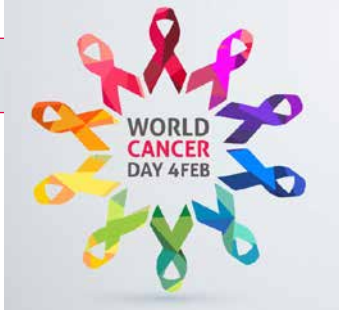

Colorectal Cancer Overview

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Introduction

Colorectal cancer (CRC) is the second most common cancer in Ireland and Europe, accounting for 12% of malignancies in females and 15% in males.[1] In Ireland, 2,000 people are diagnosed with the disease every year. The incidence of cases of CRC in Ireland has been increasing since the 1990s.[1] There is >10-fold difference in regional incidence rates of CRC; previously it was more common in high-income countries but rates are currently increasing in middle- and low-income countries.[2] The incidence rate is increasing in younger people (<50 years) for reasons that remain unclear.[3] The 5-year survival rate is approximately 40%–60%.[4] Adenocarcinomas represent 95% of CRCs; 5%–10% of these arise as a result of recognised hereditary conditions, mainly familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC).[5]

The pathogenesis of CRC is a multistep process, the molecular basis involves genetic instability.[6] The loss of stability drives CRC by facilitating acquisition of multiple tumour associated mutations.[6] Most sporadic cases (85%) have chromosomal instability involving disruption of genes that regulate growth; the tumour-suppressor gene APC is key. This pathway is associated with FAP.[6] The remaining 15% have a high frequency of microsatellite instability (MSI) phenotypes, characterised by disruption to genes that maintain genetic stability; also involved in development of HNPCC. Several tumour-suppressor genes are mutated in this pathway.[6] These patients are more likely to benefit from immunotherapy.

Eighty percent of CRCs are located in the colon and 20% in the rectum.[2] Right sided colon cancers have different clinicopathological characteristics than left sided cancers. Right-sided tumours are associated with older age, female sex, later presentations and tend to arise in flat sessile polyps.[7] In addition, they are more likely to be poorly differentiated with a mucinous or signet ring cell histology and often metastasize to the peritoneum.[7] There have been significant treatment advances in the last 15 years, due to an increasing use of surgery in the metastatic setting but also more effective systemic treatments.[8]

Screening

Early detection can be facilitated by screening programmes. In October 2012, BowelScreen launched in Ireland.[9] Currently, this bowel cancer screening programme is targeted at people aged between 60 and 69 and overtime this will expand to include those between the ages of 55-74.[9] Eligible people undergo a faecal immunochemical test which evaluates for the presence of occult blood in stool.[9] Approximately, 6% of participants will have a positive result and require a screening colonoscopy. In 2015, BowelScreen had an overall cancer detection rate of 2.65 per 1,000 people screened. Importantly, in 2018, fewer than 40% of eligible people availed of BowelScreen.[10]

Treatment of Localised Rectal Cancer

Rectal cancer is defined as a lesion located within 12cm of the anal verge by rigid proctoscopy.[11] The risk of local recurrence in the pelvis is higher in patients with rectal cancer than colon cancer and this has implications for the approach to management. The MRI characteristics, including the primary tumour extent, presence of nodal involvement, sphincter involvement and mesorectal fascia (MRF) involvement are important in determining the appropriate treatment.[11] In patients with cT1-T3 mid or high rectal tumours with limited or no nodal involvement, no EMVI and a clear MRF, it is recommended that upfront surgery be undertaken in the form of total mesorectal excision (TME).[12] Neoadjuvant chemoradiation or short-course radiation prior to surgery is recommended in patients with cT3-4 low rectal tumours with nodal or MRF involvement or EMVI. Chemoradiation is delivered in the form of radiation (50-54 Gy) and fluoropyrimidine (infusional 5-fluorouracil or capecitabine) which acts a radiosensitizer.[12]

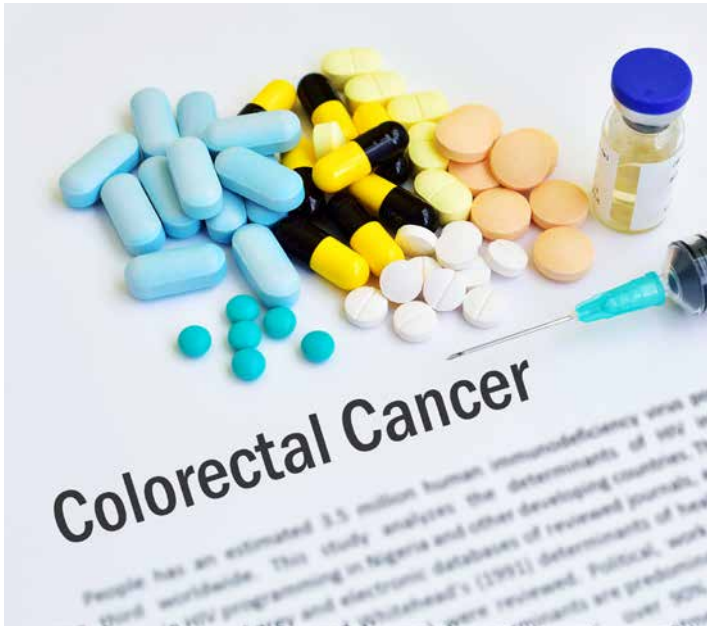
Treatment of Localised Colon Cancer

In patients with localised disease the primary tumour should be resected and the TNM staging system used for post-operative decision making. Adjuvant chemotherapy has been shown to improve survival in resected node positive colon cancer which represents Stage III disease. If the patient has node negative disease (Stage II) but has high risk features such as a T4 primary tumour, poorly differentiated histology, <12 nodes in the resection specimen or invasion of vessels or lymphatics they should also be considered for adjuvant treatment.[13] Single agent fluoropyrimidine chemotherapy [intravenous 5-fluorouracil (5-FU) or oral capecitabine] or combination therapy with oxaliplatin (FOLFOX) may be used for stage II/III disease.[13] It has been established that adjuvant systemic therapy decreases the risk of death by an absolute 3-5% in high risk stage II colon cancer with single agent fluoropyrimidine and by 10-15% in stage III disease with 5-FU alone, with a further 4-5% improvement with oxaliplatin-containing combinations.[13] Fluoropyrimidine alone has not been shown to be effective in patients with Stage II colon cancers that have defective mismatch repair and MSI tumours.[13]

TREATMENT OF METASTATIC COLORECTAL CANCER

Chemotherapy

If performance status allows, patients with metastatic colorectal cancer typically expect a median survival of approximately 30 months as a result of the 'continum of care' approach in the



form of first line chemotherapy, followed by maintenance chemotherapy, resection of metastasis, if possible, and second and further lines of chemotherapy and targeted therapies. First line chemotherapy is fluoropyrimidine based and progression free- and overall survival are improved by the addition of one or two further chemotherapeutic agents and a targeted agent.[14] This is normally in the form of FOLFOX with Bevacizumab (anti-vascular endothelial growth factor) for 6 – 8 cycles followed by maintenance treatment of 5-FU and bevacizumab (OPTIMOX approach).[14] Other regimens that may be utilized in the first-line setting include FOLFIRI (5-FU/irinotecan), CAPOX or a triplet regimen in the form of FOLFOXIRI.[14] The decision on which regimen to used should be patient-centred as oxaliplatin can cause significant peripheral neuropathy and irinotecan is associated with more diarrhoea and alopecia.[14] TAS-102 and regorafenib are oral therapies approved for use in refractory disease in the third-line setting.[14]

Targeted Therapy

The major breakthrough in the treatment of CRC over the last decade has been the ability to target signalling pathways.[15] The main biologic targets in CRC are anti-EGFR (anti-epidermal growth factor receptor), anti-VEGF (anti-vascular endothelial growth factor), and multikinase inhibitors.[15]

A key pathway in CRC pathogenesis is the EGFR pathway. One of the most important of these is the Ras/Raf/MEK/ERK pathway.[16] KRAS is a small plasma membrane bound G-protein that acts a molecular switch which can result in the activation of various growth factor receptors that regulate the expression of genes associated with survival, proliferation, angiogenesis and metastasis. Permanent mutations of RAS lead to a permanently active state of the cell that permits it to evade apoptosis and enhance the malignant behaviour of cells. Oncogenic activating mutations in KRAS occur in 40-45% of patients with CRC.[17] Patients who do not have these mutations are eligible for anti-EGFR antibodies (eg. cetuximab and panitumumab) which will block downstream signalling in these pathways. These targeted treatments can be given as monotherapy but are more effective when given in combination with chemotherapy. Notable side effects of this class of drugs is an acneiform rash which occurs in most patients (with the hypothesis that development of a rash predicts response) and hypomagnesaemia.[18]

HER2 is amplified in 2% of metastatic CRC and its overexpression has been associated with resistance to cetuximab based treatment.[19] The simultaneous inhibition of EGFR and HER2 can result in increased anticancer activity and restore sensitivity to EGFR-directed therapies.[20] Research is currently ongoing to try to improve the activity of and overcoming resistance to anti-EGFR monoclonal antibodies (mAbs), and developing more efficient mAbs or combination strategies.

Bevacizumab is an antibody that binds to VEGF-A and has been shown to improve the efficacy of the cytotoxic backbone. Its class related side effects are hypertension, proteinuria, arterial thrombosis, gastrointestinal perforation and interference with wound healing. Bevacizumab should not be administered within 6 weeks of planned surgery. There are no validated predictive molecular markers available for bevacizumab.[14]

Regorafinib is an oral multikinase inhibitor that inhibits several targets, including anti-angiogenesis. It is considered a standard option in the third-line setting.[14] Response rates associated with this agent are low and its impact on progression-free and overall survival is relatively modest. Some relevant side effects are palmar-plantar erythrodysesthesia, fatigue and elevated liver enzymes. TAS-102 has similar efficacy in this setting.

Immunotherapy

Phylogenetically, CRC can be divided into two molecular subtypes; those with chromosomal instability (CIN) and those with microsatellite instability (MSI).[21] MSI is present in 15% of patients. These patients more often have right sided cancers, often appearing poorly differentiated and mucinous with a lymphocytic infiltration. They carry a better prognosis than the 85% of patients with CIN associated cancers.[21] One third of these patients have hereditary non-polyposis colorectal cancer (HNPCC). MSI-high patients are significantly more likely to respond to checkpoint inhibitors including the anti-programmed death (PD)-1 antibodies, nivolumab and pembrolizumab, or the combination of nivolumab with the anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4) antibody ipilimumab.[22] With the generally tolerable side-effect profile of checkpoint inhibitors, and their success in a multitude of different solid tumour malignancies, immunotherapy has become a highly attractive option in patients with MSI-high CRC.

Metastatectomy

Given that over 20% of metastatic disease in CRC is confined to the liver[23], many local treatments have been developed including surgery, embolization with chemotherapy or radiotherapy and stereotactic radiotherapy. These treatments are associated with improved outcomes if the metastasis developed metachronously during the follow-up period rather than synchronous with the initial presentation.[24] Surgical resection of colorectal liver metastasis is a potentially curative treatment with a reported 5 year survival of 35-55%.[25] In cases of isolated metastasis at other sites local treatment can also be considered in the form of resection of lung metastasis and cytoreductive surgery with HIPEC (hyperthermic intraperitoneal chemotherapy) for peritoneal metastasis.[8]

Survivorship

With improved survival from CRC due to earlier detection and improving treatments, there are an increasing number of patients requiring surveillance and survivorship care. There are approximately 200,000 cancer survivors in Ireland, equivalent to 3% of the population, and at the end of 2014, 17,136 people were living with a history of CRC.[26] The impact of a CRC diagnosis on health and quality-of-life (QoL) is not insignificant, particularly as interventions have become more complex over time. Although many survivors maintain a good QoL without significant cancer related symptoms, many are at risk of multiple survivorship issues and late side effects.[27] In addition, patients often feel lost in transition following the acute phase of their care. The recently published National Cancer Strategy (NCS) has recognized the need to enhance survivorship care in Ireland. Comprehensive knowledge of late toxicities and survivorship issues (e.g. fatigue, altered bowel function, stoma care, neuropathy, genetic risk, psychosocial issues and increased risk of chronic disease) is required. There is also evidence that lifestyle interventions are important. Physical activity and reduced intake of simple sugars and total carbohydrates in the diet have been associated with a reduced risk of disease recurrence. Investment is needed to improve co-ordination of care between hospital specialists, advanced nurse practitioners (ANPs) and General Practitioners (GPs).[28]

Conclusion

In conclusion, CRC is a disease with increasing progression-free and overall survival due to screen detection and improved treatments. In Ireland, efforts are required to encourage people to be more actively involved in the screening programme to increase participation rates. Ongoing research is investigating future treatment and mechanisms of overcoming resistance to current targeted agents. Further investment is needed in the area of survivorship of cancer in Ireland.

References available on request