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REVIEW

Colorectal cancer in Chinese patients: current and emerging treatment options

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Abstract: Colorectal cancer is the second most common cancer in Hong Kong and its incidence is rising in economically developed Chinese cities, including Hong Kong and Shanghai. Several studies conducted in the People's Republic of China have characterized the unique molecular epidemiology of familial colorectal cancer syndromes and molecular biomarkers such as microsatellite instability and genetic mutations (eg, *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *ERCC1*) in Chinese populations. Interethnic differences in anticancer drug response and toxicity have been well described in many cancers, and this review examined the literature with regard to the tolerance of Chinese patients to commonly used chemotherapeutic regimens and targeted therapies for metastatic colorectal cancer. Studies on the pharmacogenomic differences in drug metabolizing and DNA repair enzymes between Chinese, North Asians, and Caucasian patients were also reviewed.

Keywords: Chinese, colorectal cancer, treatment

Epidemiology

According to the Global Cancer Statistics, the incidence of colorectal cancer (CRC) is rising in East Asia, probably as a result of multiple factors, including the adoption of a more Western style of high-fat and low-fiber diet and an increased prevalence of obesity and smoking.[1] In the People's Republic of China, although the age-standardized incidence of CRC was reported as 27/100,000 in men and 23/100,000 in women, which is significantly less than Western Europe and Australia, the incidence of CRC in the more economically developed cities such as Hong Kong and Shanghai has risen by 10% and 50%, respectively, between the 1980s and 2002.[1] This is in contrast to the decreasing trend among Chinese emigrants living in the US between 1990–2008, where an annual percentage change of –1.9% in males and –0.7% in females has been reported.[2] A rising trend has also been observed in many countries of the Asia–Pacific region.[3] In Hong Kong, the mortality-to-incidence ratio for CRC was 41% in males and 37% in females from 2007–2011.[4]

However, a recent study has shown that the mortality of CRC in East Asian regions such as Japan, South Korea, Singapore, and Hong Kong has been declining in the last 40 years, especially in the younger age groups.[4] Improvement in early diagnosis and in the management of CRC may be contributory factors.

In this review, the authors examined the literature regarding the epidemiology and molecular characteristics of CRC in the Chinese population, and addressed the question of whether Chinese patients may have different tolerance of chemotherapy and targeted

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therapy for the treatment of CRC compared with other ethnic groups. Such knowledge may be important to clinicians and researchers who are involved in the development of new drugs in Asia. Online search engines, including PubMed and Google, were searched using key terms, including "Chinese," 'colorectal cancer', "China," and "Hong Kong." Articles published in English or Chinese from peer-reviewed journals were selected for this review.

Colorectal cancer screening in the Chinese

Various European trials have confirmed the efficacy of screening sigmoidoscopy for people aged 55–64 years in reducing the incidence of CRC,[5–7] as well as in mortality and in an intention-to-treat analysis.[5] Given the increasing incidence of CRC, there is rising support for population-based endoscopic screening in Hong Kong from the government and academic circles. A local review addressed some of the challenges of screening in Hong Kong because of the more frequent occurrence of nonpolypoid small CRC without preceding adenoma (de novo carcinoma) in Asia.[8] These lesions tend to have deep invasion early and are more difficult to detect endoscopically and radiologically. Since 2008, investigators from the Chinese University of Hong Kong have initiated a Hong Kong-wide screening program. As of 2012, over 5,800 participants have undergone fecal occult blood tests and over 4,800 have had a colonoscopy. This program has identified precancerous polyps or bowel cancer in 1,512 people out of a total of 10,732 participants.[9] Advanced CRC was identified in around 5.6% of all asymptomatic participants, and factors such as obesity, hypertension, and alcohol consumption were associated with higher incidence of advanced CRC at colonoscopy in this Chinese cohort. The Hong Kong government has recently announced a plan to initiate a pilot program of population-based CRC screening in 2014.[10]

Molecular genetics and pathology of colorectal cancer

Hereditary polyposis syndrome – prevalence in Chinese

The incidence of familial adenomatous polyposis in the People's Republic of China is approximately 1.5/100,000 population and accounts for 0.94% of all CRCs in the People's Republic of China. Malignant transformation usually occurs in the third or fourth decade.[11] Familial adenomatous polyposis is caused by germline mutation in the *APC* gene and is inherited in an autosomal dominant manner. De novo germline mutations, sporadic somatic mutations in CRC, and various novel APC gene mutations have been well characterized in Chinese patients.[11–16]

Hereditary nonpolyposis colorectal cancer (HNPCC) and genetics

HNPCC (Lynch syndrome) results from germline mutations in one or more of the DNA mismatch repair (MMR) genes – *MLH1*, *MSH2*, *MSH6*, *MLH3*, and *PMS1*. These mutations pose a heightened risk of developing malignancy because the presence of a sporadic mutation in the remaining allele results in the inactivation of that gene product. The resultant defective DNA MMR protein commonly manifests as repetitive nucleotide sequences called microsatellites, which can be found in different regions of the DNA strands forming regions of microsatellite instability (MSI). MSI increases the vulnerability of DNA strands to breakage during DNA replication, which in turn increases the risk of gene mutations and rearrangements. Mutations in *MLH1* and *MSH2* account for the majority of HNPCCs.[17] Affected subjects have an increased lifetime risk of developing colorectal, endometrial, and other cancers.

In the People's Republic of China, HNPCC accounts for 2.2% of all CRCs if the Amsterdam criteria are applied.[18] However, these criteria are not sensitive enough in reflecting the true prevalence of HNPCC in a country where national birth control policy has resulted in mostly small-sized families. Therefore, the National Hereditary CRC Network of the People's Republic of China proposed Chinese HNPCC criteria that reduced the number of affected relatives required for establishing a diagnosis of HNPCC in order to better capture affected individuals and families.[11] Furthermore, novel MMR gene mutations that were not found in international databases have been discovered from time to time in the People's Republic of China and various Asian countries, suggesting a difference in genetic polymorphisms between Caucasian and Asians. This poses difficulty in establishing genetic diagnosis of HNPCC in the People's Republic of China using Western data alone.[19–26]

MSI is a well-observed phenomenon in all CRCs and may arise from different mechanisms besides inherited mutations of the MMR genes. MSI can also result from sporadic germline mutations, somatic mutations, or epigenetic modifications of the MMR genes. Various Asian studies have investigated these diverse mechanisms of MSI in CRC in Asian patients.[27–30] It is important to detect sporadic germline mutation in MMR genes because although affected subjects do not have significant family history, their offspring could

inherit the condition in an autosomal dominant manner. The presence of MSI in CRC has been found to predict better survival following surgery in Asian and non-Asian populations.[31–33] In a study conducted in Hong Kong,[29] a high incidence of MSI-high tumors (>60%) were found in Chinese patients aged ≤31 years at diagnosis compared with 15% in patients aged ≥46 years. Germline mutations in *MSH2*, *MLH1*, or *MSH6* could be found in >80% of those patients who were <31 years in this study.

RAS, *BRAF*, and *PIK3CA* genes

Activating mutations of *KRAS*, one of the isoforms of the *RAS* oncogenes, have been shown to predict a lack of response to EGFR antibodies in advanced CRC.[34,35] Overall, around 30%–60% of CRCs harbor *KRAS* mutations, where 90% of all mutations are found in codons 12 and 13 of exon 2 and <5% are found in other locations such as codon 61, exon 3, and exon 4.[36] On the contrary, the mutation G13D in exon 2 has been associated with better response to EGFR antibodies than other *KRAS* mutations, but the data are mixed.[37,38] In addition to the exon 2 *KRAS* mutation, other mutations such as *KRAS* mutation exons 3–4 and *NRAS* mutation exons 2–4 have also emerged to be clinically relevant biomarkers of a lack of response to EGFR antibodies. For example, treating *RAS*-mutant tumor patients with panitumumab may even have a detrimental effect on survival as shown in the Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic CRC to Determine Efficacy (PRIME) study, where patients were randomized to first-line chemotherapy with or without panitumumab.[39] Survival benefit was observed only in patients without *RAS* mutation.

To date, most Chinese studies have reported a similar prevalence of *RAS* mutations in CRC as Western studies, while the prevalence of rarer mutations such as non-exon 2 *RAS* mutations, *BRAF*, and *PIK3CA* mutations are less consistent. In the largest Chinese series to date, 966 CRC tumors were analyzed and the mutation rates of *KRAS* and *BRAF* were 38.8% and 4.4%, respectively. The most common *KRAS* mutations were found in codon 12 and 13 (G12D, G12V, and G13D), and the V600E type was the most common *BRAF* mutation.[40] Despite some reports claiming a lower incidence of *BRAF* mutations in Chinese patients with CRC (<5%),[41–43] the reported incidence rate is within the range of 4.7%–10% as reported in large Western series.[44,45]

Some new and uncommon non-exon 2 *KRAS* mutations that are found in codons 45, 69, and 80 have also been identified in Chinese patients with CRC, but their clinical significance has yet to be defined.[46] *BRAF* mutation has been implicated as a prognostic marker in stage II/III and metastatic CRC in Western studies.[45,47] Some Chinese studies from Mainland China and Taiwan have also reported similar findings.[43] Table 1 summarizes the findings of various Chinese studies on *RAS* mutations.[40–43,46,48–55]

Tolerability to systemic therapy for colorectal cancer in Asians

Fluoropyrimidines and dihydropyrimidine dehydrogenase (DPD) polymorphisms

DPD is a key catabolic enzyme of 5-fluorouracil (5FU). It is encoded by the *DPYD* gene and its enzymatic activity is affected by genetic polymorphism. DPD deficiency is a syndrome with reduced DPD enzymatic activity that may cause excessive toxicity after treatment with fluoropyrimidine – typically severe diarrhea, mucositis, and pancytopenia.

The more common allelic variants that have been associated with the DPD deficiency syndrome are *2A, *9B, and *13.[56] Differences in the allelic frequency and

Table 1 Chinese studies focusing on *RAS*, *BRAF* and *PIK3CA* mutations

Author	Region	Sample size	*KRAS* mutation %	*NRAS* mutation %	*BRAF* mutation %	*PIK3CA* mutation %
Gao[40]	People's Republic of China	966	38.8		4.4	
Shen[41]	People's Republic of China	676	35.9	4.2	7	9.9
Zhu[55]	People's Republic of China	557	40.4		5.1	
Hsieh[42]	Taiwan	182	33.5		1.1	7.1
Shen[52]	People's Republic of China	118	34.7		1.7	
Yunxia[46]	People's Republic of China	101	32.7			
Ko[49]	Hong Kong	99	30 (codon 12)			
Yen[50]	Taiwan	95	43.2			
Li[53]	People's Republic of China	90	33.3			
Li[51]	People's Republic of China	78	33			
Liao[48]	People's Republic of China	61	19.7		4.7	
Lin[54]	Taiwan	42	38.1		7.1	0

DPD activity between Asians and Caucasians have been previously reported.[57–60] This may partially explain the observed differences between Asians and Caucasians in the tolerance of fluoropyrimidines.

Toxicities such as diarrhea, neutropenia, and hand–foot syndrome seem to be more common in Caucasians compared with Asians.[61–63] There is a paucity of studies in Chinese populations. In one study of 142 patients with CRC, the prevalence of *DPYD* mutations was 2.8%. No correlation between the presence of *DPYD* mutations and toxicity to 5FU was found.[64]

Capecitabine-related toxicity in Chinese

In a US study of 1,189 patients with CRC who received adjuvant capecitabine or 5FU, Haller et al reported that East Asians are less likely to develop serious adverse events, including hand–foot syndrome, from fluoropyrimidines than other populations.[61] The incidence of hand–foot syndrome of any grade or grade III in severity in Hong Kong Chinese receiving capecitabine in the palliative or adjuvant setting has been reported to be between 32%–49% and 1%–3%, respectively.[65,66]

S-1 (TS-1)

S-1 is an oral fluoropyrimidine, consisting of tegafur (ftorafur), gimeracil (5-chloro-2,4-dihydroxypyridine), and potassium oxonate at a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5FU, gimeracil is an inhibitor of DPD, and potassium oxonate inhibits phosphorylation of intestinal 5FU and may contribute to treatment-related diarrhea.

The pharmacokinetics and pharmacodynamics of S-1 were compared in Asians and Caucasians by Chuah et al.[62] Drug exposure for tegafur was significantly higher in Asians, while that for fluoro-b-alanine (a 5FU metabolite implicated in various toxicities) was significantly higher in Caucasians, but there was no difference in exposure to 5FU. Grade III/IV gastrointestinal toxicities occurred in 21% of Caucasians and 0% of Asians. This result is in line with the general trend of better tolerance of fluoropyrimidines amongst Asians compared with Caucasians. The majority of Phase II/III studies using S-1 are from Japan and Korea. Various dosing schedules of S-1 have been evaluated and the incidence of grade III/IV diarrhea in S-1 is generally around 10% when used as monotherapy, and around 17% when combined with irinotecan. Grade III/IV neutropenia is uncommon with single agent S-1, but the incidence has been reported to be 9%–53% when combined with irinotecan. Treatment-related mortality is low, with one report suggesting a 4% incidence rate in a study of 70–85 year olds.[67]

Irinotecan and pharmacogenomics

Genetic polymorphisms in the enzyme UGT1A1, such as the *UGT1A1**28 allele, results in reduced UGT enzymatic activity causing excessive irinotecan toxicities – typically severe neutropenia, while severe diarrhea is less common in Chinese subjects.[68]

Patients who are homozygous for the *UGT1A1**28 allele ([TA]7/7) are at increased risk of neutropenia; thus, the initial dose should be reduced. Heterozygous carriers of the *28 allele may have an increased risk of toxicity as well, but most patients tolerated normal starting doses. Genetic variation at the *28 allele is more commonly found in Caucasians compared with Asians. It has been estimated that homozygosity of the *28 allele can be found in around 10% of the North American population, while 40% of the population could be heterozygotes.[69] A series reported the rate of *28 allelic frequency in the Chinese to be around 10.5%.[70] In a multiethnic study that included 39 Chinese subjects, the incidence of homozygosity of *UGT1A1* ([TA]7/7) was found to be 8% in Chinese, 5% in Asians, and 13% in Caucasians.[71]

The observed differences in toxicities and underlying genetic constitution between Asians and Caucasians have prompted multinational collaborative research into pharmacogenomic variations between the different populations. A study has identified many differences in the frequencies of several key functional polymorphisms of genes encoding enzymes such as UGT1A1, cytochrome P450s, N-acetyltransferase, glutathione S-transferase (GSTM1/GSTT1), and human leukocyte antigens between East Asians and Europeans. Interestingly, the frequencies of these genetic polymorphisms are quite similar amongst East Asians such as the Chinese, Japanese, and Koreans.[72]

Oxaliplatin

Infusional leucovorin/5FU/oxaliplatin (FOLFOX4) has been found to be well tolerated in Asians in a meta-analysis that compared the tolerability of FOLFOX4 in Asian and Western populations.[73] Toxicity profiles were largely similar with the exception of grade III neurosensory toxicity and diarrhea, which appeared to be significantly lower in Asian than in Western populations. Severe anaphylactic reaction to oxaliplatin was reported to be 1.9% in a Taiwanese series of 412 Chinese patients, which is comparable to what has been generally reported for other non-Chinese populations.[74]

ERCC1 gene polymorphism has been extensively investigated as a potential predictive biomarker for oxaliplatin and platinum agents in a variety of cancers. Protein products of these genes are responsible for nucleotide excision repair of damaged DNA, especially those caused by platinum DNA adducts, and thus are implicated in overcoming the anticancer effect of platinum chemotherapy. Two Chinese studies have reported that the *ERCC1* codon 118C → T polymorphism was associated with higher expression of ERCC1 protein and lower response rate and survival in Chinese patients who received FOLFOX4 for CRC.[75,76] Another study reported that certain *ERCC1* and *XRCC* genotypes may be associated with better survival.[77] In a retrospective series of 180 Chinese patients with stage III CRC who received adjuvant FOLFOX4, ERCC1 overexpression was found to be an independent predictor of poorer disease-free survival and overall survival (OS).[78]

Antiangiogenesis agents – bevacizumab, aflibercept, and regorafenib

Results from the Phase III Avastin® in Combination With Chemotherapy in Chinese Patients with Metastatic CRC (ARTIST) and S-1/Oxaliplatin (SOX)/Bevacizumab versus FOLFOX/Bevacizumab in Treating Patients With Metastatic CRC (SOFT) trials have provided data regarding the tolerance of bevacizumab among Asians.[79,80] The ARTIST trial evaluated the benefit of first-line bevacizumab plus irinotecan-based chemotherapy over chemotherapy alone in metastatic CRC, while the SOFT trial examined whether SOX/bevacizumab was noninferior to modified FOLFOX6/bevacizumab as first-line treatment of metastatic CRC. From these trials, the incidence of grade III/IV bevacizumab-related toxicities was comparable to Western Phase III studies. To date, there is no published data on the tolerability of Chinese patients to aflibercept and regorafenib. As shall be discussed in the subsequent section of this review, Phase III studies of these two agents are ongoing in the People's Republic of China and Asian–Pacific regions.

EGFR antibodies – cetuximab and panitumumab

In Hong Kong and some major oncology centers in the People's Republic of China, the *KRAS* mutation is now routinely determined in patients prior to starting EGFR antibody treatment for metastatic CRC. In the largest study involving Chinese (ie, Mainland, the People's Republic of China, and Taiwan) and Asian–Pacific patients to date, the Asian Pacific Erbitux in Colorectal cancer (APEC) study was an open-labeled Phase II study of 289 patients with *KRAS* wild-type metastatic CRC who were treated with cetuximab and chemotherapy of the physician's choice (FOLFOX or irinotecan/infused 5FU/leucovorin [FOLFIRI]).[81] The incidence of cetuximab-related toxicities was comparable to that reported in Western Phase III studies.

Treatment options in adjuvant therapy

A population-based study in the US has shown that East Asian Americans with colon cancer had significantly better prognosis than White or African Americans, suggesting a racial disparity in the treatment outcome for CRC.[82] However, there is a lack of population-based studies conducted in the People's Republic of China. In a retrospective analysis of 100 Chinese patients in Hong Kong who received adjuvant capecitabine/oxaliplatin (XELOX) for stage III colon and upper rectal cancers, the 4-year disease-free survival was found to be 81% and 67% for colon and rectal cancers, respectively, while the 5-year OS for the whole group was 84%.[66] In Hong Kong, most patients have ready access to Western style oncological care since public health care is heavily subsidized by the government. Chemotherapeutic agents such as capecitabine and oxaliplatin are categorized as "special drugs" by the public Hospital Authority and are thus offered free of charge for the treatment of stage III/IV CRC. Therefore, there is a preference for prescribing oral 5FU as a chemotherapeutic backbone over an infusional regimen such as FOLFOX (which requires central venous access and ambulatory infusion pump) amongst oncologists working in the public sector. In the US and Japan, other oral drugs of 5FU such as tegafur/uracil and S-1 have been evaluated in the Phase III adjuvant setting with positive results.[83,84] However, these agents are not widely available for the treatment of CRC in Hong Kong at present.

Treatment options for metastatic disease

FOLFOX, XELOX, and FOLFIRI are commonly used chemotherapeutic regimens for unresectable metastatic CRC.[85–89] Before targeted therapy became available, FOLFOX and FOLFIRI were found to yield similar results in terms of progression-free survival (PFS) and OS when used in the first-line setting.[90] Therefore, exposure to all three cytotoxic agents (ie, 5FU, oxaliplatin, and irinotecan) – rather than the sequence – exerts more impact on survival.[91] The use of oral 5FU as a backbone has also been confirmed in studies that showed that XELOX is noninferior to FOLFOX in both first-line[92–94] and second-line[95] settings.

Oral 5FU – S-1 and tegafur/uracil

To date, many studies have been published on the use of S-1 and tegafur/uracil in Korean and Japanese patients, but few in Chinese patients with metastatic CRC. The SOX regimen has been shown to be noninferior to CAPOX in a multicenter, open-label, randomized controlled Phase III trial in Korea,[96] where 340 patients were randomized to SOX and XELOX. The median PFS was 8.5 months in the SOX group and 6.7 months in the XELOX group, a result which met the noninferiority criteria. Overall response rate was significantly higher in the SOX arm (47%) than in the XELOX arm (36%). Although hematological toxicity and hand–foot syndrome were lower in the SOX arm, grade III/IV neutropenia and thrombocytopenia were significantly higher. The addition of bevacizumab to the SOX regimen has been shown to be noninferior in terms of PFS to modified FOLFOX6/bevacizumab in the first-line treatment of metastatic CRC.[80] S-1 combined with irinotecan was found to be noninferior to FOLFIRI in a Japanese randomized Phase II/III trial.[97] The rate of grade III/IV neutropenia was significantly lower in the S-1/irinotecan arm (36%) compared with the FOLFIRI arm (52%), but diarrhea was significantly worse (21% versus 4.7%, respectively).

Oxaliplatin- and irinotecan-based regimens

Besides the ARTIST study,[79] the majority of studies published to date in Chinese patients are single-arm Phase II studies. There is no definite evidence from the literature that Chinese patients respond differently to FOLFOX and FOLFIRI than other ethnic groups.[73,98–101]

In a relatively small survey of a few Asian centers conducted in 2010 on the patterns of use of chemotherapeutic regimens for metastatic CRC,[102] FOLFOX was found to be the most popular first-line regimen in Taiwan, while FOLFOX and FOLFIRI were equally popular in Hong Kong. However, this pattern has changed in Hong Kong, where the costs of irinotecan, oxaliplatin, and capecitabine are now reimbursed by the government for the treatment of metastatic CRC in public hospitals. Therefore, capecitabine-based regimens such as XELOX and irinotecan/capecitabine (XELIRI) are often the preferred regimens in Hong Kong given its convenient administration in the outpatient setting.

Antiangiogenesis agents – bevacizumab, aflibercept, and regorafenib

Bevacizumab in combination with first-line chemotherapy (5FU/leucovorin, capecitabine, FOLFIRI, IFL, FOLFOX, XELOX) improved response rate and PFS when compared with chemotherapy alone.[103–107] OS benefit was demonstrated when bevacizumab was added to IFL, FOLFIRI, or 5FU/leucovorin. In the People's Republic of China, the multicenter, randomized, open-label Phase III ARTIST trial examined the benefit of first-line bevacizumab plus irinotecan-based chemotherapy over chemotherapy alone in 214 patients.[79] The addition of bevacizumab significantly increased response rate from 17% to 35%, prolonged median PFS from 4.2 months to 8.3 months, and increased OS from 13.4 months to 18.7 months. In a report from Taiwan where bevacizumab is reimbursed by the government for the first-line treatment of metastatic CRC when combined with irinotecan-based chemotherapy, the efficacy and toxicity of bevacizumab-based chemotherapy seemed to be comparable with the Western studies.[108]

In another study, Claret et al investigated whether there is any ethnic difference in some new metrics for correlating tumor size response and OS in Western and Chinese patients who underwent bevacizumab treatment and chemotherapy for metastatic CRC.[109] They found that the time to tumor growth was the best metric to predict OS in bevacizumab-treated patients irrespective of their ethnicity. This could be a relevant factor when designing and interpreting the results of clinical trials of bevacizumab in metastatic CRC. A randomized Phase III study of first-line bevacizumab in combination with FOLFIRI versus FOLFIRI alone in Chinese patients with metastatic CRC has completed enrollment and its result is pending (NCT00642577).[110]

The randomized Phase III Aflibercept Versus Placebo in Combination With Irinotecan and 5FU in the Treatment of Metastatic CRC After Failure of an Oxaliplatin-based Regimen (VELOUR) trial demonstrated the addition of aflibercept to second-line FOLFIRI increased response rate, PFS, and OS when compared to FOLFIRI alone.[111,112] A multinational randomized double-blind, placebo-controlled Phase III study named Aflibercept Versus Placebo With FOLFIRI in Patients With Metastatic CRC Previously Treated With an Oxaliplatin Chemotherapy (AFLAME) – with a similar design to the pivotal VELOUR study – is currently ongoing in multiple centers from the People's Republic of China, Hong Kong, Taiwan, and other East Asian countries.[113] The primary endpoint is PFS and this trial has just completed accrual (NCT01661270).

The registration Phase III study named the Patients With Metastatic CRC Treated With Regorafenib or Placebo After Failure of Standard Therapy (CORRECT) trial[114] has shown that the multitargeted VEGF receptor regorafenib can mod-

estly improve PFS and OS when compared to best supportive care in patients who had exhausted all systemic options for metastatic CRC. A registration Phase III study named Asian Subjects With Metastatic CRC Treated With Regorafenib or Placebo After Failure of Standard Therapy (CONCUR) has just completed accrual in the People's Republic of China, Hong Kong, and other Asian–Pacific centers. This study compared regorafenib with best supportive care in patients with metastatic CRC who had been previously treated with at least two lines of chemotherapy (NCT01584830).[115] The primary endpoint is OS and the result will be available in 2014.

EGFR antibodies – cetuximab and panitumumab

In a survey of oncology centers from Asia, Europe, and Latin America conducted just around the time when the US Food and Drug Administration updated the labels of cetuximab and panitumumab on the mandatory testing of *KRAS* mutation in 2009, <50% of all sites surveyed in the People's Republic of China and some Asian centers (Philippines, Singapore, Hong Kong, and Korea) would perform this analysis before starting EGFR antibodies.[116] Of the Chinese sites that participated (the People's Republic of China and Hong Kong) in another Asian-based survey, cetuximab was used mainly in the second- to third-line setting since panitumumab was not available at the time, while bevacizumab was used less commonly in the first-line setting compared to Western countries.[102] These studies need to be interpreted with caution since only a few centers were invited and thus may not be representative of the standard of practice across the People's Republic of China. Nowadays, in the public hospitals of Hong Kong, RAS (*KRAS* and *NRAS*) mutation testing is mandatory in every patient prior to starting EGFR antibodies for metastatic CRC.

In the APEC study as described above,[81] the response rates of FOLFOX/cetuximab (n=188, 61.2%) and FOLFIRI/cetuximab (n=101, 54.5%) were comparable to that reported in other randomized studies conducted in the West, such as the Oxaliplatin and Cetuximab in First-line Treatment of Metastatic CRC (OPUS; FOLFOX/cetuximab response rate 57%) and Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic CRC (CRYSTAL; FOLFIRI/cetuximab response rate 57.3%) studies.[116–120] There was no difference in PFS or OS, although the study was not powered to detect a survival difference. The R0 resection rate for liver metastases was higher (11.7%) in the FOLFOX/cetuximab arm than in the FOLFIRI/cetuximab arm (6.9%). It is interesting to note that the Asian investigators of the APEC study preferred to use oxaliplatin as a partner with cetuximab in the first-line setting in this study. Furthermore, this study did not suggest that the combination of cetuximab and oxaliplatin was significantly inferior to a partnership with irinotecan, a controversial observation that has been supported by some Phase III studies.[121,122] Several Phase III trials evaluating first- and second-line cetuximab in combination with chemotherapy in Chinese patients with metastatic CRC are now ongoing (NCT01228734 and NCT01550055).

Limited unresectable liver or lung metastases

Resection of isolated colorectal liver/lung metastases could produce long-term relapse-free survival in up to 25%–50% of patients.[123] Therefore, resection is recommended for patients with resectable liver or limited lung metastasis. However, for those with unresectable metastases, conversion therapy using a regimen with high response rates (eg, bevacizumab or cetuximab/panitumumab in combination with chemotherapy) may render the disease resectable. The optimal choice of therapy depends on the tumor and patient characteristics, including *RAS* mutational status. In order to definitely address the question of whether the addition of EGFR antibodies to chemotherapy improves survival for patients with *KRAS* wild-type metastatic CRC, a randomized Phase III trial in 138 Chinese patients with *KRAS* wild-type CRC with synchronous unresectable liver metastasis who received treatment at a single institution in the People's Republic of China has been published.[124] Overall response rate significantly favored the cetuximab arm over the chemotherapy alone arm (57% versus 29%, respectively), and the complete resection rate also significantly increased (26% versus 7%, respectively). This study was the first to demonstrate that the addition of cetuximab prolonged the median OS (31 months versus 21 months for chemotherapy alone). As expected, patients in the cetuximab arm had a significantly higher rate of grade III/IV acneiform rash (13%), while the incidence of allergic reaction in the cetuximab arm was 2.9%. Among patients receiving cetuximab, the presence of acneiform rash was a predictive factor for higher overall response rate, but not survival. A Chinese guideline has been published on a comprehensive multidisciplinary approach to the evaluation and treatment for liver metastasis from CRC.[125]

Traditional Chinese medicine

Traditional Chinese herbal medicine is frequently utilized in the Chinese community and has been investigated

in a randomized manner in various studies. Although a meta-analysis suggested that Chinese herbal medicine may have a positive effect on survival, tumor response, and performance status, the studies were in general of low quality, making it difficult to draw conclusions.[126] This calls for high-quality randomized, double-blind, placebo-controlled trials to evaluate the benefit of Chinese herbal medicine in CRC patients.

Practice in the People's Republic of China and Hong Kong

Common practice in Asian countries was discussed in the CRC Working Group report in the 30th Asia–Pacific Cancer Conference. FOLFOX was the most popular first-line regimen. Cetuximab was mainly used as a second- or third-line regimen with reference to KRAS status. Oxaliplatin-based adjuvant chemotherapy is commonly used for stage III disease, whereas the clinical practice for stage II disease varied.[102] A guideline has been published on the management of colon cancer in the adjuvant and metastatic settings as well as a screening strategy for the Asia–Pacific region; it also summarizes the availability of national funding for chemotherapeutic and targeted agents for CRC in various Asian countries.[3] There are few published guidelines within the People's Republic of China, but some consensus statements have been published. These are not national guidelines but are from selected academic groups; therefore, they are not universally accepted. Anecdotally, the European Society for Medical Oncology and National Comprehensive Cancer Network guidelines are popularly used in some centers across Hong Kong.[127]

Conclusion

CRC is fast becoming the most common cancer in Hong Kong and its incidence is also rising in urbanized regions in the People's Republic of China. This review has highlighted the differences between Chinese and other populations, such as Caucasians, in terms of the prevalence of genetic polymorphisms involved in hereditary cancer syndromes and the metabolism of fluoropyrimidines and irinotecan. The current literature suggests that Chinese patients have better tolerance to oral 5FU than Caucasians, but whether this extends to efficacy remains unclear. Disparities in access to medical health care and government subsidies for anticancer drugs may also influence the treatment outcome for Chinese patients with CRC. The multidisciplinary model of oncological care has been practiced in Hong Kong for decades and has been adopted in many major oncology centers in the People's Republic of China.

Disclosure

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