Oncologic Management of Hereditary Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is the second most common cancer in females and the third most common cancer diagnosed in males. Familial CRC comprises ~20 to 30% of all CRC cases. Lynch syndrome (LS), previously called hereditary nonpolyposis CRC (HNPCC), is the most common of the hereditary CRC syndromes. In this review, the oncological management of hereditary colorectal cancer from the medical oncologist perspective is discussed with special emphasis on Lynch syndrome. Lynch syndrome is characterized by the presence of germline mutations in the mismatch repair genes (MMR)-MSH2, MLH1, MSH6, and PMS2. The available data regarding the prognostic role of mismatch repair genes (MMR), the predictive role of MMR genes, and the implications of that in the management of patients with deficient MMR genes (dMMR/MSI-H) tumors including Lynch syndrome patients are also discussed.

Keywords
- hereditary colorectal cancer
- Lynch syndrome
- microsatellite instability
- chemotherapy

Objectives: On completion of this article, the reader should be able to summarize the oncological management of hereditary colorectal cancer from the medical oncology perspective.

Colorectal cancer (CRC) is the second most common cancer in females and the third most common cancer diagnosed in males.[1] Familial CRC comprises ~20 to 30% of all CRC cases. Of these, only 6 to 7% of the hereditary CRCs are due to highly penetrant germline mutations in single-genes whose clinical presentations have been well characterized.[2] The genetics of remaining familial CRCs are not clearly defined, but likely due to less penetrant mutations.

Identifying the genetic basis of CRC syndromes has led to improved genetic testing to diagnose and treat CRC. This review will discuss the medical oncologic management of hereditary CRC with emphasis on the prognostic and predictive value of microsatellite instability (MSI) in determining treatment options for patients with CRC.

Lynch Syndrome

The process of DNA replication that is a prerequisite for cell division is error-prone. These errors if not repaired in a timely fashion result in tumorigenesis. Mismatch repair is one of the DNA repair systems in humans. Lynch syndrome is characterized by the presence of germline mutations in the mismatch repair genes (MMR)-MSH2, MLH1, MSH6, and PMS2. Deficient mismatch repair (dMMR) can also occur sporadically and is more common in CRC than the familial dMMR CRC. dMMR results in the alteration of the length of short, repetitive DNA sequences called microsatellites that occur in the human genome. dMMR CRCs have MSI (also called MSI-high).[3]

MMR gene mutations can be assessed by DNA sequencing and immunohistochemistry can be used to evaluate for the absence of MMR proteins in CRC. Assessing for MSI in the tumor samples could be used as a quick screen for dMMR CRCs, though additional testing may be required in tumors that are MSI-low with strong suspicion for familial dMMR CRC. Familial CRCs with MSI occur in younger individuals and may be KRAS mutated. Sporadic CRCs with MSI occur in older individuals and carry BRAF (V600E) mutations in ~50% of the tumors. BRAF mutations rarely occur in familial CRCs with MSI.[4]

Microsatellite Instability as a Biomarker in Colorectal Cancer

Biomarkers can be classified as being prognostic or predictive. Prognostic biomarkers can give us information on the likely

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outcome of a cancer in an untreated individual. Presently, this term is also used to predict outcomes in patients treated with chemotherapy, which has the potential to impact the natural history of the disease. Predictive biomarkers give information on a subpopulation of patients that can respond to a given therapy. MSI can serve as a prognostic and predictive biomarker in colon cancer.

Microsatellite Instability and Outcomes in Colorectal Cancer

CRCs with MSI have a significantly better prognosis compared with those with intact mismatch repair.[5] Tumor specimens were collected by Ribic et al from patients with colon cancer who were enrolled in five randomized trials of fluorouracil-(FU-) based adjuvant chemotherapy.[6] Among 287 patients who did not receive adjuvant therapy, those with tumors displaying high-frequency MSI had a better 5-year survival rate than patients with tumors exhibiting microsatellite stability or low-frequency instability (hazard ratio for death [HR], 0.31; 95% confidence interval [CI], 0.14–0.72; $P = 0.004$).[6] Popat et al reviewed 32 eligible studies of 7642 patients, including 1277 with MSI. The combined HR for overall survival (OS) associated with MSI was 0.65 (95% CI, 0.59–0.71; $P = 0.16$). This benefit was maintained when restricting analyses to clinical trial patients (HR, 0.69; 95% CI, 0.56–0.85) and patients with locally advanced CRC (HR, 0.67; 95% CI, 0.58–0.78).[5] An analysis of MSI from archival tissues from four National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant chemotherapy trials was conducted by Kim et al.[7] In an analysis using the entire cohort of patients (treated and untreated), there was a suggestion of an increased relapse-free survival (RFS) for the MSI-H versus the MSS/MSI-L patients. The estimated relative risk (RR) of relapse for MSI-H patients versus MSS/MSI-L patients was 0.68 (95% CI, 0.42–1.09, $P = 0.10$). In this cohort, there was little evidence of an association with OS. RR of death for MSI-H patients versus MSS/MSI-L patients was 0.91 (95% CI, 0.59–1.4; $P = 0.67$).[7] In a pooled analysis of 1027 patients by Sargent et al, dMMR status was associated with improved disease-free survival (DFS; HR, 0.51; 95% CI, 0.29–0.89; $P = 0.009$) and OS (HR, 0.47; 95% CI, 0.26–0.83; $P = 0.004$) in patients who were not treated with 5 FU-based adjuvant therapy. No association was observed between MMR status and outcome in FU-treated patients (DFS: HR, 0.79; 95% CI, 0.49–1.25; $P = 0.30$; OS: HR, 0.78; 95% CI, 0.49–1.24; $P = 0.28$).[8] All these studies support the prognostic role of MMR status.

Microsatellite Instability as Predictive Biomarker

Preclinical data have suggested possible 5-FU resistance in MSI patients.[9] One study found that 5-FU treatment killed MSS cells that were proficient in MMR, but spared MSI-H colon cancer cells. Other in vitro studies showed similar outcomes.[10–12] A retrospective review of 92 patients with stage III colon cancer from the HNPCC Dutch Registry found equal survival among those who received adjuvant 5 FU (5-year survival = 70%; 95% CI, 49–90%) and those who did not receive adjuvant therapy (5-year survival = 70%; 95% CI, 59–83%) suggesting no benefit from adjuvant therapy.[13]

In another retrospective study, Carethers et al evaluated 204 patients with stage II and III CRC.[9] Patients with microsatellite stable (MSS) tumors who received 5-FU had better survival compared with patients who were not treated ($P \leq 0.05$). Conversely, patients with MSI-H tumors who were treated with 5-FU had no survival difference compared with patients without treatment ($P = 0.52$). Ribic et al evaluated 570 tissue specimens, 95 (16.7%) patients of those exhibited high-frequency MSI.[6] The group found that in patients who received adjuvant chemotherapy, MSI-H was not correlated with increased overall survival (HR, 1.07; 95% CI, 0.62–1.86; $P = 0.80$). Adjuvant chemotherapy improved overall survival among patients with MSS or tumors exhibiting low-frequency microsatellite instability (MSI-L; HR, 0.72; 95% CI, 0.53–0.99; $P = 0.04$). By contrast, there was no benefit of adjuvant chemotherapy in the group with MSI-H (HR, 2.17; 95% CI, 0.84–5.55; $P = 0.10$). This was true for both stage II and stage III cancer. HR was 3.28 (95% CI, 0.86–12.48) among patients with stage II cancer and 1.42 (95% CI, 0.36–5.56) among patients with stage III cancer. Sargent et al analyzed data from five randomized adjuvant trials in stage II and III colon cancer patients. Data for 457 patients from these trials were collected.[8] These patients were previously randomly assigned to FU-based therapy versus no postsurgical treatment. Adjuvant therapy significantly improved DFS (HR, 0.67; 95% CI, 0.48–0.93; $P = 0.02$) in patients with MSS tumors. Patients with dMMR tumors receiving FU had no improvement in DFS (HR, 1.10; 95% CI, 0.42–2.91; $P = 0.85$) compared with those randomly assigned to surgery alone. In a subsequent analysis, the authors combined these data with data from the previous analysis by Ribic et al, which included patients from four of the same trials.[6] They also included data from one additional completed trial used in Ribic's analysis.[14] In this pooled analysis of 1027 patients the previous findings were maintained for all patients. They were also maintained for patients with stage II and III disease. No benefit from treatment was observed in the pooled dataset for patients with either stage II (HR, 2.30; 95% CI, 0.85–6.24; $P = 0.09$) or stage III (HR, 1.01; 95% CI, 0.41–2.51; $P = 0.98$) disease with dMMR. No treatment benefit was present in patients with MSS and stage II disease (HR, 0.84; 95% CI, 0.57–1.24; $P = 0.38$). In contrast, in patients with stage III disease and MSS tumors, a benefit from treatment was observed (HR, 0.64; $P = 0.001$.[8]

In contrast, other studies have reported that patients with MSI-H tumors had similar outcomes[7,15] with chemotherapy or appeared to receive a greater benefit from FU-based adjuvant treatment.[16,17] In the previously described study by Kim et al, HR for overall survival for MSI-H patients versus MSS/MSI-L patients were 0.82 (95% CI, 0.44–1.51) in the untreated group and 1.02 (95% CI, 0.56–1.85) in the treatment group.[7] Hutchins et al performed IHC staining on tumor tissues of patients enrolled in the QUASAR trial in which patients with stage II colon cancer were randomly assigned

between 5-FU/leucovorin (FU/LV) adjuvant chemotherapy and observation.[15] Risk of recurrence of dMMR tumors was half that of MMR-proficient tumors. Risk of recurrence was significantly lower with adjuvant FU/LV chemotherapy than in the observation group (22% vs 26% recurred; RR, 0.79; 95% CI, 0.69–0.91; $P = 0.001$). The reduced risk of recurrence with chemotherapy was not significantly different in dMMR and MSS tumors. Elsaleh et al evaluated retrospectively 876 patients with stage III colon cancer.[16] The authors found no difference between dMMR and MSS tumors (5 year survival = 43% vs 36%; $P = 0.644$) in the nonadjuvant-treated group, whereas a significant difference (5-year survival = 85% vs 44%; $P = 0.012$) was seen for the chemotherapy-treated group. However, the patients who did not receive chemotherapy were older than those who did, which may have introduced a bias into the study. Similar results were reported in a smaller study by Hemminki et al. The study evaluated 95 patients with stage III cancer who had received adjuvant 5-FU. The 3-year recurrence-free survival rate was 90% in the MSI-H group ($n = 11$) compared with 43% in the MSS group ($n = 84$; $P = 0.020$).[17]

In summary, data remain conflicting regarding the potential benefits from 5-FU chemotherapy in the adjuvant setting in patients with MSI colorectal cancer. Several of the studies that supported the concept of a lack of benefit from adjuvant 5-FU in MSI-H tumors directly compared patients with MSI-H tumors who received adjuvant 5-FU versus observation.[6,8,9,13] However, the other studies that suggested a benefit from adjuvant 5-FU did not do a similar comparison except for the study by Hutchins et al. Rather, they looked at differences in outcome between MSI and MSS patients who received chemotherapy. The better outcome in MSI patients may have been secondary to better prognosis in those patients and not necessarily a benefit from treatment. Prospective trials are needed to evaluate the role of 5-FU in MSI patients in the adjuvant setting.

Response to Palliative Chemotherapy in Stage IV Patients

The predictive value of MSI status in selecting appropriate chemotherapy for patients with metastatic disease has not been well studied. A small, retrospective study of 42 patients compared median survival in patients with MSI-H and MSS patients treated with first-line palliative 5-FU chemotherapy.[18] MSI-H patients had a better response rate (72% vs 41%; $P = 0.072$) and a significantly better median survival (33 months, 95% CI, 20–46; vs 19 months, 95% CI, 10–28; $P = 0.021$) than microsatellite stable (MSS) patients ($n = 36$). The improved survival does not necessarily indicate benefit from 5-FU in MSI-H patients and may have been secondary to better prognosis in general in MSI-H patients. Another larger prospective study allocated 244 patients to high-dose 5-FU plus leucovorin chemotherapy (HDFL) versus observation.[19] The authors compared the outcome in both groups for MSI-H positive patients and MSI-H negative patients. Four subgroups were identified as follows: MSI-H (+)HDFL(+), $n = 35$; MSI-H(-)HDFL(+), $n = 134$; MSI-H(+) HDFL(-), $n = 17$; MSI-H(-)HDFL(-), $n = 58$. In patients who received chemotherapy, those with MSI-H(+) tumors had improved survival when compared with those patients with MSI-H(-) tumors, with median survival times of 24 months (95% CI, 20.2–27.9) and 13 months (95% CI, 11.6–14.4) months, respectively ($P = 0.0001$). In contrast, in patients who did not receive chemotherapy, the prognosis was poor irrespective of MSI status, with median survival times of 7.0 months (95% CI, 4.6–9.4) and 7.0 months (95% CI, 6.1–7.9) in the MSI-H(+) and MSI-H(-) patients, respectively ($P = 0.8205$). MSI-H cancers responded significantly better to 5-FU chemotherapy with a mean response rate of 65.71% to 43.15% in MSI-H (-) patients. A multivariate analysis of all patients further indicated that MSI-H and chemotherapy were independent favorable prognostic parameters ($P < 0.05$). The authors concluded that the better prognosis of stage IV sporadic colorectal cancers with MSI-H may be associated with better chemosensitivity as opposed to decreased biologic aggressiveness as seen in dMMR CRC. Of note, patients in this study were not randomly allocated to the treatment and the observation groups. In the advanced CRS, although data are limited, there does not appear to be enough evidence to support the lack of benefit from 5-FU in patients with MSI tumors.

MMR Status as a Predictive Marker for Response to Oxaliplatin

A small study obtained tissue samples from 40 patients with metastatic colon cancer treated with FOLFOX 4 and FOLFOX 6. This study did not show a difference in response rate or overall survival between MSI and MSS patients suggesting that the efficiency of FOLFOX chemotherapy was independent of the MSI status.[20] This is in accordance with the fact that MMR-deficient cells are not resistant to oxaliplatin.[21] In another study, tissue samples were derived from patients with metastatic CRC participating in a prospective randomized phase III first-line chemotherapy trial of the AIO Group treated with either 5-FU/folinic acid (FA) and oxaliplatin or capecitabine and oxaliplatin by Muller et al.[22,23] Out of 474 patients included in the phase III adjuvant trial, tumor tissues from 108 patients were investigated There was no correlation between MSI-H and progression-free survival or overall survival. However, MSI-H was correlated with a lower rate of disease control (defined as PR, CR or SD) compared to non-MSI-H patients. Disease control was observed for 50% of MSI-H-positive and 95.6% of non-MSI-H patients ($p = 0.02$). The authors concluded that MSI-H may be correlated with a poorer response to a 5-FU/oxaliplatin treatment. However, the small sample size (four patients out of 104 analyzable samples had MSI-H) and lack of a non-oxaliplatin containing arm severely limits the conclusions. Kim et al analyzed tissues of 135 patients, who had been treated by adjuvant chemotherapy containing 5-FU and oxaliplatin (FOLFOX) after curative resection (R0) for colon cancer. MMR status was not significantly associated with DFS ($P = 0.56$) or OS ($P = 0.61$) in patients with colon cancer receiving adjuvant FOLFOX.[24] The same group analyzed data for 171 patients with

metastatic colon cancer receiving first-line chemotherapy with FOLFOX or CAPOX (capecitabine and oxaliplatin). According to the MMR status, there was no significant difference for progression-free survival (PFS; $P = 0.50$) and OS ($P = 0.47$) in patients with recurrent or metastatic colon cancer treated with first-line CAPOX or FOLFOX. In summary, although data are limited, it does not appear that MMR status affects response or survival in oxaliplatin-treated patients.

MMR Status as a Predictive Marker for Response to Irinotecan

Bertagnolli et al evaluated tumor tissues from patients enrolled in the CALGB 89803 trial, which randomly assigned patients with stage III colon cancer to postoperative weekly bolus FU/leucovorin or weekly bolus irinotecan, 5-FU, and LV (IFL).[25] Tumor MMR status did not predict OS, either for analysis within each treatment arm or for a predictive analysis comparing treatment with FU/LV to treatment with IFL for each genomic category.

Of 723 tumor cases examined by genotyping and IHC, 96 (13.3%) were dMMR/MSI-H. Patients treated with IFL whose tumors were dMMR/MSI-H had better 5-year DFS than those whose tumors were MMR-proficient/MSI-L/S, which was not observed for patients treated with FU/LV. In a predictive analysis, DFS for patients with MMR-D/MSI-H tumors was compared among those receiving FU/LV and IFL. This showed a trend toward improved DFS for patients treated with IFL, with a HR of 0.76 (95% CI, 0.64–0.88) for IFL and 0.57 (95% CI, 0.42–0.71) for FU/LV ($p = 0.07$). Patients whose tumors were MMR proficient/MSI-L/S did not show a similar trend. The authors concluded that loss of tumor MMR function may predict improved outcome in patients treated with the IFL regimen as compared with those receiving FU/LV.

In the metastatic setting, a small study of 82 patients with metastatic colon cancer treated with irinotecan-based chemotherapy showed better response rates in patients who had tumors with negative/weak MMR protein expression compared with patients with tumors with moderate/strong expression.[26] In contrast, another retrospective review of 197 patients with metastatic colorectal cancer treated with irinotecan-based chemotherapy found no significant difference in response rates, progression-free survival, or overall survival between patients with MSS and dMMR.[27] In summary, irinotecan does have a benefit in patients with MSI tumors—whether patients with MSI tumors have a greater benefit than patients with MSS tumors remains to be defined.

Conclusion

The genetics of only a small percentage of hereditary CRC have been clearly defined. Though numerous conditions make up this small proportion of hereditary CRCs; Lynch syndrome is the most common among them. Lynch syndrome results due to a dMMR pathway which in turn results in MSI. Several studies have evaluated the prognostic implication of a tumor's MMR status. It is clear from the studies that we have presented in this review that the MMR status of a tumor has a prognostic role where patients with MSI-H (dMMR) tumors have a better outcome when compared with patients with MSS (proficient MMR) tumors. The predictive role of the MMR status is more controversial with several studies showing conflicting results. Despite the limitations of these studies, we believe that there is enough evidence to suggest a lack of benefit from 5-FU chemotherapy in the adjuvant setting in patients with MSI-H (dMMR) tumors at least in stage II colon cancer. Prospective studies are needed to address this controversial issue, as well as to determine the impact of oxaliplatin in overcoming potential 5-FU resistance.

In the advanced setting, there is not enough evidence to support lack of benefit from 5-FU in patients with MSI tumors who are not candidates for combinational chemotherapies like FOLFOX. Therefore, there is no evidence supporting MSI as a predictive biomarker in this setting. Similarly, MMR status does not affect survival in patients with colorectal cancer treated with oxaliplatin or irinotecan based chemotherapy whether they are treated in the adjuvant setting or the metastatic setting.

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