


NEW HOPE IN Colorectal C A N C E R

Perspectives in Colorectal C A N C E R

The emergence of new therapeutic agents, advances in surgical and screening techniques, and improvements in our knowledge of the molecular and genetic changes in colorectal cancer (CRC) have led to significant improvements in patient care. Awareness of progress in CRC treatment has grown rapidly among patients, clinicians and the industry, and in consequence, an annual European meeting for colorectal cancer experts was established and first held in Geneva in 1998. Attendance at these meetings is growing annually.

The Fifth International Congress: Perspectives in Colorectal Cancer, held in Barcelona, Spain, on June 26-28, 2003, continued the successful tradition of bringing together leading physicians and scientists to share cutting edge information in this rapidly evolving field. The conference was convened by an eminent panel of European oncologists: Mario Dicato (Luxembourg), Eric Van Cutsem (Belgium), and Jacques Wils (The Netherlands).

During the three days of the meeting, over 1500 attendees, including oncologists, surgeons and radiotherapists, had an opportunity to hear and discuss the latest research surrounding the biology, prevention, diagnosis and treatment of colorectal cancer. Selected highlights of the meeting are summarized in this newsletter. 

The Adenoma Carcinoma Sequence in Colon Cancer

Dr Richard Houlston (United Kingdom) opened the first of two keynote lectures by highlighting the importance of understanding the pathways leading to colorectal cancer (CRC) in order to identify susceptible individuals and to identify novel targets for treatment interventions. In addition, the predictive value of genotypic markers may, in the future, allow for tailored therapies based on predicted response to treatment.

It is well known that most CRCs develop from colorectal adenomas and that familial adenomatous polyposis (FAP) is associated with the development of multiple polyps and a 95% risk of developing colorectal cancer. FAP is characterized by inactivating mutations of the APC gene which is essential for the degradation of β catenin. Over-accumulation of β catenin due to mutant APC results in nuclear activation of c-myc and other important nuclear transcription factors leading to cellular proliferation and adenoma formation.

APC gene mutation is also the most common mutation in sporadic CRC. It is found in 80-90% lesions. "This [APC mutation] is considered to be the 'gate keeping' event," said Dr Houlston, "and one of the most fun-

damental mechanisms of the CRC pathway." In FAP, the APC mutation is an inherited germline mutation inactivating one of both alleles in all cells. A single additional mutation of the other allele leads to the formation of adenomas and cancer. In sporadic CRC both alleles need to undergo an inactivating mutation in order to develop into adenomas and subsequent cancer (Figure 1).

Though mutations of the APC gene are the primary factor involved in the transition of normal epithelium to early adenoma, the MYH gene can play a role as well, as was recently illustrated by a case of three brothers with a mild form of polyposis. Investigators found a high frequency of rare mutations in the APC gene, indicative of oxidative damage. The MYH and OGG1 gene products protect DNA from oxidative damage. When specific gene sequencing was performed on these brothers, it revealed that each had two mutations in MYH on different alleles. Such heterozygosity accounts for about 30% of multiple adenoma cases and 2-3% of all CRC cases. Also interesting is the fact that these mutations confer recessive inheritance—the only observed example in cancer to date.

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New Hope in Colorectal Cancer is a summarization of the scientific content presented at the Fifth International Congress: Perspectives in Colorectal Cancer.

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The Adenoma Carcinoma Sequence in Colon Cancer *(continued from page 1)*

Turning to other initiation events, mismatch repair (MMR) genes are, as their name suggests, involved in repair of single base pair mismatches during DNA replication. Microsatellite markers can easily detect mispairing to identify any deficit within the MMR genes, referred to as microsatellite instability (MSI). The probability of any cancer having MMR deficiency is a function of age. It is observed in 50% of cases diagnosed before age 35, but in only 10-15% of cases diagnosed after age 50. Hereditary MSI is associated with accelerated polyp transformation and a 70% risk of CRC; however, only 15-20% of all CRC cases involve MSI, most of which (>80%) are not due to an inherited gene defect but rather somatic mutation or methylation. There is some evidence suggesting that MSI confers a better prognosis compared to patients with stable MMR.

The transition from early to late adenoma is characterized by k-ras mutations, found in a significant proportion of CRC tumors. Late adenomas are characterized by TP53 mutations, and early carcinomas are associated with a plethora of chromosomal changes that lead to late carcinoma and invasion of metastases.

Dr Houlston concluded that genetic events that lead to CRC are much better understood than in other common cancers, and that “one should be optimistic that this will have enormous clinical dividends, in terms of developing relationships between genotype and phenotype to allow targeted screening and the introduction of novel therapies.”

Screening techniques

Digestive cancers account for the highest mortality worldwide, and of these CRC has the highest incidence (Table 1). In a second keynote lecture, Dr Sidney Winawer (United States) addressed the importance of endoscopy as an early detection measure for CRC, quoting a 1997 publication that “Screening for colorectal cancer and adenomatous polyps should be offered to all men and women without risk factors beginning at age 50.”

Dr Winawer remarked that the polyp-to-carcinoma pathway typically spans 10 to 20 years, and that “this represents a large window of opportunity for intervention.” He noted that the current trend is to try to identify people with adenomatous

polyps for removal to decrease the incidence of CRC. This can be done as a one-stage screening with colonoscopy or a two-stage screening, with fecal-occult blood testing and/or flexible sigmoidoscopy, or in the future perhaps virtual colonoscopy.

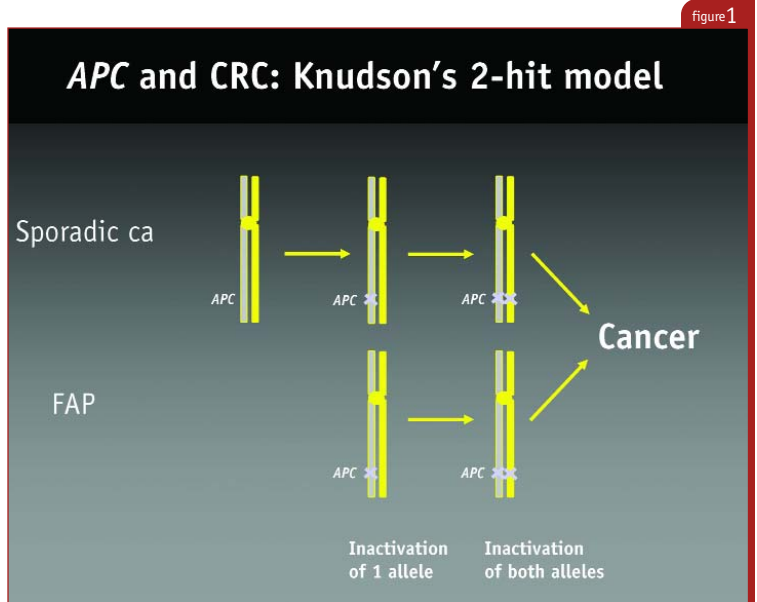
The fecal-occult blood test (FOBT) has been the best studied test for CRC screening and has demonstrated consistency across several studies, providing an approximate 20% reduction in mortality with biennial screening and greater reductions with more frequent follow-up. Sigmoidoscopic screening can also reduce CRC mortality. Dr Winawer mentioned two retrospective studies that resulted in 30% and 40% mortality reductions. Three large prospective studies are in progress, two of which have so far uncovered advanced adenomas in 12% and 18% of patients.

Virtual colonoscopy is a new imaging technique. As a screening tool for colorectal polyps, it is associated with a wide range of sensitivity and specificity which, as is often the case with new techniques, is highly operator dependent. Other new screening tests for CRC include a DNA stool test which has shown good sensitivity and specificity for invasive cancer and advanced adenomas in preliminary studies. Two large trials are ongoing and will further characterize its utility in this setting.

Colonoscopy allows the detection and removal of polyps in a one-stage procedure, but at this time there are still no randomized trials with mortality as an endpoint, leaving open the question as to its value compared to other modalities. However, data from ongoing and completed screening colonoscopy studies suggest that adenomas can be found in 18-38% of asymptomatic men and women of age 50 or more. However, in addition to efficacy, a number of issues require consideration, including benefit, safety, resources, cost-effectiveness, and quality control.

	Incidence	Deaths
Colorectal	950,000	500,000
Stomach	875,000	650,000
Liver	560,000	550,000
Esophagus	400,000	330,000
Pancreas	200,000	200,000

Source: Winawer, SJ, PICC 2003.



Source: Houlston R, PICC 2003.

Screening and Prevention of Colorectal Cancer

Screening for familial and hereditary cancer

Immediate relatives of persons with colon cancer have an approximate two-fold increased risk of adenomatous polyps and large bowel malignancy as compared to average-risk controls. Colon cancer risk is three-fold or even higher if two or more first-degree relatives have colon cancer or a single first-degree relative with colon cancer was diagnosed under the age of 50 or even 60 years.

A small percentage of CRC cases are accounted for by rare inherited colorectal cancer syndromes. These syndromes are commonly classified into hereditary polyposis and nonpolyposis syndromes. Families associated with these syndromes carry a particularly high-risk for the development of colorectal cancer.

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by the progressive development of hundreds to thousands of colorectal adenomas. It accounts for 1% of all cases of CRC. FAP families should undergo routine colon screening for adenomatous polyposis by annual flexible sigmoidoscopy beginning at about age 12. The frequency may be decreased to every three years after age 40.

Hereditary nonpolyposis colorectal cancer (HNPCC) is another autosomal dominant disorder in which affected patients develop small numbers of colorectal adenomas. HNPCC accounts for about 5% of all cases of CRC. The initial Amsterdam criteria defined a HNPCC family as having 1) three or more close relatives with HNPCC, one being a first-degree relative of the other two; 2) two or more generations are affected with CRC, and 3) at least one cancer diagnosed before age 50, in the absence of gastrointestinal polyposis.

"This creates a problem," said Dr Winawer, "because there are many families that fulfill the first two criteria, but we cannot identify an individual less than 50 years of age, so we call these HNPCC-like." In order to cast a wider net and identify people with HNPCC who are not identified by the Amsterdam criteria, a meeting in Bethesda earlier this year tried to capture high-risk

individuals by adding criteria such as 1) a patient having two HNPCC related cancers or 2) a CRC patient having a first degree relative with HNPCC cancer and one of them is under age 50, or under age 40 with an adenoma. Using these additional criteria, Dr Winawer stated that in some studies it was possible to identify 95% of individuals at high risk for HNPCC.

HNPCC patients are at increased risk for early onset of colorectal cancer, at an average age of diagnosis of 40-45 years. Colorectal screening in HNPCC patients should be performed by colonoscopy because of the increased incidence of proximal cancers and adenomas. At-risk individuals should have a colonoscopy every 1-2 years beginning at age 20.

Screening in the general population

One prominent question is: "Are there adequate resources to conduct screening colonoscopy in the general population?" One US model estimates that 2.5 million people would have to be screened each year as part of a national screening program. Dr Winawer suggested that this figure could be reduced by stratifying patients who had polyps removed for risk factors such as the multiplicity of adenomas, age, and family history, with less frequent follow-up for low-risk patients. In terms of cost, the cost benefit ratio of CRC screening is superior to screening for hypertension and mammography.

There are many guidelines for CRC screening—two recent sets from the US are shown in Table 2. The guidelines notwithstanding, CRC screening is still widely underused.


The International Digestive Cancer Alliance was recently formed to try and build campaigns for CRC screening, "but it really comes down to the individual physician or healthcare provider," said Dr Winawer, highlighting a survey by the American Cancer Society that said the most frequent reason for not getting screened was that it was "not recommended by my doctor" (88%). In closing, Dr Winawer stated that "the best screening test is the one that gets done." 

Table 2: Guidelines for Colorectal Cancer Screening in Average Risk Men & Women 50 Years of Age or Older

	Options					
	Digital Rectal Exam	FOBT	FS	FOBT & FS	DCBE	Co.
US Multi Society Task Force (2003)	w/ endoscopy	Annual	5 yrs	Ann FOBT 5 yrs FS	5 yrs	10 yrs
American Cancer Society (2001)	w/ endoscopy	Annual	5 yrs	Ann FOBT 5 yrs FS	5 yrs	10 yrs

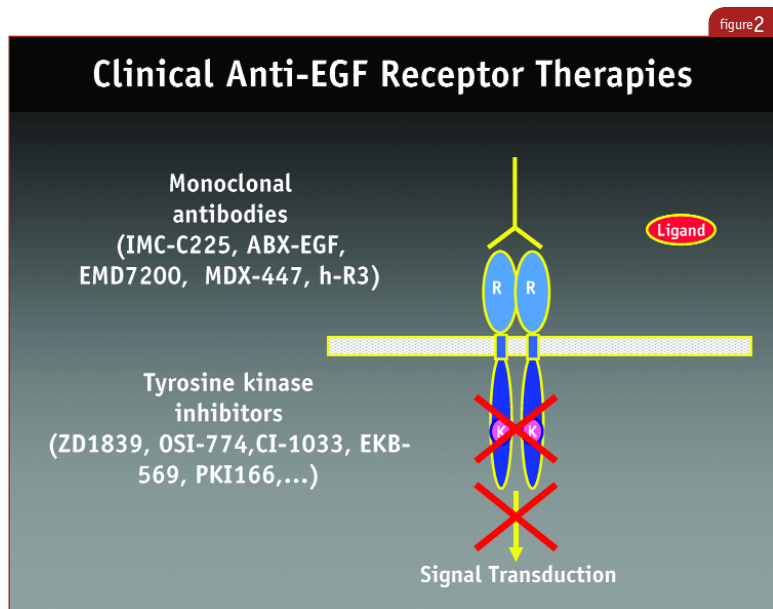
Source: Winawer SJ, PICC 2003.

Signal Transduction Inhibition

“We are now 20 years from the cloning of the [epithelial growth factor] receptor, but it is only now that we are really beginning to understand how this family of receptors is working” said Dr. Jose Baselga (Spain). Expressed at the cell surface, ligand induced conformational changes trigger a complex cascade of signaling through different pathways. Mutations in the Ras/Raf MAP-kinase pathway are well known for their role in CRC progression, but another pathway of increasing importance is controlled by PI3 kinase and AKT, which appears to play a critical role in apoptosis. The end result of epithelial growth factor receptor (EGFR) signaling is increased gene transcription and cell cycle progression.

“The EGFR plays a major role in the malignant growth of some cells,” said Dr Baselga, adding that “CRC cells have the capacity to not only produce receptors, but also to produce increasing quantities of ligands...and become independent from their environment.” A review of the literature shows that approximately two-thirds of human tumors express EGFR, including the majority of CRC tumors. Strategies for EGFR signaling inhibition include monoclonal antibodies against the EGFR and its ligand, as well as kinase inhibitors (Figure 2).

Kinase inhibitors (KIs) can be orally administered and are distributed more rapidly than monoclonal antibodies, which require intravenous administration. However, KIs may cross-react with other kinases. KIs may also exhibit dose-limiting systemic toxicities not seen with monoclonal antibodies and do not down-regulate EGFRs. Dr Baselga reviewed a number of recent studies evaluating monoclonal antibodies against EGFR such as cetuximab, and concluded that “there is an emerging



Source: Baselga J, PACC 2003.

amount of data suggesting that anti-EGFR antibodies are going to be active and key players in CRC disease.”

“The challenge is how to integrate these new therapies with what we already have. There ought to be fascinating years ahead for all of us,” said Dr Baselga. “I think that it is not an overstatement to say that these therapies will change the way we envision and treat CRC. These data present proof of principle that targeted therapy is a very promising approach for CRC.”

Chemoprevention of Colorectal Cancer

The most successful (and cost effective) method for the prevention of sporadic CRC is a complete colonoscopy and removal of all detectable polyps. However, adenomatous polyps recur at high rates (approximately 40% in three years). Thus, pharmacological methods to inhibit growth and progression of colorectal polyps are under intensive investigation, a summary of which was provided by Dr Wolff Schmiegel (Germany).

Various studies suggest that non steroidal anti-inflammatory drugs may reduce the development of CRC. The basis of their chemopreventive effect is thought to be the inhibition of the cyclooxygenase isoform 2 (COX-2) which is known to be up-regulated in colorectal adenoma and carcinoma. Although a number of trials have investigated chemoprevention in sporadic CRC, clinical interpretation is challenging given the variable patient

populations, study designs and primary endpoints. “What we are lacking so far are prospective, randomized controlled studies of long duration,” said Dr Schmiegel.


In addition to non-selective COX inhibitors (aspirin, sulindac), selective COX-2 inhibitors have also been investigated for their ability to reduce recurrence of sporadic adenomas after polypectomy. Mesalazine is another agent under investigation, although the molecular mechanisms underlying its potential chemopreventive effect are not fully understood. Recent data suggests that besides increasing caspase dependent apoptosis, mesalazine may also inhibit cell cycle progression by arresting cells in mitosis. A long-term multicenter trial will evaluate whether mesalazine treatment reduces the risk of adenoma recurrence after polypectomy. The first data are expected by the end of this year.

Virtual Endoscopy

Dr Jörg Debatin (Germany) started his presentation with the question: "Why bother with virtual endoscopy when conventional colonoscopy is an established method, widely available, and with high diagnostic accuracy?" His answer was that too few people take advantage of it because it requires sedation and preparatory bowel cleansing, or because of fear of diagnosis.

To overcome poor patient acceptance, virtual endoscopy has been proposed as an emerging alternative technology that utilizes MRI imaging as part of a short (<15 min) and painless screening exam. Patients must undergo a rectal enema (water or air) for bowel distension as the 3D data set of the abdomen and colon is collected. Analysis of an MR colonography requires about 5 minutes of interactive viewing and studies have demonstrated detection of most

lesions larger than 10 mm, while lesions of less than 5 mm and flat lesions are often missed.

Dr Debatin conceded that bowel cleansing needs to be eliminated to assure high patient acceptance of this procedure. To this end, fecal tagging is one strategy that modulates the signal intensity of fecal material by consuming barium sulfate contrast with each of four meals beginning 36 hours prior to the procedure. Initial results in patients with known or suspected CR tumors have confirmed the diagnostic accuracy of this approach, although other avenues are being explored (e.g., adding iron oxide to ready to eat meals) to eliminate the need to drink a lot of contrast fluids. 

The Management of Liver Metastases

Surgical resection of liver metastases

Dr Bernard Nordlinger (France) reviewed the surgical management of liver metastases, which develop in 40-50% of patients with CRC and represent the major cause of death, with median survival rarely exceeding 9 months in the absence of treatment. Only 10-20% of patients are candidates for surgery; however, following resection five-year survival rates vary from 20% to 45%, even though recurrences develop in two-thirds of patients.

A number of strategies including portal vein embolization, new ablation methods, and neoadjuvant chemotherapy are aimed at increasing the resectability of liver metastases and reducing the risk of recurrence after surgery. Response rates after preoperative chemotherapy with 5-Fluorouracil and folinic acid are only approximately 20%, but the addition of newer agents such as oxaliplatin or CPT-11 pushes the response rate closer to 50%. Dr Nordlinger expressed optimism that "the distinction between resectable and unresectable liver metastases could become obsolete with the emergence of a new group of unresectable patients becoming resectable after response to chemotherapy."

Similarly, it was reported that the best way to reduce the risk of recurrence after surgical resection may be adjuvant chemotherapy. A limited number of randomized studies have been published to date using hepatic artery and/or systemic infusion, demonstrating little benefit over surgery alone. However, planned and ongoing trials are in place to evaluate the benefits of perioperative chemotherapy with newer agents such as oxaliplatin and irinotecan in patients with resectable liver metastases.

The contribution of ablation techniques

Local tumor ablative techniques are typically used in patients with unresectable liver metastases. In terms of overall survival, phase II studies show promising results with two-year survival rates between 50 and 75% and median survival times of more than 30 months. Although this is longer than standard chemotherapy treatment with a median survival of 17-19 months, Dr Ruers (The Netherlands) pointed out that this difference may be due to patient selection, since patients selected


for aggressive local treatment have only a limited number of liver metastases in contrast to chemotherapy patients who may have widespread liver involvement or extrahepatic disease.

Cryo- and radiofrequency ablation are two of the most common ablation techniques for liver metastases. Cryoablation is more invasive and has a higher morbidity rate (10-30%) than radiofrequency ablation (<10%), therefore radiofrequency ablation has become the method of choice, said Dr Theo Ruers.

Two ongoing studies will better define the role of local tumor ablation. A French study compares radiofrequency ablation to resection in the treatment of resectable colorectal liver metastases, and an EORTC study is comparing local ablation plus chemotherapy to chemotherapy alone.

The role and value of locoregional chemotherapy

Dr Michel Ducreux (France) reviewed the results of intra-arterial hepatic chemotherapy (IAHC) for liver metastases of CRC, citing data from two recent clinical trials that failed to show any benefit in favor of IAHC (using 5FU + leucovorin) compared to intravenous administration. Other problems associated with IAHC include the potential for hepatic and biliary toxicity which could lead to sclerosing cholangitis and biliary obstruction, the cost of the infusion pumps, and the possibility that extra-hepatic lesions are present. Given the improvement of intravenous chemotherapy with combined 5FU + leucovorin + oxaliplatin or irinotecan, the future role of IAHC in the treatment of colorectal liver metastases is questionable.

However, it has been shown that IAHC with FUDR (5-fluoro-deoxyuridine after resection improves survival. Newer agents have been used in IAHC with promising results. Dr Ducreux concluded that the current role of IAHC is difficult to define, but that it may have potential indications with newer agents in combination with intravenous chemotherapy or after intravenous chemotherapy failure, or as adjuvant treatment after resection of liver metastases. 

Prognostic and Predictive Markers

Biological and molecular prognostic markers

Dr Patrick Johnston (Ireland) started his presentation by pointing out that the use of chemotherapy in patients with advanced CRC has been suboptimal. Complete responses in patients with metastatic disease are infrequent and partial responses are seen in less than 20% of patients receiving 5-FU based regimens.

In recent times investigators have tried to identify variables or markers that could help identify patients with better or worse prognosis and patients who are likely not likely to respond to certain treatments. Biologic markers fall into two categories: 1) prognostic markers that reflect the prognosis of the patient and reflect the clinical biology of the disease; and 2) predictive markers that provide information about the chance of a patient responding to a particular treatment. Dr Johnston listed the main markers that have been evaluated over the last decade (Table 3), but focused his talk on thymidylate synthase (TS), thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase (DPD), loss of heterozygosity and microsatellite instability (MSI).

Table 3: Molecular Determinants of Outcome in Colorectal Cancer

- > Thymidylate Synthase
- > Thymidine Phosphorylase
- > Dihydropyrimidine dehydrogenase
- > Loss of heterozygosity. Microsatellite Instability
- > P53
- > Ki-67
- > P21
- > BCL-2
- > ERCC1/XPD
- > GSTP-1

Source: Johnston P, PICC 2003.

He cited data from the Intergroup study 0089 which revealed that the presence or absence of heterozygosity at chromosome 18 and MSI was predictive of prognosis, establishing an early algorithm for the use of biological markers. In addition, a number of studies have shown a survival benefit for lower levels of TS, TP, and DPD, in both metastatic CRC and the adjuvant disease setting.

He further commented that subgrouping CRC patients based on the actual molecular phenotype will become a reality over the next 10 years, given technological advances that allow rapid screening of tumors for well defined genes. These systems include systematic DNA or oligonucleotide arrays of known sequences that can be used for 1) expression profiling to identify specific drug targets and 2) mutation detection to identify disease specific mutations and polymorphic variations.

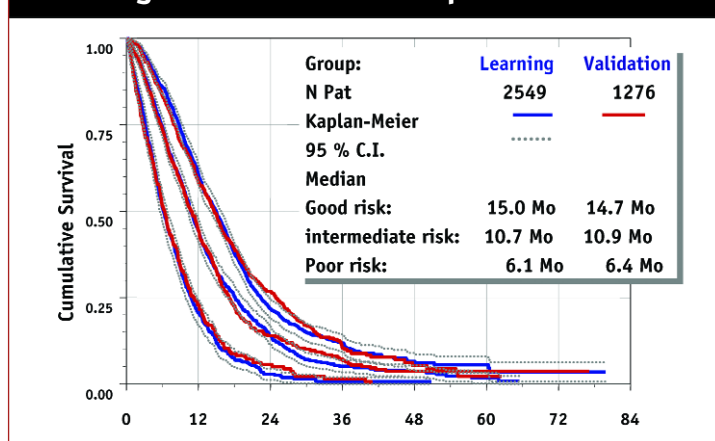
Dr Johnston reviewed research using microarrays to evaluate gene expression following treatment with 5-FU, which has revealed a number of genes that may be important predictors of resistance. He concluded that future studies combining information from more than one independent marker has the potential to identify a high percentage of responding patients, but this needs to be confirmed in prospective clinical trials.

Commenting on the multitude of exciting talks on new agents at this meeting, Dr Johnston pointed out that “we now have to find new ways of putting these agents together, based on techniques such as pharmacogenomic profiling, to best use these agents in combination.”

Clinical predictive markers

Intrigued by the differences in survival rates in clinical trials that use similar patient selection criteria, Dr Claus-Henning Köhne (Germany) analyzed the data from 3,825 patients treated with 5-FU in 19 prospective, randomized phase III clinical trials in a multivariate analysis in order to identify relevant clinical parameters for prognosis. Twenty-three potential predictors were examined.

Survival according to risk groups: Learning and validation sample



Source: Köhne CH, et al. ANN ONCOL 2002;13:308-317.

Results of this analysis showed that patients can be divided into at least three risk groups (poor, intermediate, good) depending on four baseline clinical parameters: performance status, white blood count, alkaline phosphatase and number of metastatic sites. As shown in Figure 3, median survival for these risk groups were 6, 11, and 15 months respectively. Dr Köhne indicated that such stratification could be utilized in clinical trials, validating molecular or biological markers against these clinical parameters.

Pharmacogenomics

Dr Heinz-Josef Lenz (United States) has identified a number of markers that are predictive of the response to fluoropyrimidines and platinum-based chemotherapy in colorectal cancer. These markers include TS, DPD, TP for fluoropyrimidine therapy and ERCC, XPD and GSTP1 for platinum based chemotherapy.

It has been shown that tumors with high levels of TS expression are less likely to respond to fluoropyrimidines and therefore should preferably be treated with non-TS directed anticancer drugs such as CPT-11 or oxaliplatin. Patients with high expression of ERCC1 should be treated with non-platinum based regimens whereas patients with low levels would be good candidates for cisplatin or oxaliplatin. Dr Lenz underscored the clinical importance of understanding the metabolism and the mechanism of resistance to newer agents to better assess why some patients develop life-threatening toxicity and why some tumors are resistant to 5-FU or oxaliplatin.

Chemotherapy for Colorectal Cancer: Where Are We in 2003?

Adjuvant chemotherapy

Is there a current standard adjuvant therapy for colorectal cancer? In his review of this topic, Dr Daniel Haller (United States) answered that there was no standard adjuvant treatment for CRC. Adjuvant treatment approaches for high-risk colorectal patients are quite heterogeneous, he pointed out.

Clinical studies over the last 40 years have shown that 5-FU can be administered in many different ways to improve toxicity without affecting efficacy. More recently, studies have shown that the addition of irinotecan and oxaliplatin can improve efficacy, but Dr Haller cautioned that results from a number of other ongoing trials with other agents should be awaited before any new 'standard' combination chemotherapy is broadly adopted. However, he commented that current research appears to have "pushed the envelope" in terms of response rates.

He noted that adjuvant therapy can also be improved in terms of convenience, by using oral fluoropyrimidines, and a number of studies are ongoing in this regard. Other improvements include reducing therapy duration and toxicity, particularly in combination regimens. These aspects will be addressed by the OPTIMOX and MOSAIC2 studies.

Finally, Dr Haller stressed that adjuvant treatment should be individualized because the current CRC staging system "defines patients as high risk when in fact the risk of death from their disease is anywhere from 20% to 80%." Referring to the previous presentation by Dr Johnston, he noted that the field is moving towards evaluating the molecular profile of tumors to identify patient groups that will benefit from different treatments. One such trial has been proposed using TS as a predictor marker to assign patients to different treatments and generate data that could be applied to the adjuvant setting.

Progress in the treatment of metastatic colorectal cancer

30% of CRC patients have advanced disease upon presentation, either locally or at distant sites, and chemotherapy has an established role in improving survival and palliating symptoms for these patients, said Dr Eric Van Cutsem (Belgium).

Chemotherapy for CRC has significantly improved over the last few years. Until the early 1990s 5-FU was the only available chemotherapeutic agent. One step forward was the use of 5-FU in association with folinic acid, and even more progress resulted from the availability of new drugs such as irinotecan and oxaliplatin. The median survival of patients with metastatic CRC is now more than 18 months. The oral fluoropyrimidines, capecitabine and UFT further expand the therapeutic options and may improve patient outcome.

Looking to the future, a number of agents directed specifically at new targets are in development and have shown promising activity in phase I and II studies. These include epidermal growth factor inhibitors, like cetuximab, vascular endothelial growth factor inhibitors and COX-2 inhibitors. These new agents will most likely have a role in the treatment of CRC in the future, either in combination with or sequentially after currently used agents.

Therapy for advanced CRC has significantly improved over the last few years but many questions remain:

- Do all patients benefit from combination treatment?
- What is the optimal treatment for elderly patients and for patients with poor prognostic characteristics?
- How can we select patients benefiting more from a fluoropyrimidine alone or from combination chemotherapy?
- How long should combination treatment be administered?
- Is there a role for maintenance treatment with 5-FU/FA or with oral fluoropyrimidines?
- What is the role of new drugs (novel targeted agents): combination upfront, combination in refractory patients, monotherapy in failures?

Further studies should define the role of new agents and new combinations and the merits of clinical and biochemical predictive markers in the management of metastatic CRC.

Oral fluoropyrimidines in combination therapy for colorectal cancer

Dr David Cunningham (United Kingdom) provided an extensive review of the use of oral fluoropyrimidines, namely capecitabine and tegafur (UFT), in the treatment of CRC. As first line therapy for advanced CRC, these drugs have demonstrated favorable response rates and toxicity profiles. In four large phase III studies, median progression-free and overall survival rates were comparable to bolus 5-FU/leucovorin (LV).

Capecitabine, in combination with oxaliplatin or irinotecan produced response rates of 33-55% in recent phase II trials (Table 4), with median progression-free survival (PFS) of 5.9-10.5 months and median overall survival (OS) of 11.5-17.1 months in advanced CRC. Similar results have been observed with UFT and irinotecan in a first-line setting.

Lower response rates have been observed with capecitabine and oxaliplatin in second-line treatment (15%) with a median PFS of 4.2 months and median OS of 11.5 months. UFT plus oxaliplatin in second- and third-line settings resulted in a response rate of 12.9%, median PFS of 2.2 months and median OS of 6.5 months.

The first-line combination of capecitabine plus mitomycin C has also been evaluated in a phase II study, with a response rate of 39.6%, a median PFS of 7.2 months, and median OS of 14.7 months.

In the pre-operative setting, Dr Cunningham reported that the combination of capecitabine plus oxaliplatin prior to chemoradiation (using single agent capecitabine) and surgery has been evaluated in a small phase II trial with an overall response rate of 100%, resulting in 95% of patients undergoing a R0 resection, of whom 28% achieved a pathological complete remission and a further 47.4% had only microscopic tumor foci left.

Table 4: Colorectal cancer trials using oral fluoropyrimidines**Capecitabine + oxaliplatin: First-line phase II studies**

Author	Regimen	Pts (n)	ORR (%)	Median OS (months)	Median PFS (months)
Bonner et al (2003)	Cap 1250mg/m ² BD D1-14 Ox 130mg/m ² D1 q3 weekly	43 26*	49 15*	17.1 11.5*	5.9 4.2*
Scheithauer et al (2003)	Cap 1000mg/m ² BD D1-14 Ox 130mg/m ² D1 q3 weekly	45	42.2	NR	6.0
	Cap 1750mg/m ² BD D1-7, D14-21 Ox 85mg/m ² D1+14 q4 weekly	44	54.5	NR	10.5
Van Cutsem et al (2003)	Cap 1000mg/m ² BD D1-14 Ox 130mg/m ² D1 q3 weekly	96	45	19.5	7.7
Grothey et al (2003)	Cap 1000mg/m ² BD D1-14 Ox 70mg/m ² D1+8 q3 weekly	82	51.3	>16.0	7.9
Shields et al (2002)	Cap 750-1000mg/m ² BD D1-14 Ox 130mg/m ² D1 q3 weekly	48	34.3	NR	6.2
Sumpter et al RMH (2003)	Cap 1000mg/m ² BD D1-14 Ox 130mg/m ² D1 q3 weekly	15 10*	33.3 36.5	13.4	6.5
		21+	19		

*Second-line treatment
+Third-line treatment
ORR – overall response rate

Capecitabine + irinotecan: First-line phase II studies

Author	Regimen	Pts (n)	ORR (%)	Median OS (months)	Median PFS (months)
Grothey et al (2003)	Cap 1000mg/m ² D1-14 Iri 80mg/m ² D1+8 q3 weekly	77	37.1	>16.0	8.3
Patt et al (2003)	Cap 1000mg/m ² D1-14 Iri 250mg/m ² D1 q3 weekly	52	42	NR	7.1
Borner et al (2003)	Cap 1000mg/m ² BD, D1-14, D22-35 Iri 70mg/m ² D1,8,15, 22,29 q6 weekly	37	42	NR	7.2
	Cap 1000mg/m ² BD, D1-14, D22-35 Iri 240mg/m ² D1+22 q6 weekly	38	41	NR	9.9

NR = not reached
ORR – overall response rate

UFT/LV + oxaliplatin: First-line phase II studies

Author	Regimen	Pts (n)	ORR (%)	Median OS (months)	Median PFS (months)
Bennouna et al (2003)	UFT 300mg/m ² /day D1-14 Ox 130mg/m ² D1 q3 weekly	64	32.0	NR	NR
Kim et al* (2002)	UFT 350mg/m ² /day D1-14 Ox 130mg/m ² D1 q3 weekly	34	12.9	6.5	2.2

*Second-line treatment
NR = not reached
ORR – overall response rate

UFT/LV + irinotecan: First-line phase II studies

Author	Regimen	Pts (n)	ORR (%)	Median OS (months)	Median PFS (months)
Alonso et al (2003)	UFT 300mg/m ² /day D1-21 Iri 100mg/m ² D1,8,15 q4 weekly	45	33.4	16.2	6.5
Mackay et al (2003)	UFT/LV 250mg/m ² D1-14 Iri 250mg/m ² D1 q3 weekly	32	20.0	16.5	6.0

ORR – overall response rate

Source: Cunningham D, PICC 2003.

Dr Cunningham added that a number of phase III trials have now been initiated in both the advanced disease and perioperative settings, that should further define the tolerability, toxicity and efficacy of oral fluoropyrimidines in combination therapy for colorectal cancer.

Results of the EORTC GI group study 40986

Dr Van Cutsem, presented the final results of the EORTC GI group study 40986 evaluating whether adding irinotecan (IRI, 80 mg/m²) improves the activity of the infusional 5-FU/LV (AIO) regimen in metastatic CRC. Patients enrolled in this trial had histologically confirmed CRC with chemo-naïve metastatic disease. Previous adjuvant treatment was allowed if completed 6 months prior to randomization. Reference treatment was the AIO schedule (24 hr infusion).

The major study endpoint was progression-free survival and the aim was to demonstrate a 35% increase from 7 to 9.5 months. 430 patients were enrolled (215 in each arm) and patient characteristics (including risk groups) were balanced between both arms.

The first 89 patients in the AIO+IRI arm had higher toxicities related to 5-FU leading to a dose reduction to 2000 mg/m²). Following dose reduction, the incidence of grade 3/4 toxicities was similar in both arms.

The overall response rate was significantly higher in the AIO+IRI arm (54.2% vs. 31.5%; p<0.0001) and was associated with fewer treatment discontinuations (44% vs. 62%). Progression-free survival was significantly increased (8.5 vs. 6.4 months; p=0.0001), although overall survival (20.1 vs. 16.9 months) was not statistically significant at 36 months.

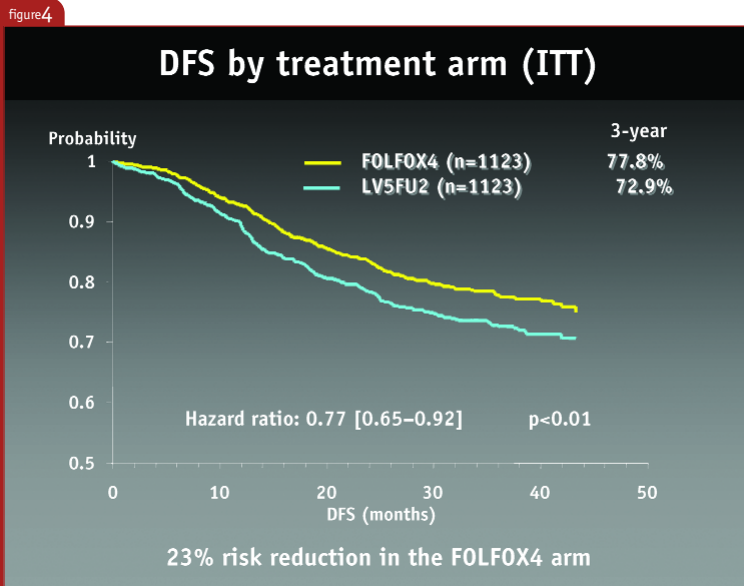
“These results show that irinotecan + AIO is a safe regimen, and that irinotecan significantly increases the objective response rate and progression-free survival of the AIO-regimen,” said Dr Van Cutsem.

Results of the MOSAIC trial

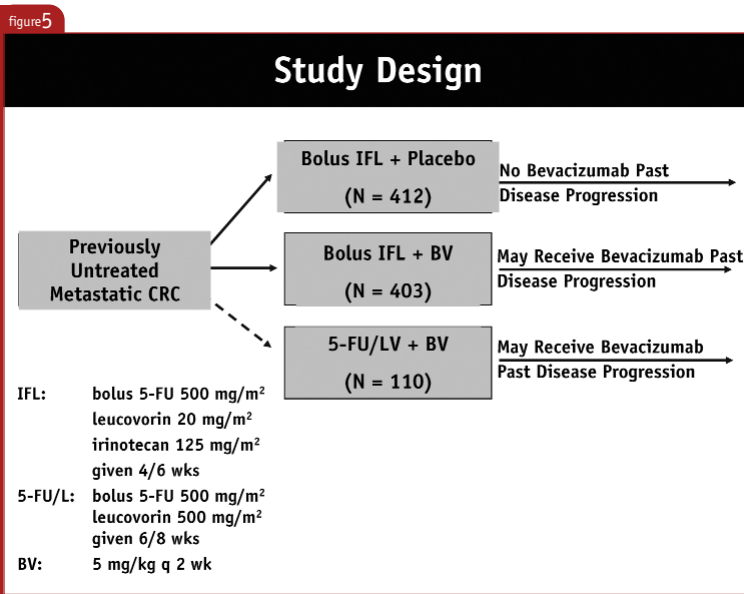
Dr Corrado Boni (Italy), followed with the results of the international randomized phase III MOSAIC trial, evaluating whether the addition of oxaliplatin (85mg/m²) to the standard adjuvant 5-FU/LV regimen reduces the risk of recurrence in patients who have undergone surgery for their primary tumor. The study enrolled 2,246 patients with stage II and III CRC who had received no prior chemo-, immuno-, or radiotherapy. The primary endpoint was disease-free survival (DFS), measured every 6 months by diagnosis of recurrence based on imaging, cytology or biopsy.

With a median follow-up of 3 years, DFS was higher in the FOLFOX4 arm (77.8%) compared to control (72.9%) and was associated with an overall 23% reduction in the risk of recurrence as shown in Figure 4. Looking at stage II and stage III patients, the reduction in the risk of recurrence was 18% and 24% respectively.

Analysis of grade 3/4 adverse events showed that neutropenia was much higher in the FOLFOX4 arm (41.0% vs. 4.7%) but was complicated by fever in only 0.7% of cases. Overall, mortality was the same for both arms (0.5%). Sensory neuropathy was also peculiar to the FOLFOX4 arm, although partial or total recovery was observed in almost all cases within a period of one year following treatment.



Source: Boni C, PICC 2003.



Source: Hurwitz H, PICC 2003.

Bevacizumab prolongs survival in first-line treatment of metastatic CRC

Angiogenesis plays a key role in the development of human cancer, since tumors need to recruit a physiological blood supply and extravasate into the circulation. Vascular Endothelial Growth Factor (VEGF) is probably the best characterized angiogenic factor, but it is only part of a complex network of tumor angiogenic interactions. Angiogenesis is one of the main outcomes of VEGF stimulation in endothelial cells, but this factor is also responsible for increased permeability, and vasodilation.

Bevacizumab (BV) is a recombinant anti-VEGF monoclonal antibody that binds and neutralizes all isoforms of VEGF. It has a pharmacodynamic half life of 14-21 days which allows 2-3 week dosing intervals. It has been shown to reduce free plasma VEGF to undetectable levels after one dose, and has therefore been evaluated as an agent in the setting of metastatic CRC.

Dr Herbert Hurwitz (United States), presented results from a double-blind, randomized placebo-controlled study of 925 metastatic CRC patients with no prior treatment (although adjuvant therapy more than a year before was permitted). Initial study arms included 1) standard irinotecan, 5FU, and leucovorin (IFL) + placebo, 2) IFL + BV, 3) 5-FU/LV + BV as shown in Figure 5.

Patients randomized to the BV arm were allowed to continue BV in combination with second line therapy at the discretion of the treating physician; patients who were not randomized to BV were not allowed to cross over to receive BV in any further setting. Eligibility criteria included untreated metastatic CRC with good performance status and adequate hematopoietic, renal and hepatic function.

Results of the study showed that median survival improved from 15.6 to 20.3 months in the BV arm with significantly improved hazard ratio of 0.65 ($p=0.00003$). Second line therapies were similar in both arms; oxaliplatin-based therapy was utilized in approximately 25% of patients in both arms. Median time to progression was 10.6 months vs. 6.2 for the control arm, with a hazard ratio was 0.54 ($P<0.00001$). Response rates were significantly improved (34.7 vs. 44.9%) as was response duration (7.1 vs. 10.4 months).

The incidence of any grade 3/4 adverse event was higher in the BV arm (85% vs. 74%; $p<0.01$), although there was no difference in adverse events or toxicities leading to study discontinuation, death on study, or 60-day mortality. It should be noted that adverse events reported for both arms were not adjusted for the time spent on treatment, which was significantly higher for patients in the BV arm. One serious adverse event possibly associated with BV was gastrointestinal perforation, reported in 6 patients in the BV arm and resulting in 1 death and 2 permanent treatment discontinuations. 3 patients were able to restart treatment without subsequent side effects.

Dr Hurwitz concluded that “the addition of bevacizumab to standard first-line chemotherapy for metastatic CRC results in a clinically meaningful and statistically significant improvement in survival,” adding that “this is the first phase III validation of an anti-angiogenesis strategy to treat human cancer.”

Eloxatin® in Adjuvant Colon Cancer Therapy: A Major Step in Patient Care

From a symposium supported by Sanofi-Synthelabo

The risk of relapse after complete surgery of colon cancer, which can reach up to 50%, depends on the stage of the disease at initial diagnosis. Both stage II and III usually correspond to the population of patients eligible for adjuvant chemotherapy and account for 50-70% of disease stage at diagnosis.

Eloxatin in metastatic colorectal cancer (CRC): A strong basis for early stage development

Phase III trials have demonstrated that Eloxatin (oxaliplatin) in combination with 5-fluorouracil (5-FU)/leucovorin (LV) is superior to 5FU/LV alone as well as to the combination of 5FU/LV/irinotecan known as IFL^{1,2}. Furthermore, the safety profile of oxaliplatin combined with 5FU/LV is predictable and manageable. These data support the investigation of the role of oxaliplatin/5FU/LV as adjuvant treatment of colon cancer.

State of the art adjuvant therapy in CRC

Since 1990, several studies were undertaken to evaluate chemotherapy in stage II/III colon cancer. These trials established the combination of 5FU/LV given for 6 months as standard adjuvant treatment of colon cancer with no specific 5FU/LV regimen proven to be superior to the other in this setting.

MOSAIC: Rationale and design

MOSAIC is a large, international, randomized trial that compares the combination of 5FU/LV (LV5FU2) to the same regimen combined with oxaliplatin (FOLFOX4) in stage II/III colon cancer. The trial was designed after the demonstration that FOLFOX4 was superior to LV5FU2 in the metastatic setting assuming that these results should translate into better outcome for patients with earlier stage disease. LV5FU2 regimen was chosen for the standard arm since it had demonstrated better tolerance and superior efficacy to the monthly bolus regimen in metastatic colorectal cancer³.

MOSAIC: The results

A total of 2246 patients were enrolled in the MOSAIC study including 40% stage II and 60% stage III. The trial is positive for its primary end-point showing an increase in 3-year DFS from 73 to 78% ($p < 0.01$) corresponding to a 23% risk reduction for

patients treated in the FOLFOX4 arm. The benefit of FOLFOX4 was observed in all subsets of patients. Furthermore, the regimen was safe since there was no increase in the rate of mortality under treatment (0.5% in both arms), limited GI toxicity and less than 2% febrile neutropenia/neutropenic infection. Grade 3 sensory neuropathy was observed in 12% of patients during treatment and was reversible in the majority of cases (1% of patients at 1 year follow-up)

Perspectives with other ongoing studies

MOSAIC is the first trial that has shown superiority of a new combination over 5FU/LV alone. Other trials comparing combination regimens to 5FU/LV are underway but their results are not known yet. Based on the MOSAIC results, several ways to further improve the outcome of patients treated in the adjuvant setting could be explored: intensify the doses of the FOLFOX regimen to shorten duration and improve tolerance of treatment (e.g.: 3 months FOLFOX7 vs. 6 months FOLFOX4⁴), improve convenience by replacing 5FU with oral fluoropyrimidines, increase efficacy of treatment by adding new biological agents to the FOLFOX combination such as in the new planned NSABP and NCCTG studies.

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The Future

For the past five years, the "*Perspectives in Colorectal Cancer*" congress has served as a forum where specialists in cancer research, leading oncologists, and practicing clinicians reviewed the state of the art and shared the newest information on the management colorectal cancer. The success has been tremendous, and the number of attendees has grown rapidly over the years. The quality of the program, the expertise of the presenters and discussants, and the efficiency of the organization have all been widely appreciated.

The rapid progress in the management of colorectal cancer has also sparked more interest and research in the treatment of other gastrointestinal cancers. Because there is currently no adequate forum for discussion of upper GI cancers, the organizers decided to expand the topic of the congress to include all gastrointestinal cancers and to rename the meeting to better reflect its truly international scope. Please join your colleagues in Barcelona, 16 to 19 June, 2004 for the "*World Congress on Gastrointestinal Cancer*."

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