5-fluorouracil (5-FU) was the only treatment. The efficacy of 5-FU has been largely improved by folinic acid (LV), continuous infusion and oral fluoropyrimidines. In the last years, therapeutic options have broadened considerably with the introduction of oxaliplatin and irinotecan. More recently, promising results have been reported with the development of biologically targeted agents which aim to inhibit cancer signalisation and represent a significant step forward.

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Cytotoxic agents

The last 10 years have seen considerable changes in the management of ACC with the emergence of novel cytotoxic agents like irinotecan, oxaliplatin and oral fluoropyrimidines.

For a long time, ACC have been considered as resistant to chemotherapy, and 5-FU was the only drug used in these patients. In the 80's, fluoropyrimidines' efficacy was increased by their biomodulation and their administration in continuous infusion. Modulation of 5-FU by LV or 5-FU continuous infusion double the tumor response rate achieved with 5-FU bolus [1-3]. The biweekly LV5FU2 regimen takes advantage of these findings [4], but overall best 5-FU regimens led to only small improvements in survival.

The introduction of irinotecan and oxaliplatin opened new perspectives. Globally, 5-FU/LV/irinotecan or 5-FU/LV/oxaliplatin lead to tumor response of 50%, progression–free survival around 9 months, and overall survival around 18 months (*Tab. 1*) [5-9]. Clearly, a step forward had been done.

Oral fluoropyrimidines

Oral fluoropyrimidines, such as tegafur/uracil (UFT) and capecitabine, mimic infusional 5-FU and make easier drug administration to preserve as far as possible the quality of life.

UFT and capecitabine have demonstrated their efficacy in large randomized phase III trials in which they were compared to bolus 5FU/LV [10-13]. Both oral fluoropyrimidines are interesting alternatives to 5-FU/LV bolus regimens and have recently been approved in Europe for first-line treatment. Furthermore, the development of oral fluoropyrymidines in metastatic cancers has opened new perspectives in the field of adjuvant chemotherapy [14-16].

Table 1. **Advances in first line treatment**

Endpoint	5-FU bolus	5-FU/LV or CI 5FU	5-FU/LV + CPT-11 or 5-FU/LV + oxaliplatine
Tumor response rate	~ 10%	~ 25%	~ 50%
Median progression-free Survival	~ 4 months	~ 6 months	~ 9 months
Median overall survival	~ 12 months	~ 12 months	~ 18 months

CI: continuous infusion

Targeted therapies

A better understanding of oncogenesis has allowed the development of highly efficient agents able to target critical pathways involved in cancer progression. Targeted therapies have also the potential to be better tolerated and therefore may be alternatives to conventional chemotherapy. Recent studies have shown their ability to increase cytotoxics efficiency when administered in association, and even to reverse acquired drug resistance in some cases. At present time, treatment of advanced colorectal cancers represents a promising field of clinical investigations.

Targeting epidermal growth factor receptor

The Epidermal Growth Factor Receptor (EGFR) family consists of 4 members: HER-1 (erb-B1/EGFR), HER-2 (Erb--B2), HER-3 (Erb-B3) and HER-4 (Erb-B4). Each of these proteins is composed of an extracellular binding domain, a transmenbrane segment and an intracellular protein kinase domain. The binding of epidermal growth factor (EGF) drives to the dimerization of ligand-receptors and therefore the triggering of intrinsic protein kinase activity. Several intracellular substrates are phosphorylated, leading to the activation of two major signalling pathways (Ras-Raf-Map-kinase, PI3K-AKT and Jak/Stat) which regulate transcription of molecules involved in oncogenesis [17]. The EGFR is frequently deregulated in colorectal carcinoma [18], and overexpression of the receptor confers a poor prognosis.

The crucial role of EGFR in tumor proliferation and its frequent overexpression provide the rationale for the treatment of ACC.

The targeting of EGFR and its downstream signalling pathways include inhibitors of tyrosine kinase activity (ZD1839, OSI-774) and monoclonal antibodies directed against the extracellular domain of EGFR (C225, ABX-EGF).

Up to now, studies using EGFR tyrosine kinase inhibitors remain disappointing. However, a phase II study evaluating the efficacy of gefitinib (ZD1839, Iressa) associated with FOLFOX yielded 75% partial response if patients were previously untreated, and 23% otherwise [19].

Several monoclonal antibodies to the EGFR (EGFRMabs) have already been used in phase II or phase-III clinical trials with interesting results. Among them, the one furthest ahead in clinical development is the IMC-C225 also called C225 (cetuximab). C225 is a murine chimeric monoclonal antibody which binds selectively to EGFR with a higher affinity than either EGF or TGF α. Cetuximab is usually administered as a 400 mg/m^2 intravenous loading dose followed by a weekly dose of 250 mg/m^2. Most common side-effects consist of acneiform skin rash (60%) and anaphylactic reactions (2%) which may be prevented by prophylactic antihistamin therapy. Cetuximab is effective in single-agent administration, but the major innovation brought by this drug is the potential to reverse resistance to cytotoxic agent.

Cetuximab has been tested in different phase II trials alone or associated to ironotecan or oxaliplatin. Cetuximab was first used in patients with refractory metastatic colorectal cancer and progressing on an irinotecan based regimen [20]. Combination of cetuximab to irinotecan yielded a 23% response rate and a 6 months median duration in a non-comparative trial enrolling 121 patients; 31% patients presented a stable disease [21]. These results were confirmed in a large randomized phase II trial (474 patients) [22] demonstrating a 23% response rate. Median time to progression was 126 days (versus 45 days for cetuximab alone) proving the efficiency of cetuximab in heavely pretreated patients. Toxicity appeared manageable; grade 3-4 toxicity included diarrhea (20%), asthenia (13%), neutropenia (11%), acne (7%) and vomiting (6%).

On the basis of these results, cetuximab was approved in numerous countries for patients progressive under irinotecan regimen.

Three other trials used cetuximab associated to irinotecan in first line therapy. They respectively enrolled 21, 25 and 19 evaluable patients. Response rate were comprised between 43 and 58% [23-25].

More recently, cetuximab has been associated to oxaliplatin in three studies; two of them are still going on. First results of the EXPLORE study [26] has been presented at the 2004 ASCO meeting. This trial aims to include 1100 patients and to compare FOLFOX 4 to FOLFOX 4+ cetuximab in second line therapy. First analysis showed that the regimen seems feasible and safe. The ACROBAT study [27] evaluated FOLFOX4 + cetuximab as first line treatment in 61 patients. Efficacy results are very encouraging with 81% response rate (including 2 complete responses) and 7 stable diseases (12%). Data suggest that cetuximab is safe and effective when combined to FOLFOX 4. Grade 3-4 toxicity included diarrhea (26%), acne (21%), neutropenia (14%), mucositis (9%), asthenia (9%), vomiting (5%) and neurotoxicity (2%).

Futures directions of cetuximab development include its combination with other cytotoxic or targeted therapies.

Targeting vascular endothelial growth factor

The development of new vessels (angiogenesis) is essential for tumoral growth, invasion and metastasis. Several mechanisms and molecules are involved in the angiogenesis, and each of them represents a potential target. Currently vascular endothelial growth factor (VEGF) is thought to be the major growth factor. Therefore, targeting VEGF appears as a promising strategy. VEGF acts via two receptors (VEGF-R1 and VEGF-R2) which are located on endothelial cells and present

a protein kinase activity. Overexpression of VEGF is associated with metastatic phenotype and poor prognosis [28-29].

Rhu-mab-VEGF (bevacizumab, AVASTIN®) is a humanized monoclonal antibody against VEGF which has been furthermore investigated in a 3 arms randomized phase II trial [30] enrolling 104 patients. Bevacizumab (5 mg/kg or 10 mg/kg) combined to 5-FU/LV obtained better response rate (40 and 24%), median time to progression (9.2 and 7.2) and median survival (21.5 and 16.1 months) than 5-FU/LV.

These results were confirmed in 2003, when for the first time, a phase III trial demonstrated an angiogenic agent can improve overall survival [31]. In this trial involving 815 previously untreated patients, the addition of bevacizumab (5 mg/kg/two weeks) to irinotecan/5-FU/LV increased response rate (45% versus 25%, p=0.0029), progression-free survival time (10.6 versus 6.2 months, p<0.00001) and overall survival time (20.3 versus 3.2 months, p=0.00003). Toxicity was equivalent except hypertension. In 2004, bevacizumab received approval for use in first-line treatment in combination with 5-FU based chemotherapy.

Currently, the oral angiogenesis PTK/ZK222584 which selectively targets the VEGF-R tyrosine kinase inhibitor is evaluated in association with 5-FU/LV plus irinotecan or oxaliplatin [32-33].

Conclusion

Irinotecan and oxaliplatin have widely expanded the options available for the management of patients with ACC, with consequent improvements in survival. More recently, promising results have been reported with new agents such as angiogenic inhibitors and anti-EGF receptors which represent another step forward. The association of targeted therapies with cytotoxic chemotherapies exploit their complementary mechanism of actions. The use of these new strategies such as maintenance therapy after achieving best response must be further explored. Ongoing and future trials will demonstrate the optimal schedules of drug administrations, and will better quantify their benefit upon standard approaches. One must also keep in mind that these advances are an economic challenge. For example 8 weeks of 5-FU/LV Mayo Clinic regimen cost $63 whereas for the same duration, FOLFIRI costs $9.381 and FOLFIRI + cetuximab $30.675 [34]. Cost-effectiveness analyses are wanted to evaluate the real financial implications of these drugs.

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