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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Management of locally advanced and metastatic colon cancer in elderly patients

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Abstract

Colon cancer is the second leading cause of cancer mortality in the United States with a median age at diagnosis of 69 years. Sixty percent are diagnosed over the age of 65 years and 36% are 75 years or older. At diagnosis, approximately 58% of patients will have locally advanced and metastatic disease, for which systemic chemotherapy has been shown to improve survival. Treatment of cancer in elderly patients is more challenging due to multiple factors, including disabling co-morbidities as well as a decline in organ function. Cancer treatment of elderly patients is often associated with more toxicities that may lead to frequent hospitalizations. In locally advanced disease, fewer older patients receive adjuvant chemotherapy despite survival benefit and similar toxicity when compared to their younger counterparts. A survival benefit is also observed in the palliative chemotherapy setting for elderly patients with metastatic disease. When treating elderly patients with colon cancer, one has to consider drug pharmacokinetics and pharmacodynamics. Since chronological age is a poor marker of a patient's functional status, several methods of functional assessment including performance status and activities of daily living (ADL) or instrumental ADL, or even a comprehensive geriatric assessment, may be used. There is no ideal chemotherapy regimen that fits all elderly patients and so a regimen needs to be tailored for each individual. Important considerations when treating elderly patients include convenience and tolerability. This review will discuss approaches to the management of elderly patients with locally advanced and metastatic colon cancer.

Key words: Colon cancer; Elderly; Chemotherapy; Management; Toxicity

Core tip: Despite survival benefit, fewer older patients with colon cancer receive chemotherapy, likely due to concerns regarding safety and efficacy of chemotherapy. The decision to treat elderly patients with advanced and metastatic colon cancer requires the incorporation of a thorough evaluation. Fit elderly patients are especially appropriate for treatment and should be offered the same regimens as their younger counterparts. Treatment related toxicities and quality of life should be monitored very closely in elderly patients receiving chemotherapy and more frequent follow-up should be arranged. In frail elderly patients, sequential single agent chemotherapy may be more tolerable than combination therapy.

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INTRODUCTION

An estimated 142820 new cases of colorectal cancer, including 102480 new cases of colon cancer will be diagnosed in 2013 with 50830 deaths expected in the United States[1] Approximately 39% of these patients will have locally advanced disease and 19% will be diagnosed with metastatic disease. In both settings, systemic therapy has been shown to improve survival[2].

Most cancer occur in the elderly population[1]. Developed countries have accepted the chronological age of 65 and older as a definition of an elderly population[3]. Currently, more than 50 percent of all cancer diagnoses and over 70% of cancer deaths occur in those over age 65[4]. Colon cancer has a median age of 69 years at diagnosis, in which 60% are over the age of 65 and 36% are 75 years or older[1,5].

Adjuvant chemotherapy has been the standard of care for stage III colon cancer following complete surgical resection. Palliative chemotherapy also improves progression free survival (PFS) and overall survival (OS) in patients with metastatic colon cancer. However, since fewer elderly patients are included in clinical trials, establishing a standard adjuvant or palliative treatment regimen may be challenging.

Treatment of cancer in elderly patients often requires greater attention due to multiple factors, including disabling co-morbidities as well as a decline in organs function. Cancer treatment of elderly patients is often associated with more severe toxicities and hospitalizations during treatment[6]. Elderly patients also have a shorter life expectancy. These factors often influence physicians decision to withold chemotherapy. A SEER database analysis showed that the older the patient, the less likely they received chemotherapy[7,8].

BENEFITS OF CHEMOTHERAPY IN LOCALLY ADVANCED AND METASTATIC COLON CANCER

Adjuvant setting in locally advanced disease

In the 1980s, the use of fluorouracil (5-FU) and leucovorin (LV) extended survival for stage III colon cancer, even in elderly patients[9,10]. The use of 5-FU/LV in stage Ⅲ patients age 65 and older provided a survival advantage[8]. Another SEER-Medicare database analysis also found survival benefit for adjuvant therapy in patients age 75 and older[7]. The toxicities of 5FU/LV were similar in older and younger patients.

However, fewer elderly patients received adjuvant chemotherapy[7]. Since older patients are underrepresented in clinical trials, concerns regarding safety and efficacy of chemotherapy have always been raised.

Palliative chemotherapy in metastatic colon cancer

In metastatic disease, treatment options include metastatectomy (particularly in patients with isolated liver metastases) and systemic chemotherapy for palliation. For many years, 5-FU/LV was the only active regimen used in this setting.

Chemotherapy for metastatic colon cancer markedly improves outcomes over best supportive care alone[11]. The availability of newer agents, such as irinotecan, oxaliplatin, and targeted therapies, has markedly improved response rates (RR), time to progression (TTP), and overall survival (OS)[12]. Between 1995 and 2005, an analysis of patients age 65 and older who received chemotherapy for metastatic colon cancer demonstrated a 6-mo improvement in OS[13].

ACTIVE AGENTS FOR LOCALLY ADVANCED AND METASTATIC COLON CANCER

The following represent a list of active agents for colorectal cancer and their most common side effects. In general, strategies to prevent toxicities are to identify the side effects early and provide immediate symptom management as well as dose adjusment as necessary.

5FU/Leucovorin

Flurouracil (5-FU) in combination with leucovorin (LV) has been used alone for decades before the introduction of other agents in the late 1990s and early 2000. To date, 5-FU is still the backbone drug used in combination with other newer agents. Flurouracil is a pyrimidine nucleoside analog that impairs DNA synthesis *via* inhibition of thymidylate synthase and also inhibits RNA synthesis[14]. LV enhances 5-FU cytotoxicity by prolonging the 5-FU enzymatic inhibition of thymidylate synthase[15,16].

The side effects of 5-FU may vary based on the method of administration: Ⅳ bolus *vs* continuous Ⅳ infusion. Bolus 5-FU is more likely to be associated with diarrhea and myelosuppresion, which may be more pronounced in patients with dihydropyrimidine dehydrogenase (DPD) deficiency[17]. Continuous infusion 5-FU is more likely to cause hand-foot syndrome and mucositis, especially in older patients (> 70-year-old)[18,19].

Capecitabine

Capecitabine (fluoropyrimidine carbamate), an orally administered chemotherapeutic agent, is a pro-drug that is converted enzymatically to 5-FU following absorption[20]. Capecitabine is approved in the United States for first-line treatment of metastatic colon cancer as a single agent or in combination with other agents.

As monotherapy capecitabine has similar efficacy when compared to 5-FU/LV for treatment of metastatic colon cancer[21,22]. However, in patients who failed 5-FU-based regimens, replacing 5-FU with capecitabine as a second line monotherapy is an inappropriate treatment strategy due to a low objective response rate[23,24].

The most common side effect of capecitabine is grade 3 or 4 palmar-plantar-erythrodysthesia (PPED) also known as hand-foot skin reaction. Capecitabine may also cause diarrhea and mucositis. However, there is a lower incidence of grade 3 or 4 myelotoxicity when

compared with infusional 5-FU. Therefore, it is generally well tolerated. Dose tolerance is also different among patients treated in the United States *vs* Europe (a lower dose is often given in the United States)[25].

Irinotecan

Irinotecan, a topoisomerase I inhibitor, is used alone or in combination with 5-FU, as well as with targeted agents. In metastatic disease, several phase Ⅲ trials demonstrated a survival benefit for combined irinotecan plus 5-FU/LV compared to 5-FU/LV alone[26-28].

Diarrhea and myelosuppression are the dose-limiting side effects of irinotecan, which may be severe. Premedication with atropine sulfate (0.25-0.5 mg subcutaneous) often prevents the development of irinotecan-induced diarrhea. Early use of a antimotility agent such as loperamide has been shown to decrease the severity of diarrhea and is essential to prevent treatment-related mortality[29]. Blood counts should be monitored and dose modification may be required. Other toxicities include nausea, vomiting, alopecia, and asthenia. Medications for symptom management should be made available if needed[30].

Oxaliplatin

Oxaliplatin is a platinum analog approved for colon cancer in combination with 5-FU or capecitabine, with or without a targeted agent. Three clinical trials have shown a significantly greater RR and PFS but similar overall survival for oxaliplatin plus short-term infusional 5-FU and LV (FOLFOX regimen) compared to 5-FU plus LV alone in the first-line treatment of metastatic colon cancer (mCRC)[31,32].

The dose limiting toxicity of oxaliplatin is peripheral neuropathy. Patients should be closely monitored for the development of neuropathy and educated to avoid cold exposure to prevent worsening of this symptom. Although proposed as a strategy to delay peripheral neuropathy, there is no firm evidence for the use of calcium and magnesium infusions[33,34]. Dose modifications or interruption is often required when symptoms start. Oxaliplatin can also cause pancytopenia, nausea, vomiting, and fatigue. Therefore, complete blood counts should be followed and dose modification may be required[35].

ANTI-ANGIOGENESIS (ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR)

Bevacizumab

Bevacizumab is a humanized monoclonal antibody (MoAb) targeting vascular endothelial growth factor (VEGF). The addition of bevacizumab to first-line regimens used for metastatic colon cancer improves outcomes modestly. It is usually given with fluoropyrimidines alone or fluoropyrimidines in combination with oxaliplatin (FOLFOX/XELOX) or irinotecan (FOLFIRI)[36-42].

Serious adverse events of this agent include hemorrhage, gastrointestinal perforation, and impaired wound healing. Other significant side effects include hypertension and thromboembolic events (especially in patient age 65 and older). Therefore, the use of this agent should be avoided in high-risk patients (*i.e.* history of bowel perforation, non-healing wounds, history of recent cerebrovascular accident, or uncontrolled hypertension). Blood pressure needs to be monitored and anti-hypertensive agents are often required. Bevacizumab can also lead to proteinuria and regular monitoring of urine protein secretion with urine dipstick or 24-h urine protein to creatinine ratio may be required. Holding the agent at least six to eight weeks prior to elective surgery is recommended[43].

Aflibercept

Intravenous aflibercept is a recombinant fusion protein consisting of VEGF binding portions from key domains of human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1. It is approved in the United States for use in combination with FOLFIRI for the treatment of patients with metastatic colon cancer resistant to or who have progressed following an oxaliplatin-containing regimen[44,45].

Due to a similar mechanism of action as bevacizumab (anti-VEGF), aflibercept shares a similar side effect profile including hemorrhage, hypertension, thromboembolism, bowel perforation, and impaired wound healing. Identification of and early symptom management, as well as dose modification as necessary are important in managing toxicities. If patients develop recurrent or severe hypertention, treatment needs to be withheld until blood pressure is controlled and then resumed with a permanent dose reduction. Treatment should be discontinued if patients develop a hypertensive crisis, fistula formation, GI perforation, or severe hemorrhage (see manufacturer package insert).

ANTI-EGFR MONOCLONAL ANTIBODIES

Cetuximab, panitumumab

Activation of epidermal growth factor (EGF) pathway is dependent on ligand binding to its receptor (EGFR), with subsequent homo- and heterodimerization leading to activation of signaling pathways. Cetuximab and panitumumab are monoclonal antibodies directed against EGFR. However, they exert their action on both malignant and normal cells. Cetuximab and panitumumab are only effective in patients who have K-ras wild type tumor[46-48]. While cetuximab is more commonly used in combination with irinotecan based regimens, panitumumab is approved only as a single agent after failure of other regimens[48,49]. Whether panitumumab is of benefit in patients who are refractory to cetuximab is unknown[50].

Since anti-EGFR monoclonal antibodies also bind to EGFR receptors in normal tissue, these agents affect organs with abundant receptors and may cause skin and gastrointestinal toxicities (rash, dryness, pruritus, and diarrhea). Of particular interest, early identification and

proper grading of skin toxicity, as well as symptom management are important. Patients should be educated to recognize the signs and symptoms of toxicity, as well as general prevention strategies such as applying sunscreen and alcohol-free moisturizing creams[51,52]. Hypomagnesaemia is another significant toxicity of this class of drug. Frequent laboratory monitoring and repletion are often required[53,54].

RECEPTOR TYROSINE-KINASE INHIBITOR

Regorafenib

Regorafenib is a new oral multikinase inhibitor that blocks the activity of several protein kinases, including the VEGF and EGFR pathways. It is approved as a single agent for the treatment of patients with refractory mCRC[55].

The most common side effects of Regorafenib are grade 3 or 4 PPED also known as hand-foot skin reaction, fatigue, hypertension, diarrhea, and skin rash. These toxicities tend to occur during the first treatment cycle and then diminish over time[55]. Early identification, intervention, and dose reduction, are key to managing these side effects.

ACTIVE REGIMEN FOR LOCALLY ADVANCED AND METASTATIC COLON CANCER

The following regimens are summarized in Table 1.

FOLFOX

A SEER-Medicare database analysis found that the addition of oxaliplatin to 5-FU/LV adjuvant therapy in elderly patients with stage Ⅲ disease resulted only in a small but non-significant OS benefit[7].

A subset analysis of major adjuvant therapy trials also showed a lack of benefit with the addition of oxaliplatin in older patients. The NSABP C-07 trial found that the addition of oxaliplatin to 5-FU/LV did not prolong survival in patients age 70 and older with stage Ⅱ or Ⅲ colon cancer. There was actually a trend toward decreased survival[56]. A subset analysis of the MOSAIC trial did not show survival benefit with the addition of oxaliplatin for patients of age 70-75 with stage Ⅱ or Ⅲ colon cancer[57]. However, the median age of patients enrolled in the MOSAIC study was 59 with only one-third of these patients were over the age of 65. Due to the small number of elderly patients included in this retrospective analysis, the use of oxaliplatin as adjuvant treatment in elderly patients remains inconclusive.

In the metastatic setting, however, the addition of oxaliplatin to fluoropyrimidine-based regimens significantly improved outcomes without worsening toxicity in elderly and frail patients[58].

If indicated, oxaliplatin 85 mg/m^2 Ⅳ is usually given in combination with LV 400 mg/m^2 Ⅳ over 2 h and 5-FU (400 mg/m^2 Ⅳ bolus on day 1 followed by 2400 mg/m^2 continuous Ⅳ infusion over 46 h)[59]. The cycle is repeated every two weeks for a total of 12 cycles in adjuvant setting.

CAPOX/XELOX

In a randomized trial comparing capecitabine plus oxaliplatin (XELOX) *vs* FOLFOX regimen, XELOX was found to be non-inferior as a first line treatment regimen for mCRC[60]. In the adjuvant setting, the combination of oxaliplatin and capecitabine has been shown to improve disease free and overall survival with less toxicity when compared to standard bolus 5-FU/LV[61-63]. The standard regimen is capecitabine 850-1000 mg/m^2 orally twice daily, from day 1 to 14, with oxaliplatin 130 mg/m^2 Ⅳ on day 1 of every three week cycle.

Single agent capecitabine

The approved dose of oral capecitabine is 1250 mg/m^2 twice daily for 2 wk, every 21 d, either as monotherapy or in combination with other agents[21,22]. The dose is often reduced to 1000 mg/m^2 twice daily (in combination with oxaliplatin) on days 1-14 of a three week cycle[60,62,64]. No clinical trial has yet been done to compare these different dosing regimens. In one study of 51 elderly patients (mean age 76) with advanced CRC, treatment with capecitabine was well tolerated[65].

FOLFOX + bevacizumab

The benefit of adding bevacizumab to an oxaliplatin-containgin regimen has been addressed in several clinical trials and showed an improvement in RR, PFS, and OS[38-40]. However, the use of bevacizumab also increased the risk of bowel perforation, impaired wound healing, grade 3 or 4 hypertension, and bleeding events[38].

In the TREE-2 trial, bevacizumab was added to oxaliplatin and fluoropyrimidine regimens. These regimens were well tolerated as first-line treatment of mCRC with similar overall toxicity. The first-line oxaliplatin and fluoropyrimidine-based regimen with bevacizumab resulted in a median OS of approximately 2 years[38].

The dosing regimen is oxaliplatin 85 mg/m^2 Ⅳ, bevacizumab 5 mg/kg Ⅳ, LV 400 mg/m^2 Ⅳ, and 5-FU 400 mg/m^2 Ⅳ bolus on day 1, followed by 2400 mg/m^2 continuous Ⅳ infusion over 46 h; every 2 wk.

FOLFIRI + bevacizumab

A phase Ⅲ randomized clinical trial comparing the addition of bevacizumab to 5-FU-based combination chemotherapies (irinotecan, bolus fluorouracil, and leucovorin [IFL]) showed improved objective RR, PFS, and OS[42]. Another randomized trial comparing 5-FU given as continuous infusion *vs* bolus (FOLFIRI *vs* IFL), both with bevacizumab, showed a superior result with the former[66]. In the bevacizumab expanded access trial (BEAT), bevacizumab added to first-line chemotherapy showed a comparable efficacy and safety profile compared to chemotherapy alone[39].

Table 1 Chemotherapy regimen in locally advanced and metastatic colon cancer

No.	Regimen	Dosing	Frequency	Adjuvant	Palliative
1	5-FU/LV	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h	Every 2 wk	Y	Y
2	Capecitabine	Capecitabine 1000-1250 mg/m^2 by mouth twice daily for 2 wk, then 1 wk off	Every 3 wk	Y	Y
3	FOLFOX	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Oxaliplatin 85 mg/m^2 IV on day 1	Every 2 wk	Y	Y
4	CAPOX	Capecitabine 850-1000 mg/m^2 by mouth twice daily for 2 wk, then 1 wk off Oxaliplatin 130 mg/m^2 IV on day 1	Every 3 wk	Y	Y
5	FOLFIRI	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Irinotecan 180 mg/m^2 IV over 90 min on day 1	Every 2 wk	N	Y
6	FOLFOX + Bevacizumab	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Oxaliplatin 85 mg/m^2 IV on day 1 Bevacizumab 5 mg/kg IV on day 1	Every 2 wk	N	Y
7	FOLFIRI + Bevacizumab	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Irinotecan 180 mg/m^2 IV over 90 min on day 1 Bevacizumab 5 mg/kg IV on day 1	Every 2 wk	N	Y
8	CAPOX + Bevacizumab	Capecitabine 850-1000 mg/m^2 by mouth twice daily for 2 wk, then 1 wk off Oxaliplatin 130 mg/m^2 IV on day 1 Bevacizumab 7.5 mg/kg IV on day 1	Every 3 wk	N	Y
9	Capecitabine + Bevacizumab	Capecitabine 850-1000 mg/m^2 by mouth twice daily for 2 wk, then 1 wk off Bevacizumab 7.5 mg/kg IV on day 1	Every 3 wk	N	Y
10	5-FU/LV + Bevacizumab	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Bevacizumab 5 mg/kg IV on day 1	Every 2 wk	N	Y
11	FOLFIRI + Cetuximab	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Irinotecan 180 mg/m^2 IV over 90 min on day 1 Cetuximab 400 mg/m^2 IV loading on treatment day 1, then 250 mg/m^2 IV every week	Every 2 wk	N	Y
12	FOLFIRI + Ablifercept	Leucovorin 400 mg/m^2 IV over 2 h before 5-FU on day 1 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 IV over 46 h Irinotecan 180 mg/m^2 IV over 90 min on day 1 Aflibercept 4 mg/kg, over 1 h on day 1	Every 2 wk	N	Y
13	Panitumumab	Panitumumab 6 mg/kg IV	Every 2 wk	N	Y
14	Regorafenib	Regorafenib 160 mg by mouth once daily for 3 wk, then 1 wk off	Every 4 wk	N	Y

5-FU: Fluorouracil.

The dosing regimen is irinotecan 180 mg/m^2 IV, bevacizumab 5 mg/kg IV, LV 400 mg/m^2 IV, and 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 continuous IV infusion over 46 h; every two weeks[67].

CAPOX + bevacizumab

The addition of bevacizumab to either XELOX or FOLFOX4 showed improved median PFS when compared to either regimen without bevacizumab[40].

The dosing regimen is oxaliplatin 130 mg/m^2 *iv*, bevacizumab 7.5 mg/kg *iv* on day 1; capecitabine 850-1000 mg/m^2 by mouth twice daily on day 1 to 14, every three weeks.

Fluoropyrimidines + bevacizumab

Bevacizumab adds benefit to first-line 5-FU/LV or capecitabine with improvement in RR, PFT, and OR[36,37]. The addition of bevacizumab to capecitabine also improves PFS compared to capecitabine alone in elderly patients age 70 and older. However, more treatment-related adverse events, inlcuding hand-foot syndrome, diarrhea, venous thrombotic events, and hemorrage were observed with the addition of bevacizumab[68,69].

The dosing regimen is bevacizumab 7.5 mg/kg IV on day 1 with capecitabine 850-1000 mg/m^2 by mouth twice daily on day 1 to 14, every three weeks. When combine with 5-FU/LV containing regimen, the dosing is bevacizumab 5 mg/kg IV, LV 400 mg/m^2 IV, and 5-FU 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m^2 continuous IV infusion over 46 h, every two weeks.

FOLFOX + cetuximab

Several studies have shown higher RR and prolongation in PFS with the addition of cetuximab, but without significant effect on OS[70]. However, other trials showed no clear benefit in adding cetuximab to a first-line oxaliplatin-containing regimen in patients with K-ras wild-type tumors with only a modest improvement in RR[71,72]. For this reason, the benefit of adding cetuximab to a first-line oxaliplatin-containing regimen remains unclear.

FOLFIRI + cetuximab

Cetuximab can be used in combination with irinotecan for patients with wild-type K-ras tumors. Multiple phase

Ⅲ randomized controlled trials have shown improvement in RR and PFS, but failed to show significant OS benefit[73-75]. Cetuximab is given as a weekly infusion, although some data support the safety and efficacy of every other week dosing, which is often done for patients convenience.

The dosing regimen is cetuximab 400 mg/m^2 Ⅳ loading on first treatment day 1, and then 250 mg/m^2 Ⅳ weekly, with irinotecan 180 mg/m^2 Ⅳ, bevacizumab 5 mg/kg Ⅳ, LV 400 mg/m^2 Ⅳ, and 5-FU 400 mg/m^2 Ⅳ bolus on day 1, followed by 2400 mg/m^2 continuous Ⅳ infusion over 46 h; every 2 wk.

FOLFIRI + aflibercept

Aflibercept in combination with FOLFIRI is approved for treatment of patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen. A placebo controlled trial compared FOLFIRI with or without aflibercept given in patients who failed a oxaliplatin containing regimen. An improved median PFS and OS were observed in patients receiving aflibercept[44].

The dosing regimen is aflibercept 4 mg/kg, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m^2 Ⅳ, bevacizumab 5 mg/kg Ⅳ, LV 400 mg/m^2 Ⅳ, and 5-FU 400 mg/m^2 Ⅳ bolus on day 1, followed by 2400 mg/m^2 continuous Ⅳ infusion over 46 h) every 2 wk.

Single agent panitumumab

Panitumumab as a single agent is approved for treatment of K-ras wild-type mCRC. Studies evaluating the addition of panitumumab to either FOLFOX or FOLFIRI have shown improvement in PFS, but no survival benefit. However, lower survival and increased toxicity were observed when panitumumab was combined with other agents, including oxaliplatin and bevacizumab[48,76-78]. For this reason, panitumumab is not indicated for use in combination with chemotherapy. The dosing regimen is 6 mg/kg Ⅳ every 2 wk.

Single agent regorafenib

Oral regorafenib is approved for patients with metastatic colon cancer that has progressed after all standard therapies. In a randomized trial comparing regorafenib to best supportive care, regorafenib showed a modest though statistically significant improvement in PFS and median OS[55].

The dosing regimen is 160 mg once daily for 21 d of a 28-d cycle.

METASTASECTOMY

In a large international multicenter cohort study evaluating the outcome of liver surgery for metastatic colon cancer in patients age 70 and older, a 3-year survival rate of 57% and a 60-d perioperative mortality rate of 4% were observed[79]. These results were comparable to previous studies with younger age groups.

Therefore, the management of potentially resectable liver metastases in elderly patients with good performance status should be the same as in younger patients. Older patients may also benefit from neoadjuvant chemotherapy to convert borderline resectable lesions to resectable disease. Several studies showed a similar response rate and five-year OS among younger and older individuals who received neoadjuvant chemotherapy followed by liver resection[80,81].

Although there is no firm data on solitary pulmonary metastases, metastasectomy may be considered for fit older patients with isolated pulmonary metastases[82]. Older age (> 60-year-old), male, and increased lung metastases are negative predictors for survival after pulmonary metastatectomy[83].

TOLERABILITY OF CHEMOTHERAPY IN ELDERLY PATIENTS

When treating elderly patients with cancer one has to consider drug pharmacokinetics and pharmacodynamics. Elderly patients have age related changes in organ function as well as comorbidities. Drug toxicities may be due to a reduction in renal or hepatic function. Also, impaired drug efficacy may be due to age-related decreased intestinal absorption (for oral medications).

ASSESSING FUNCTIONAL STATUS OF ELDERLY PATIENTS

Since chronological age is a poor marker of a patient's functional status, several methods of functional assessment may be used.

Eastern Cooperative Oncology Group performance status

Eastern Cooperative Oncology Group (ECOG) performance status (PS) (Table 2) is useful to assess a patient's ability to tolerate chemotherapy and their short-term prognosis. Patients with a poor performance status (PS) (*e.g.*, ECOG PS > 2) usually tolerate chemotherapy poorly and have shorter median OS. Older patients with poor PS also often have more functional impairment[84].

ADL and IADL scales

Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales are more representative of a patient's functional status. ADL refers to the skills that are necessary for basic living such as self-care and include feeding, grooming, transferring, and toileting. IADL refers to the skills required to live independently in the community including shopping, managing finances, housekeeping, preparing meals, and the ability to take medications.

Comprehensive geriatric assessment

Assessment of functional status with the ADL and IADL

Table 2 Eastern Cooperative Oncology Group performance status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

scales is a component of the comprehensive geriatric assessment (CGA) scale that is used by geriatricians to identify frail older patients at high risk of adverse outcomes such as falls, hospitalization, and death. The task force of International Society of Geriatric Oncology recommends the use of CGA in the care of older cancer patients[85].

CHEMOTHERAPY SELECTION IN ELDERLY PATIENTS

There is no ideal chemotherapy regimen that fits all patients and so a regimen needs to be tailored to each individual. Important considerations when treating elderly patients include convenience and tolerability. While using a 5-FU based regimen, patients will require a portable outpatient infusion pump and an indwelling venous catheter. Otherwise, patients will have to be admitted to the hospital for at least 48 h in order to complete a 5-FU continuous infusion. In our institution, bolus 5-FU is often omitted if there is a concern for increased toxicity in the metastatic setting.

Capecitabine, on the other hand, is given orally. Often times, this drug may be a better alternative for selected patients. However, since capecitabine has to be taken twice daily for 14 d, compliance may be an issue. We recommend that patients who are treated with oral capecitabine use a pill container with scheduled compartments to help with compliance. Nursing staff can also monitor the frequency of refills. In our center, patients are given an individualized chemotherapy calendar.

In the adjuvant setting, we recommend 5-FU continuous IV infusions or oral capecitabine alone for six months for patients age 70 and older.

In the metastatic setting, FOLFOX has a comparable activity to FOLFIRI[86,87]. The choice of which to use should be based upon the expected toxicities of each regimen and the patients comorbidities. If there are no contraindications, bevacizumab may be added to either regimen. A fluoropyrimidine can be given to a patient either *via* an intravenous infusion (5-FU) or by an oral route (capecitabine). If patients are not considered candidates for more intensive therapy due to a poor functional status, then oxaliplatin or irinotecan should not be given. In that case, either an intravenous 5-FU infusion or oral capecitabine with or without bevacizumab is an appropriate option.

Short term 5-FU/LV continuous infusion is preferable to a 5-FU bolus due to a favorable toxicity profile[88].

When patients progress, FOLFOX can be changed to FOLFIRI, or vice-versa, while maintaining treatment with bevacizumab[89]. If the patient is initially treated with a fluoropyrimidine alone, then the addition of either oxaliplatin or irinotecan could be considered. This is especially relevant if the patient has an improvement in functional status. If the patient has a K-ras wild type tumor, cetuximab can be added to FOLFIRI, especially if a FOLFIRI-based regimen was not used first-line. Another alternative is to give FOLFIRI plus ziv-aflibercept when a FOLFOX regimen has already been given as first-line therapy and the patient has progressed.

If the patients functional status declines or does not improve, therapy with single agent panitumumab, cetuximab, regorafenib, or even best supportive care (BSC), are options.

BEST SUPPORTIVE CARE

Many clinical trials were designed to compare drug therapy versus BSC, especially for patients resistant to multiple lines of chemotherapy[90]. BSC is palliative treatment without using chemotherapy with the intent to maximize quality of life (QOL). Appropriate BSC includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and also focal external-beam radiation for symptomatic control[91].

Symptom assessment and management is paramount to provide BSC. Once assessed, symptoms should be managed in accordance with one of the many existing evidence-based guidelines[92].

WHOM TO TREAT

There is a general agreement that frail older patients, those with significant functional impairment or an ECOG PS of 3 to 4, should be offered palliative measures aimed at maintaining QOL. Most of the time, they have poor tolerance to aggressive treatment for their cancer. However, active and fit older patients with minimal comorbidities should be treated in the same fashion as younger patients with metastatic colon cancer[93]. Patients with metastatic colon cancer who have a PS of 2 or less should be considered for chemotherapy, particularly if their PS decline is believed to be cancer related.

Table 3 Most common side effects of active agents in colon cancer and their management

Agent	Major side effects	Management
Fluoropyrimidine	Stomatitis, diarrhea, hand-foot syndrome	Identification and early symptom management
5-FU	Vomiting	Dose interuption or reduction if progression (grade 2 or worse)
Capecitabine	Pancytopenia	Adjustment of route of administration: bolus vs continuous infusion
		Predetermined treatment parameter
Oxaliplatin	Peripheral neuropathy (dose limiting)	Education about exposure to cold, dose modification, "stop and go" strategy, and use of neuromodulatory agents
	Pancytopenia	Predetermined treatment parameter
	Nausea, vomiting, diarrhea, fatigue	Identification and early symptom management.
		Dose interuption or reduction if progression (grade 2 or worse)
Irinotecan	Diarrhea	Premedication with atropine sulfate
	Pancytopenia	Proper instruction for the use of anti-motility agent to control diarrhea
		Predetermined treatment parameter
Anti EGFR	Skin toxicity (rash, dryness, pruritus)	Identification and early symptom management
Cetuximab	Mucositis	Proper instruction for the use of anti-motility agent to control diarrhea
Panitimumab	Diarrhea	Dose interuption or reduction if progression (grade 2 or worse).
Anti VEGF	Wound healing impairment	Blood pressure monitoring and adding anti-hypertensive agent if needed
Bevacizumab	Thromboembolism	Avoid in high risk patients.
Ziv-aflibercept	Bowel perforation	Close monitoring if used in patients at risk
	Proteinuria	Regular monitoring of urine protein secretion with urine dipstick or 24HR
	Hypertension	urine protein to creatinine ratio
		Holding medication prior to elective surgical procedure (6-8 wk)
		Appropriate healing time before re-starting medication post-op
Receptor TKI inhibitors	Hand-foot skin syndrome, rash	Identification and early symptom management
Regorafenib	Diarrhea, hypertension	Dose modification

5-FU: Fluorouracil; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; TKI: Tyrosine-kinase inhibitor.

Although the incidence of postoperative morbidity and mortality increases with advancing age, elderly patients still benefit from surgery and therefore should be evaluated for resectability[94].

STRATEGIES IN TREATING ELDERLY PATIENTS

After carefully selecting an appropriate chemotherapy regimen for elderly patients, the following are additional strategies to improve tolerability and successful completion of a planned treatment.

Prepare the patient for what to expect

Discussing chemotherapy and their side effects during an office visit will encourage patients to read the drug fact information sheets provided. When patients understand what to expect during treatment and what actions to take when they experience side effects they will be reassured and less anxious. In our center, patients are encouraged to participate in the chemotherapy teaching class led by oncology certified nurses.

Early side effect management

Elderly patients are more susceptible to toxicities when receiving chemotherapy. For example, patients age 70 and older with metastatic colon cancer on 5-FU-based chemotherapy are more prone to diarrhea, vomiting, stomatitis, and neutropenia[95,96]. Therefore, a follow up appointment should be scheduled early, especially during the initiation of a new regimen. Patients should have access to immediate medical attention when the expected side effects occur. We summarize the most common side effect profiles of active agents in colon cancer and their managements in Table 3.

CONCLUSION

Treating elderly patients with advanced and metastatic colon cancer is often challenging due to a lack of strong evidence from which to choose the most appropriate regimen. Elderly patients with locally advanced and metastatic colon cancer will benefit from chemotherapy and biologic agents. Fit elderly patients are especially appropriate for treatment and should be offered the same regimens as their younger counterparts. Treatment related toxicities and QOL should be monitored very closely in elderly patients. For this reason, more frequent follow-up of elderly patients receiving chemotherapy should be arranged. In frail elderly patients, sequential single agent chemotherapy may be more tolerable than combination therapy.

The decision to treat elderly patients with advanced and metastatic colon cancer requires the incorporation of a thorough evaluation of the patients functional status, including ECOG PS and also ADL/IADL capacity as well as estimated life expectancy. Chronological age does not always correlate with a patient's functional status. If a patients decline in functional status is due to cancer, chemotherapy should be considered since a treatment response may lead to clinical improvement.

Elderly patients with locally advanced and metastatic colon cancer attain significant benefit from chemotherapy and biologic agents. Chronological age does not always correlate with a patient's functional status. Fit

elderly patients should be offered the same regimens as their younger counterparts. A chemotherapy regimen should be carefully selected based on patients characteristic and underlying medical problems. Frequent follow-up for elderly patients receiving chemotherapy is often required. If a patients decline in functional status is due to cancer, chemotherapy should be considered since a treatment response may lead to clinical improvement.

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