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**Title: Metastatic Colorectal Cancer Management and Nursing
Implications**

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Abstract

The treatment of metastatic colorectal cancer (mCRC) has improved significantly in the past two decades. Several new targeted drugs and chemotherapy agents have been approved since the late 1990's resulting in significant improvements in overall survival. However, these advancements have also resulted in considerable physical, psychological and economical implications for patients and their family as treatment may now extend over many years. Oncology nurses are ideally placed to help and support patients to manage the side effects of treatment through comprehensive assessment, education and prompt management thereby maintaining the highest quality of life for the patient.

Epidemiology

Colorectal cancer is the third most common malignancy in men and the second most common malignancy in women with over 1.3 million cases diagnosed worldwide in 2012 with over 600,000 deaths per year. It accounts for 9-10% of all malignancies diagnosed and accounts for 9% of deaths (Ferlay et al 2012). For both men and women the lifetime risk of developing colorectal cancer is 5% with a median age of diagnosis aged 70 years and death aged 75 years. The 5 year relative survival rate is 91% when colorectal cancer is diagnosed at an early stage and declines to 70% in patients with regional disease (Cersosimo 2013a). The 5-year survival for patients who present with distant metastasis is only 11% (Grennon 2013). Approximately 20% of patients present with advanced disease at the time of diagnosis (McRee and Goldberg 2011). Colorectal cancer is both sporadic (accounting for 88-94% of cases) and familial (accounting for 1-6% of cases). Moreover, almost 55% of cases occur in more developed regions with the highest incidences in Australia and New Zealand and the lowest rates in Western Africa (Ferley et al 2012).

Survival rates vary internationally, generally being higher in North America, Australia, Japan and Northern and Western Europe and lower in Eastern Europe, Algeria and Brazil (Coleman et al 2008). In the past two decades the anatomical distribution of colorectal cancer has shifted from the distal colon to the proximal end indicating an environmental association linked in particular to dietary fat intake relative to dietary fibre. Johnson et al (2013) in their metaanalysis of 116 studies found that other environmental risk factors

include cigarette smoking, red meat intake, calorie consumption and physical activity as it relates to obesity and low fruit and vegetable consumption. There is increased recognition that the use of non steroidal anti-inflammatory agents including aspirin and cyclooxygenase-2 inhibitors may have a protective effect against colorectal adenomas and colorectal cancer (Johnson et al 2013, Tougeron et al 2014).

Staging and Treatment decisions

Staging of colorectal cancer is divided into four stages, 1-IV. Surgery alone is curative in 85% of patients with stage 1 or early stage II disease. For patients with more advanced stage II the 5 years survival rate is approximately 70-75%, for stage III disease the 5 year survival rate is 30-50% with resection alone. Based on numerous studies in the adjuvant setting the standard adjuvant chemotherapy for stage III colon cancer is an oxaliplatin-containing regimen (FOLFOX, XELOX) administered over 6 months resulting in an absolute benefit of 8-10% (Cersosimo 2013a).

Traditionally patients with metastatic colorectal cancer were considered incurable however some patients can be cured of their disease if their metastases are amenable to complete surgical resection (Venook 2007). Nevertheless, for the majority of patients the goal of their treatment is palliation using systemic chemotherapy. The prognosis for colorectal cancer patients with stage IV disease without specific therapy is poor with a median survival of 5-6 months (McRee et al 2011).

Up until 1996 the treatment for metastatic colorectal cancer consisted of 5-fluorouracil (5-FU) given with leucovorin with a median survival of 12 months. With the advent of newer agents the median survival has now doubled to 24-30 months. Recent trials demonstrate patients receiving many lines of treatment using modern chemotherapy and biologic agents which enhance the efficacy of systemic chemotherapy (Bekaii-Saab 2012).

The treatment of metastatic colorectal cancer is complex and involves the integration of multiple chemotherapy drugs and monoclonal antibodies targeting the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). Input from many members of the multidisciplinary team is essential. There are now seven different classes of drugs with significant anti-tumour activity used in the management of metastatic colorectal cancer (mCRC) (Table 1).

Treatment of Resectable Disease

As outlined in Table 1, a variety of treatment options for patients with metastatic colorectal cancer is now available. In order to maximise patient benefit a clear goal orientated approach must be adapted (Mc Ree et al 2011). It is essential in the first instance to establish whether the patient with metastatic disease is potentially curable by surgical resection of metastases either at the time of diagnosis or after downsizing initially unresectable metastases by neoadjuvant chemotherapy. This will guide the choice and timing of the chemotherapy.

Table 1 Classes of drugs used in mCRC (from Cersosimo 2013a)

- Fluoropyrimidines- including FU which is usually given with leucovorin (LV), Capecitabine, S-1 and tegafur plus uracil (UFT)
- Irinotecan
- Oxaliplatin
- Cetuximab and panitumumab-monoclonal antibodies directed against the epidermal growth factor receptor (EGFR)
- Bevacizumab-a monoclonal antibody targeting vascular endothelial growth factor (VEGF)
- Afibercept- a recombinant fusion protein consisting of VEGF binding portions from the human VEGF receptors 1 and 2 fused to the Fc of human IgG1 immunoglobulin that prevents intravascular and extravascular VEGF-A, VEGF-B and PlGF from binding to their receptors
- Regorafenib - an orally active inhibitor of angiogenic tyrosine kinases (including VEGF receptors 1 to 3) as well as other membrane and intracellular kinases

Patients who are potential curable will require the most appropriate treatment that offers the highest response rate and carries the greatest potential to downsize the metastasis. Conversely, patients with no curative option need treatments that offer the longest progression free survival and favourable toxicities in order to extend the duration and quality of life. A multidisciplinary approach to care is required for these patients to determine the proper timing and sequencing of treatments with close collaboration needed between the

liver surgeon, colorectal surgeon and medical oncologist in order to optimise results for the patient (Goldberg et al 2007, Saltz 2014).

For a subgroup of patients with metastatic colon cancer confined to the liver the role of hepatic resection and hepatic directed chemotherapy continues to evolve (Ariyan and Salem 2006). The average 5 year survival for patients who undergo a hepatic resection is approximately 30%. However, there is less favourable prognosis for patients with multiple lesions, a short interval between diagnosis of the primary tumour and recurrence and the presence of stage 111 disease at the time of initial diagnosis. Recent data has shown that resection in patients with a greater volume of disease is possible with the main consideration now being whether enough viable liver can be preserved to provide adequate liver function (Kemeny 2013). Preoperative chemotherapy can be used to downsize initially unresectable metastases in order to make them amenable to surgical resection and studies have shown that patients who undergo successful neoadjuvant therapy and have a RO (microscopically marginally negative) resection have the same overall survival of patients with initially respectable metastases (Adam et al 2001).

Predictive markers for response

Data from recent clinical trials has resulted in a more individualised and tailored approach to the treatment of metastatic colorectal cancer by identifying patients who are most likely to benefit from antibodies against the Epidermal Growth Factor Receptor (EGFR), cetuximab and panitumumab. The EGFR is a member of the ErbB family with tyrosine kinase activity. The

receptor is activated when the ligand binds to the receptor causing dimerisation and phosphorylation leading to the activation signalling pathway, responsible for cell growth and proliferation. KRAS is an oncogene present in colon cells. This oncogene is involved in cell proliferation and can be switched off in its normal wild type form. When this oncogene is mutated it is permanently turned on which can lead to the development of malignancy. It is known that approximately 30-50% of colorectal cancers have a mutated gene known as the *K-ras* gene. Patients with KRAS mutations do not respond to EGFR target therapies cetuximab and panitumumab. All colon cancer patients with metastatic disease therefore should have tumour tissue obtained and tested for RAS mutations before a decision is made to start EGFR antibody therapy (Lordick 2009, Cartwright 2012). However, *K-ras* wild type is not completely predictive of clinical response and other mutations in the pathway are being explored, i.e. the PIK3CA mutation is present in 10% to 20% colorectal patients and evidence is emerging that this mutation may also be a predictive biomarker (Wujcik 2014). BRAF (oncogene) mutation status should also be determined as response to anti-epidermal growth factor receptor therapy in the non first line setting for BRAF mutated colorectal cancer is virtually nonexistent (Bekaii-Saab 2012, Cersosimo 2013a). Resistance to anti-EGFR therapies can also be mediated by lower frequency mutations in KRAS outside exon 2 (a part of the gene that codes for proteins) and in NRAS (a closely related oncogene to KRAS) (Vauthey et al 2013). The testing of all RAS mutations is now the preferred option (NCCN 2014).

Management of Unresectable Disease

The best treatment strategy for patients with metastatic colorectal cancer is to expose them to all the active cytotoxic drugs available, i.e. 5-fluorouracil or capecitabine, irinotecan and oxaliplatin (Cersosimo 2013b). This has shown to result in longer median survival when compared to patients who did not experience all three agents and helps to maximise their outcome (Goldberg et al 2007). Combination chemotherapy is the standard of care for patients. Both FOLFOX (5FU and oxaliplatin) and FOLFIRI (5FU and irinotecan) are standard first line options with comparable overall survival and response rate (Goldberg et al 2007). Subsequent lines of therapy will depend on the initial choice and response to first line therapy, the presence of KRAS mutation that would preclude anti-EGFR therapy, residual toxicities from prior therapies and the patient's performance status (Cerosimo 2013a). The triplet combination of 5FU/LV with irinotecan and oxaliplatin (FOLFOXIRI) shows high activity but also has increase toxicities including alopecia, diarrhoea and neuropathy (McRee et al 2011, Cersosimo 2013b). The use of this regimen is reserved for specific situations where dramatic tumour shrinkage is required in patients with a good performance status. For patients who are not candidates for double or triple therapy, treatment with Fluoropyrimidines (e.g. 5FU, capecitabine) alone or in combination with bevacizumab may be recommended (Goldberg et al 2007).

There is still ongoing debate over which antibody should be used in front line for these patients as some studies have shown similar results when either antibody was combined. According to the results of the recent Phase 111

FIRE study the addition of cetuximab (an epidermal growth factor receptor inhibitor) to the standard first line FOLFIRI chemotherapy regimen results in longer overall survival compared with FOLFIRI plus bevacizumab (an angiogenesis inhibitor) in patients with metastatic colorectal cancer. The results were seen in patients with wild type exon 2 KRAS gene. Median overall survival was 28.7 months for patients in the cetuximab arm compared with 25 months in the bevacizumab arm. The most common grade 3 and 4 adverse events were haematological toxicities, skin toxicities and diarrhoea (Heinemann et al 2014). Recent studies including the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study and CAIRO-2 trial combining two antibody therapies with chemotherapy have demonstrated increased toxicity, decreased response rates, median progression free survival and overall survival. The triple combination of chemotherapy and anti-EGFR and anti-VEGF antibody therapy is not at present recommended for patients with advanced colorectal cancer (Cersosimo 2013).

Maintenance therapy for patients with solid tumours has become a topic of debate in recent years. Originally, patients with solid tumours were given a certain number of cycles of chemotherapy and then treatment was stopped or continued to the point when an intolerant toxicity arose. Now as the management of toxicities improves, patients may be given an induction phase of more intensive treatment followed by a maintenance approach of a dose reduced, changed or modified schedule of treatment in the maintenance window. Maintenance treatment is well established in non small cell lung cancer however a standard practice for maintenance therapy in metastatic

colorectal cancer has yet to be established. Many studies have examined the maintenance approach, as the cumulative effects of some chemotherapy agents can be debilitating for example neurotoxicity associated with oxaliplatin. In one recent trial, the CIARO3 study, patients received oxaliplatin, fluoropyrimidine and bevacizumab and after an initial response were randomised to no further treatment versus Capecitabine and 3 weekly bevacizumab. The progression free survival (PFS) in the combination arm was 8 months compared to 4 months in the non treatment arm (Koopman 2014). Also encouraging is that this treatment regime is usually well tolerated by patients.

Patients may also be offered a drug holiday which has the potential to reduce treatment related side effects, improve quality of life as well as convenience for patients and reduce the financial burden of continuous therapy for patients (Goldberg et al 2007). This would be decided based on the extent of disease, toxicities from treatment and patient preferences. Patients need to be monitored closely off treatment in order to detect disease progression (Venook 2007).

Treatment related toxicities and nursing implications

Each of the agents available in the treatment of metastatic colon cancer has significant toxicities. Chemotherapy toxicities include mucositis, gastrointestinal upset nausea, vomiting, diarrhoea, constipation, fatigue, myelosuppression, peripheral neuropathy and hand/foot syndrome. The main adverse events reported with FOLFIRI are diarrhoea, alopecia and moderate

incidence of grade 3 or 4 neutropenia. Severe chemotherapy induced diarrhoea can adversely affect patients' quality of life and lead to potentially life threatening complications. Nurses must be skilled and up-to-date in the assessment, grading based on NCCN guidelines and evidence based management of diarrhoea (Hallquist Viale and Sommers 2007).

More specifically, Irinotecan is metabolised by the liver and reduced doses are needed in the setting of hyperbilirubinemia. Oxaliplatin is less likely to cause diarrhoea and alopecia. However, in combination with 5FU, neutropenia rates are relatively high although febrile neutropenia is rare. It is safe in patients with renal or hepatic dysfunction. The dose limiting side effect of oxaliplatin is a cumulative late onset predominately sensory neuropathy which may require drug discontinuation. It occurs frequently above cumulative doses of 680mg/m². Patients with pre existing neuropathy or for whom neuropathy would be debilitating in their work may need to consider alternate chemotherapy regime. Nurses should conduct a baseline assessment of the patients before they commence their treatment and before each subsequent cycle in order to identify and grade pre existing peripheral neuropathy as well as early onset of neuropathy before it impairs functional activities (Goldberg et al 2007, Hallquist Viale and Sommers 2007).

Toxicities commonly associated with antiangiogenic agents (e.g. Bevacizumab) include hypertension, proteinuria, wound healing complications, bleeding or haemorrhage, thromboembolic events, hypersensitivity reactions and gastro intestinal perforation (Mohile et al 2013).

Patients need to be instructed regarding the potentially serious complications associated with these therapies and the prompt management of same.

Dermatological toxicities occur with the EGFR agents (e.g. cetuximab) and include acne like rash, xerosis, fissuring, abnormal hair and eye lash growth and paronychia (Hallquist and Sommers 2007, Wicham and Lassere 2007). Comprehensive education regarding skin and nail care and hygiene is essential in order to minimise the effects of these therapies. Many researchers advocate the use of antibiotics and steroid cream in the treatment of the acne form rash and early intervention is imperative in order to minimise the discomfort associated (Ocvirk et al 2013). Patient with metastatic colorectal cancer may receive combination chemotherapy and an antiangiogenic agent resulting in a higher toxicity profile. Nursing assessment and early intervention is essential as these side effects may adversely impact quality of life during treatment (Siddiqi et al 2009). Oncology nurses are integral to the care of these patients who require comprehensive education and support in the management of potential toxicities. Patient education on evidence based interventions is essential to maintain quality of life for patients with metastatic colorectal cancer (Hallquist Vale and Sommers 2007, Hallquist Viale 2010, Grenon 2013). It is also important for nurses to be aware that patients' positivity may result in them underplaying the side effects they experience (Cameron and Watherworth 2014). Moreover, this group of patients may give the impression of being 'expert patients' thus create the impression that they do not need ongoing information (Cameron and Waterwoth 2014).

The trajectory of colorectal cancer treatment has changed dramatically in the past decade. The goal of treatment for the majority of patients with metastatic colorectal cancer is largely palliative rather than curative, prolonging life and maximising quality of life. Many patients are now living with metastatic colorectal cancer for many years with lengthy treatment regimens. Advances in treatment has increased the median survival rate to more than 24-30 months with many patients experiencing extended periods of treatment and disease control and living with the disease for many years (Wickham and Lassere 2007, Cameron and Waterwoth 2014). While chemotherapy improves health related quality of life it has major implication on patients' and their families' lives (Cameron and Waterworth 2014). Many patients with advanced disease may suffer from depression, fatigue, anxiety and emotional trauma (Siddiqi et al 2009, Dyar et al. 2012). The vast majority of patients receive treatment in outpatient day units with a high turnover of patients. According to Coolbrandt et al. (2014) these shorten hospital stays have placed significant burdens on patients forcing them to manage treatment side effects at home. This also impacts significantly on patients' relatives who take on informal caregiver roles (Van Ryn et al 2011).

Nurses have significant potential to affect the experiences of mCRC patients during their palliative chemotherapy. Oncology nurses are ideally place to meet both the educational and supportive needs of these patients (Marrs and Zubal 2009). Comprehensive assessment and early intervention with treatment related toxicities can help to maximise patients' quality of life.

Experienced oncology nursing support is vital in the assessment of how patients are managing their disease and its associated treatment because toxicities can have implications on the patient's ability and desire to receive subsequent treatments. Moreover, nursing intervention that reduces the incidence and severity of toxicities has the potential to help patients adhere to the treatment regimen (Ouwkerk and Boers-Doets 2010).

Moreover, while the psychological effect of a cancer diagnosis is well documented, the effects as patients progress through protracted periods of treatment has received little attention. Patients have their highest risk of significant depressive symptoms 2 years after their original diagnosis (Cameron and Waterworth 2014). Timely referral to supportive services, particularly palliative care, for patients with advanced cancer enables patients to access the financial, social and psychological services that are provided and thereby improve their quality of life (Dyar et al 2012, Greer et al 2013).

Conclusion

Many patients are now living many years with advanced cancer. Management now aims to provide a more tailored approach to the treatment of metastatic colorectal cancer incorporating modern chemotherapy regimes and molecular targeted therapies where tumour shrinkage and overall survival rates will be maximised while minimising toxicities to these patients. Palliative chemotherapy can relieve symptoms, improve quality of life and prolong survival. The optimal way to combine and sequence these drugs is not yet

established but most commentators agree that exposure to all active drugs is more important than the specific sequence of administration. The assay of tumour RAS mutation status will help the selection of patients who may benefit from anti-EGFR therapy. Testing for all RAS mutations rather than KRAS alone is now preferred in order to identify those patients who will benefit from anti-EGFR therapy.

In conclusion, treatment options for patients with metastatic colon cancer continue to evolve and expand. Oncology nurses must keep up to date with these advances and acquire the specialist knowledge needed to administer these drugs safely, maximise patient outcomes whilst providing ongoing assessment of toxicities to ensure patients' quality of life remains a priority.

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