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PERSONALIZED MEDICINE IN COLORECTAL CANCER (WA MESSERSMITH, SECTION EDITOR)

Optimal Treatment Strategies for Localized and Advanced Microsatellite Instability–High Colorectal Cancer

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Abstract The defective mismatch repair phenotype (MMR-D) has been recognized as a distinct form of colorectal cancers with specific clinical and biologic features. It is caused by a lack of expression of mismatch repair enzymes in tumor cells either on the basis of hereditary or sporadic mutation of gene(s) encoding the enzymes such as in the Lynch syndrome, or by silencing of gene transcription due to promoter methylation. Colorectal cancers of the MMR-D phenotype have consistently shown to be associated with good prognosis and are likely, at least in early-stage disease, resistant to fluoropyrimidine monotherapy. These characteristics have significant implications for clinical practice and treatment strategies, particularly in the adjuvant setting.

Keywords Microsatellite instability · Colon cancer · Mismatch repair enzymes · Fluoropyrimidine · Irinotecan

Introduction

In the last two decades, our understanding of the molecular events involved in the tumorigenesis of colorectal cancer has dramatically increased [1, 2]. The characterization of specific genetic syndrome, in particular, FAP (familial adenomatous polyposis) and HNPCC (hereditary non-polyposis colon cancer, Lynch syndrome) has divided the pathogenesis of colorectal cancers into two pathways: the chromosomal instability pathway (CIN) with accumulation of chromosomal abnormalities, a characteristic of FAP, and the microsatellite instability pathway (MSI) which is the underlying mechanism of the Lynch syndrome [3]. About 85% of all colorectal cancers fall into the CIN category with the vast majority occurring as sporadic, non-hereditary manifestations. The remaining 15% of MSI-related cancers break down into 10%–12% sporadic tumors and 3%–5% hereditary cancers (HNPCC).

This increased understanding of the molecular background of colorectal cancer has sparked efforts to individualize medical treatment options for patients on the basis of molecular biomarkers and genetic signatures.

A pivotal example for individualized therapy based on molecular biomarkers can be found in advanced colorectal cancer where mutations in the oncogene *KRAS* have been identified as negative predictive markers for the efficacy of antibodies against EGFR (epidermal growth factor receptor) such as cetuximab and panitumumab [4, 5]. Testing for mutations in *KRAS* is now standard clinical practice before the initiation of EGFR antibody therapy in advanced colorectal cancer [6].

Colorectal cancers characterized by microsatellite instability exhibit a very distinct biologic phenotype with consequences of clinical decisions regarding adjuvant therapy in early-stage tumors, and potentially also for the palliative therapy of advanced cancer. This review focuses on the clinical implications of microsatellite instability for treatment decisions in the adjuvant and palliative setting.

The Defective Mismatch Repair (MMR-D) Phenotype

The genetic abnormality of microsatellite instability (MSI) is caused by mutations in a group of genes that code for DNA mismatch repair enzymes, including *MSH-2*, *MLH-1*, *PMS-1*, *PMS-2*, and *MSH-6* [7–10]. The defect in mismatch

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repair allows spontaneous genetic mutations to accumulate in colonic mucosa, which predisposes for the development of dysplasia, and eventually, for invasive cancers. The term "microsatellite instability" denotes that with reduced or absent DNA repair activity, the length of repetitive DNA sequences varies (becomes instable) upon DNA replication. In 1997, a workshop convened by the National Cancer Institute issued recommendations for the exact definition and testing of microsatellite instability [11]. A reference panel of five validated microsatellites probes was recommended for MSI testing. Tumors are characterized on the basis of how many of the microsatellites show instability into: high-frequency MSI (MSI-H), if two or more of the five markers show instability (ie, have insertion/deletion mutations); and low-frequency MSI (MSI-L), if only one of the five markers shows instability. The distinction between microsatellite stable (MSS) and low-frequency MSI (MSI-L) can only be accomplished if a greater number of markers is utilized. Apart from the hereditary HNPCC forms, approximately 10% to 15% of sporadic colon cancers also carry mutations (or gene promoter methylations) in the mismatch repair enzymes and are thus characterized as having MSI [12]. Depending on how much the DNA repair capacity is affected in standardized PCR tests, MSI-high or MSI-low (as well as microsatellite-stable [MSS] tumors) are distinguished. Immunohistochemistry (IHC) for protein products hMLH1 and hMSH2 provides a rapid, cost-effective, sensitive (92.3%), and specific (100%) method for screening for DNA mismatch repair defects. In a comparative study the predictive value of normal IHC for an MSS/MSI-L phenotype was 96.7%, and the predictive value of abnormal IHC was 100% for an MSI-H phenotype [13]. MSI-H tumors exhibit the defective mismatch repair phenotype (MMR-D) of colorectal cancers, which has very distinct clinical characteristics (Table 1): proximal tumor location, female gender dominance, mucinous histology, lymphatic infiltration, high number of peritumor lymph nodes, undifferentiated histology, and better prognosis than colorectal cancers with proficient mismatch repair phenotype (MMR-P) with consequently higher prevalence of MSI-H tumors in earlier than later stage cancers [3, 12, 14, 15••, 16, 17]. In addition, preclinical and clinical data suggest that colorectal cancer cells of the MMR-D phenotype are resistant to single-agent 5-fluorouracil, although the data are not perfectly consistent, as discussed below [18••, 19–25].

Table 1 Clinical characteristics of MSI-H/MMR-D colorectal cancers

Proximal tumor location
Female gender preference
Early-stage cancer (stage II>stage III>stage IV)
Lymphatic infiltration
High number of peritumor lymph nodes
Mucinous histology
Undifferentiated histology
Good prognosis
Presumed resistance to 5-fluorouracil
Potential sensitivity to irinotecan

Prognostic Implication of MSI Status

One of the key clinical features of colorectal cancers exhibiting the MMR-D phenotype is their good prognosis and non-aggressive biology in spite of a commonly found undifferentiated histology [3, 17]. One of the consequences of this behavior is that the prevalence of MSI-H colorectal cancers is higher in earlier compared with later tumor stages. Specifically, MSI-H tumors account for up to 22% of all stage II colon cancers, but only for 12% and about 5% of colorectal cancers diagnosed as stage III and IV, respectively [26]. In addition, MSI-H cancers are preferably right-sided with a decreasing prevalence of the MMR-D phenotype from proximal to distal locations, so that only around 4% of rectal cancers are MSI-H [27].

The excellent prognosis of MSI-H/MMR-D colon cancers has been demonstrated in various retrospective analyses of single-arm studies and randomized clinical trials. The initial report on the prognostic implication of MSI-H came from a population-based series of 607 patients age 50 years or younger (thereby selecting for a higher percentage of HNPCC patients) of all tumor stages (stage I, II, III, and IV 12%, 29%, 35%, and 23%, respectively). MSI-H was found in 17% of all patients, and in a multivariate analysis, microsatellite instability was associated with a significant survival advantage independently of all standard prognostic factors, including tumor stage (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27–0.67; $P<0.001$). Furthermore, regardless of the depth of tumor invasion, colorectal cancers with MSI-H had a decreased likelihood of metastasizing to regional lymph nodes (odds ratio [OR], 0.33; 95% CI, 0.21–0.53; $P<0.001$) or distant organs (OR, 0.49; 95% CI, 0.27–0.89; $P=0.02$) [28]. Several subsequent studies confirmed these findings, including a first analysis of the effect of MSI status on outcomes in an adjuvant trial [29] as well as a meta-analysis of individual patient data from 32 studies with a total of over 7,600 patients (1277 MSI-H cases) [30]. In this meta-analysis the combined HR estimate for overall survival associated with MSI-H was 0.65 (95% CI, 0.59–0.71). Additional data from randomized adjuvant trials in early-stage colon cancer, including a pooled analysis by Ribic et al. [19] and an analysis later expanded by Sargent et al. [18••], documented the excellent prognosis of MSI-H/MMR-D cancers. More recent results from large individual randomized adjuvant trials (PETACC-3 [31•]

and QUASAR [32]) clearly validated the prognostic implication of microsatellite instability with hazard ratios for relapse-free survival (RFS), disease-free survival (DFS), and overall survival between 0.16 and 0.70. Interestingly, the analysis of the PETACC-3 trial demonstrated a very strong prognostic effect of MSI-H compared with non–MSI-H for stage II colon cancers (univariate HR RFS 0.26, OS 0.16), but only an attenuated prognostic effect in stage III tumors (univariate HR RFS 0.69, OS 0.70) [33]. In analysis of the QUASAR trial, which only included patients with stage II colon cancer, the MSI-H status was also associated with an excellent prognosis and a HR of 0.31 [32]. Sargent et al. [18••] pooled the individual patient data from five randomized adjuvant trials which compared a 5-FU–based adjuvant chemotherapy against surgery alone in stage II and stage III colon cancer. Results of MMR phenotype testing (either by PCR-based microsatellite instability determination or IHC of protein expression of mismatch repair enzymes) were available for 507 patients, with 387 patients characterized as MMR-P and 70 patients as MMR-D. In a multivariate analysis adjusted for stage, sex, and age, the MMR-D phenotype was associated with improved outcome for DFS (HR 0.58) and OS (HR 0.62). In a pooled analysis with the previously presented data by Ribic et al., these results were confirmed in 1,027 patients [18••].

In conclusion, the MSI-H/MMR-D phenotype has unanimously been recognized as a marker of good prognosis. The risk of recurrence of an MSI-H stage II colon cancer is in the range of 3%–6% within the first 3 years, even without any adjuvant therapy [18••, 32]. These results have relevant clinical implications since adjuvant chemotherapy is very unlikely beneficial in the patient population of stage II MSI-H/MMR-D colon cancers due to their a priori excellent prognosis—even in the absence of discussions on potential 5-FU resistance of these cancers. The prognostic value of microsatellite instability is more attenuated in stage III cancers so that it does not influence recommendations for adjuvant therapy in this setting. A decision algorithm integrating MSI-H/MMR-D in the approach toward adjuvant therapy is outlined in Fig. 1 [34].

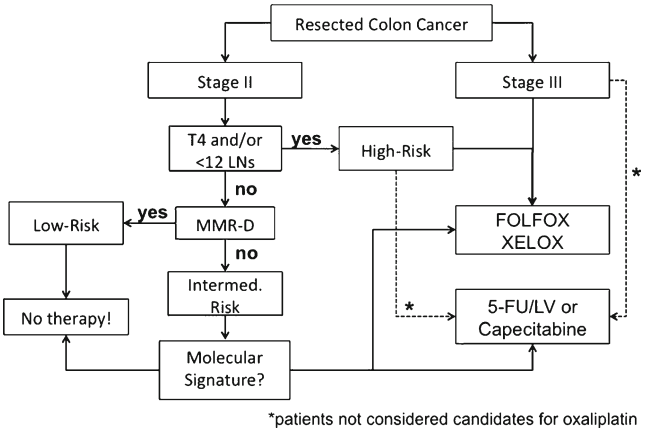

Fig. 1 Proposed decision algorithm for adjuvant therapy in colon cancer

Predictive Implications of MSI Status

While the role of MSI as prognostic marker is undisputed, its value as predictive marker is controversial. Early studies of nonrandomized series initially indicated a potentially higher activity of 5-FU–based chemotherapy in MSI-H than in MSS colorectal cancer (Table 2) [23–25].

Later analyses of nonrandomized studies could not confirm any treatment benefit with the use of a fluoropyrimidine in colorectal cancer anymore, with the limitation that most of these studies included patients of all stages [17, 35, 36]. The problem associated with all nonrandomized evaluations is that in this setting it is impossible to distinguish between prognostic and predictive properties of a specific marker [37]. A biomarker associated with excellent prognosis (like MSI-H) can suggest better outcome for a treatment intervention when no concurrent randomized arm is available for comparison.

Subsequently, data from randomized clinical trials consistently suggested that patients with tumors exhibiting the MSI-H/MMR-D phenotype did not derive any benefit from 5-FU–based adjuvant chemotherapy, but might even have a detrimental effect, although the mechanism for this potential adverse effect on outcome is unclear [18••, 19, 22].

Special attention in this context received the pooled, retrospective analysis of randomized trials by Sargent et al. [18••], which was already mentioned above. The data confirmed the good prognosis of patients with MSI-H/MMR-D colon cancer, particularly in stage II. On the other hand, there was a statistically significant detriment in OS in stage II MSI-H/MMR-D tumors treated with 5-FU–based adjuvant chemotherapy compared to the untreated cohort (HR 2.95, 95% CI 1.02–8.54, P=0.04). This negative effect of adjuvant therapy was not found in stage III colon cancers. One caveat surrounding the analysis is that only 102 stage II patients with the MMR-D phenotype were identified so that the assumptions of a detrimental effect are based on a small subset of patients. The conclusions of these data mirror the statement made earlier that patients with stage II colon cancer exhibiting the MSI-H/MMR-D phenotype should not receive a fluoropyrimidine alone as adjuvant chemotherapy, 1) in view of their excellent prognosis, and 2) because of the lack of benefit seen with 5-FU as adjuvant therapy in this setting. These clinical consequences are independent of a potential detrimental effect of 5-FU in MSI-H/MMR-D stage II cancers. It has to be noted that the available data do not yet allow to expand the assumptions on a lack of benefit from 5-FU to all other tumor stages beyond stage II.

Table 2 MSI status as predictive marker for 5-FU–based chemotherapy

Reference	Type of study	Patients, *n*	Stage	MSI-H (%)	Chemotherapy	5-FU effect
Elsaleh et al. [25], 2000	NR	656	III	8.5	5-FU/LEV	Benefit
Hemminki et al. [23], 2000	NR	95	III	12	5-FU based	Benefit
Liang et al. [24], 2002	NR	244	IV	21.3	5-FU/LV	Benefit
Ribic et al. [19], 2003	RCTs	570	II/III	16.7	5-FU/LEV 5-FU/LV	Detriment
Benatti et al. [17], 2005	NR	1263	All stages	20.3	5-FU based	No benefit
Jover et al. [35], 2006	NR	754	All stages	8.8	5-FU based	No benefit
Lamberti et al. [36], 2007	NR	416	All stages	12.5	5-FU based	No benefit
Kim et al. [22], 2007	RCTs	542	II/III	18.1	5-FU based	No benefit
Des Guetz et al. [54], 2009	MA of NR and RCTs	3690	II/III	14	5-FU based	No benefit
Sargent et al. [18••], 2010	RCTs	1027	II/III	16	5-FU/LEV 5-FU/LV	Stage II: detriment Stage III: no benefit

MA, meta-analysis; NR, nonrandomized; RCTs, randomized controlled trials.
(*Modified from* Vilar et al. [15••].)

While MSI-H tumor cells might be resistant to fluoropyrimidines, some emerging data have recently characterized these cells as particularly sensitive to irinotecan [38, 39, 40, 41•]. Irinotecan (CPT-11) as topoisomerase I inhibitor prevents DNA from unwinding during replication and transcription and subsequently leads to double-strand DNA breaks [42]. In cells with defective DNA repair mechanisms, as in MSI-H/MMR-D cells, these double-strand breaks are more likely to lead to apoptosis and cell death than in MSS/MMR-P cells.

Several clinical studies have analyzed the sensitivity of colorectal cancer with defective mismatch repair enzymes to irinotecan [33, 41•, 43, 44]. Most noteworthy are two studies in the adjuvant setting with contradicting results. Bertagnolli et al. [41] obtained MSI testing in 702 patients enrolled in the phase 3 adjuvant trial CALBG (Cancer and Leukemia Group B) 89803, which randomized a total of 1,264 patients with stage III colon cancer to receive either standard bolus 5-FU/LV or bolus 5-FU/LV plus irinotecan (IFL) as adjuvant therapy. While the trial did not confirm superiority of IFL over 5-FU/LV in the whole patient cohort [45], IFL-treated patients with MMR-D/MSI-H tumors showed improved 5-year DFS as compared with those with MMR-P tumors (0.76; 95% CI, 0.64– 0.88 vs 0.59; 95% CI, 0.53–0.64; $P=0.03$). This relationship was not observed among patients treated with 5-FU/LV. A trend toward longer DFS was observed in IFL-treated patients with MMR-D/MSI-H tumors as compared with those receiving 5-FU/LV (0.57; 95% CI, 0.42–0.71 vs 0.76; 95% CI, 0.64–0.88; $P=0.07$) [41•].

Interestingly, though, a similar analysis of the large European PETACC-3 trial which randomized patients with stage II and III colon cancer to infusional 5-FU/LV with or without irinotecan (FOLFIRI) could not confirm a higher activity of the irinotecan-based chemotherapy in MSI-H/MMR-D tumors, independent of stage [33]. The reason for this apparent discrepancy is unclear, although it has been suggested that the different 5-FU backbone used in both regimens could have contributed to the diverse findings. In conclusion, the preclinical hypothesis of increased activity of irinotecan-based regimens in early-stage colon cancer is intriguing, but a definitive confirmation in clinical trials has not yet been achieved. In view of the low incidence of MSI-H/MMR-D tumors any prospective adjuvant trial targeting these tumors specifically with an irinotecan-based regimen would need to screen an almost prohibitively large patient cohort so that it seems unlikely that such an effort will ever be undertaken, particularly in view of the overall negative data for irinotecan in the adjuvant setting in colon cancer [45, 46].

Oxaliplatin is a standard component of treatment regimens in the advanced and adjuvant setting in colorectal cancer, routinely combined with a fluoropyrimidine (5-FU/LV or capecitabine). Surprisingly limited information is currently available on the efficacy of oxaliplatin-based therapy in MSI-H/MMR-D colorectal cancers in spite of the wide use of this agent. In vitro data suggest that cellular resistance to cisplatin and oxaliplatin is not mediated by the absence of mismatch repair enzymes [47]. Available clinical data are largely retrospective in nature, and have yet failed to provide conclusive and definitive results [48–53]. The preponderance of evidence, however, does not suggest a lack of activity of oxaliplatin in MSI-H/MMR-D colorectal cancers, although further analyses of randomized trials are needed verify or refute microsatellite instability as a predictive factor for oxaliplatin in this disease.

Conclusions and Recommendations for Clinical Practice

Colorectal cancers exhibiting the MSI-H/MMR-D phenotype have consistently been shown to be associated with a better prognosis than their MSS/MMR-P counterparts. Data from randomized trials in early-stage disease suggest that

this phenotype is correlated with resistance to fluoropyrimidine monotherapy. These two observations, confirmed excellent prognosis and presumed lack of benefit from fluoropyrimidines, have notable implications for clinical practice.

Patients with stage II MSI-H/MMR-D colon cancer should not receive adjuvant chemotherapy unless other factors such as T4 stage of a low number of lymph nodes retrieved convincingly put these patients into a high-risk category.

In stage III colon cancer, where oxaliplatin-based adjuvant therapy is standard of care, the MSI status will unlikely influence treatment recommendations, unless the patient is not considered a candidate for an oxaliplatin-based therapy. The role of adjuvant single-agent fluoropyrimidine (capecitabine or 5-FU/LV) in stage III MSI-H/MMR-D colon cancers is unclear.

The preferential use of irinotecan in MSI-H/MMR-D tumors has an interesting preclinical rationale, but results of clinical trials, at least in the adjuvant setting, are controversial. Further studies are underway which could potentially identify irinotecan-based therapy as the preferred regimen in MSI-H/MMR-D advanced colorectal cancers.

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- •• Of major importance

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