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TOPIC HIGHLIGHT

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Prognostic and predictive significance of MSI in stages Ⅱ/Ⅲ colon cancer

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Abstract

In colon cancer, classic disease staging remains the key prognosis and treatment determinant. Although adjuvant chemotherapy has an established role in stage Ⅲ colon cancer patients, in stage Ⅱ it is still a subject of controversy due to its restriction to a small subgroup of patients with high-risk histopathologic features. Patients with stage Ⅱ tumors form a highly heterogeneous group, with five-year relative overall survival rates ranging from 87.5% (ⅡA) to 58.4% (ⅡC). Identifying those for whom adjuvant chemotherapy would be appropriate and necessary has been challenging, and prognostic markers which could serve in the selection of patients more likely to recur or benefit from adjuvant chemotherapy are eagerly needed. The stronger candidate in this category seems to be microsatellite instability (MSI). The recently reported European Society for Medical Oncology guidelines suggest that MSI should be evaluated in stage Ⅱ colorectal cancer patients in order to contribute in treatment decision-making regarding chemotherapy administration. The hypothetical predictive role of MSI regarding its response to 5-fluorouracil-based adjuvant chemotherapy has proven a much more difficult issue to address. Almost every possible relation between MSI and chemotherapy outcome has been described in the adjuvant colon cancer setting in the international literature, and the matter is far from being settled. In this current report we critically evaluate the prognostic and predictive impact of MSI status in patients with stage Ⅱ and stage Ⅲ colon cancer patients.

Key words: Microsatellite instability; Stage Ⅱ; Stage Ⅲ; Colon cancer; Predictive; Prognostic

Core tip: Adjuvant chemotherapy in patients with stage Ⅱ colon cancer is still a subject of controversy. Stage Ⅱ tumors are highly heterogeneous, with five-year relative overall survival rates ranging from 58.4% to 87.5%. Recently reported European Society for Medical Oncology guidelines suggest that microsatellite instability (MSI) should be evaluated in stage Ⅱ colorectal cancer patients in order to contribute in treatment decision-making regarding chemotherapy administration. The current report critically evaluates the prognostic and predictive impact of MSI status in patients with stage Ⅱ and stage Ⅲ colon cancer.

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INTRODUCTION

Colorectal cancer (CRC) remains a major public health

problem in the western world, with an estimated 143397 new cases and 51690 deaths occurring in 2012 in the United States alone[1].

In the adjuvant setting, after the oxaliplatin/fluorouracil (5-FU)/leucovorin (LV) era[2,3] we have reached a deadlock. Up until now, classic disease staging remained the key prognosis and treatment determinant. Based on that, adjuvant chemotherapy has an established role in stage Ⅲ patients, where it is restricted to a small subgroup of patients with high-risk histopathologic features and stage Ⅱ disease[4,5]. Adjuvant chemotherapy in patients with stage Ⅱ colon cancer is still a subject of controversy. Stage Ⅱ tumors are highly heterogeneous, with five-year relative overall survival (OS) rates ranging from 87.5% (ⅡA) to 58.4% (ⅡC). Several data suggest that chemotherapy is not mandatory for low risk stage Ⅱ tumors (T3N0 without risk factors), while FOLFOX or XELOX should be considered as candidates for adjuvant treatment for stage Ⅱ tumors with high risk factors (T4 or bowel obstruction, perforation, poorly differentiated tumor, < 10 or 12 examined lymph nodes, and/or histological signs of vascular, lymphatic, or perineural invasion).

Nevertheless, it is fair to admit that a significant percentage of adjuvant patients receive chemotherapy in vain. Identifying those for whom adjuvant chemotherapy would be appropriate and necessary has been challenging, and prognostic markers which could serve in the selection of patients more likely to recur or benefit from adjuvant chemotherapy are eagerly needed. Microsatellite instability (MSI), alongside 18q loss of heterozygosity[6], *KRAS*, *BRAF*, and *TP53*, are among the most investigated parameters[7-11]. While awaiting the fruits of considerable efforts being undertaken regarding the evaluation of the above mentioned markers in large prospective series, as well as the evaluation of multigene signatures on prognosis and prediction, the stronger candidate seems to be MSI. Nevertheless, it is worth noting that it has not yet found its place as a robust parameter, and it is only in the guidelines of the European Society for Medical Oncology[12] where MSI is advised to be evaluated in stage Ⅱ CRC patients in order to contribute in treatment decision-making regarding chemotherapy administration.

The current review concerns the prognostic and predictive significance of MSI status in patients with stage Ⅱ colon cancer.

BIOLOGY BEHIND THE MSI PHENOMENON

MSI in hereditary and sporadic colon cancer

The abnormal shortening or lengthening of DNA by 1-6 repeating base pair units is a phenomenon caused by the inactivation of the DNA mismatch repair (MMR) system, and leads to the MSI phenotype[13]. Nearly all patients suffering from hereditary non-polyposis colon cancer (HNPCC) or Lynch Syndrome[13-15], as well as approximately 15%-20% of patients with sporadic early CRC[15], are identified as having the MSI phenotype, which reflects the absence of protein expression encoded by the corresponding MMR genes (*hMLH1*, *hMSH2*, *hMSH6*, or *PMS2*)[13,16,17]. It has also been shown that the incidence of MSI differs between stage Ⅱ and stage Ⅲ disease, and that its prognostic impact seems to be significantly stronger in stage Ⅱ than in stage Ⅲ. In its familial form, the genetic basis of instability is largely due to inherited germline mutations of the *MMR* genes (notably *hMLH1* and *hMSH2*)[18,19], whereas, in its sporadic form, this is due to *hMLH1* inactivation by epigenetic hypermethylation of the promoter, and less frequently due to genetic alterations of *hMSH2* and *hMSH6* genes[16,20-22].

Since 1998, microsatellite genotyping of CRC patients for clinically applicable diagnosis is based on panels of specific microsatellite markers (loci containing mono- or di-nucleotide repeated sequences) and standard criteria, as published by Boland *et al*[23]. Usually the panels used consist of the five markers from the Bethesda reference panel, as well as some additional markers from the alternative panel suggested during the International Workshop on HNPCC in 1997[23]. Based on that, a locus is called unstable if unequivocal instabilities are seen in the tumor sample in comparison to the paired normal DNA in a given patient. MSI is graded as high (MSI-H) when 30% or more of the markers used are unstable, low when 10%-20% of the markers used are unstable, and stable (MSS) when all the markers used are stable.

CLINICAL VALIDITY OF MSI IN STAGE Ⅱ AND Ⅲ COLON CANCER PATIENTS

Prognostic value of MSI in stage Ⅱ colon cancer

Since approximately 1998, we have known that the majority of MSI-H CRC patients form a unique subset characterized by a differential, less aggressive clinical behavior and a favorable prognosis compared to MSS CRC patients[24,25]. Recent large trials[26-32], a meta-analysis[17], as well as a number of earlier reported retrospective studies[13,33-44], support the favorable stage-adjusted prognosis of MSI-H compared to MSS CRC patients.

Initially, it was the study by Ribic *et al*[39] which described that patients with MSI-H tumors have a modestly better prognosis than those with MSS tumors. These findings were confirmed five years later when, in a pooled population of more than 500 untreated stage Ⅱ and Ⅲ patients, a clear improvement in 5-year disease free survival (DFS) rate was observed in favor of MSI-H patients. Nevertheless, in this report containing a respective number of 5-FU adjuvantly treated stage Ⅱ and Ⅲ patients, no significant differences were found between MSI and MSS[27]. Somewhat opposing this finding is the control 5-FU treated arm of the PETACC3 trial, where over 600 stage Ⅱ and Ⅲ patients displayed a significant difference in 5-year DFS between MSI and MSS (P = 0.0077), suggesting that MSI improved prognosis can be maintained under 5-FU[31,45].

A 2011 study by Sinicrope *et al*[28] had the impressive inclusion of 2141 CRC patients and specimens from

various adjuvant trials randomized between 5-FU and no treatment or no 5-FU treatment. Of these, 344 patients had MSI tumors (164 stage Ⅱ and 180 stage Ⅲ tumors), and had an overall better prognosis compared to MSS tumor patients[28]. In the multivariate analysis of this article, MSI status was shown to be a statistically significant independent prognostic variable granting MSI CRC patients an improved TTR (P = 0.005), DFS (P = 0.035) and OS (P = 0.031) compared to MSS patients. Similarly to the PETACC3 authors[31], this improved prognosis was shown in both treated and untreated patients with stage Ⅱ and stage Ⅲ MSI CRC tumors, as it was highlighted by a statistically significant improved time to recurrence (P < 0.001), DFS, and OS (P = 0.004) compared to patients with MSS tumors. Similarly, a retrospective analysis of MSI status was reported from the QUASAR study[46], in which 1913 patients with stage Ⅱ colon or rectal cancer were randomly assigned to receive or not receive 6 mo adjuvant treatment with 5FU/LV. The recurrence rate for dMMR tumors was significantly lower in comparison with that for MMR-proficient tumors [11% (25 of 218) *vs* 26% (438 of 1695) recurred; RR = 0.53; 95%CI: 0.40-0.70; P = 0.001]. Recently, Sinicrope *et al*[32] introduced primary tumor site as another parameter in the MSI equation; supporting the observation that MSI was found to be prognostic and conferring a favorable outcome only in patients with proximal primary tumors.

Predictive value of MSI in stage Ⅱ and Ⅲ colon cancer patients

The hypothetical predictive role of MSI regarding response to 5-FU-based adjuvant chemotherapy has been proven a much more difficult issue to address. Almost every possible relation between MSI and chemotherapy outcome has been described in the international literature. Before going into this subject in more detail and in an attempt to explain the controversies, we could hypothesize that among the reported articles are some based on older studies, with small patient populations and no randomization between treatment *vs* control, allowing for potential selection bias and other inherent pitfalls of non-randomized comparisons to occur. Although, as will be described, despite this not being the case with the newer larger series, contradictory results were still documented, stressing the possibility that such findings could occur by chance and thus need careful interpretation and validation before unwarranted restriction of chemotherapy in adjuvant stage Ⅲ MSI-H patients is advocate[45].

As noted above, we have reports highlighting increased sensitivity of MSI patients to 5-FU treatment[47-50], while others are suggestive of no differential response related to MMR proficiency or deficiency[51]. Subsequently, a stronger and larger publication by Ribic *et al*[39], which incorporated data from randomized clinical trials of surgery only *vs* 5-FU-based treatment, showed that MSI patients not only did not seem to benefit from adjuvant chemotherapy, but were in fact possibly harmed by it in terms of OS. This notion seemed to be replicated in the second largest publication on the matter, where in a pooled analysis by Sargent *et al*[27] including a total of 1027 patients, no difference in 5-year DFS rate in favor of MSI patients was observed in the 512 treated stage Ⅱ and stage Ⅲ patients (contrary to what was observed in the untreated patient group), suggesting that the survival benefit of MSI patients was abolished by 5-FU treatment. In this article, a statistically significant improved DFS (P = 0.001) was observed in patients with stage Ⅲ MSS tumors receiving adjuvant 5-FU chemotherapy, but no treatment effect was observed in patients with stage Ⅲ MSI tumors. A non-statistically significant benefit of adjuvant therapy was observed in patients with stage Ⅱ MSS tumors, whereas a trend towards worse outcome was observed in patients with stage Ⅱ MSI tumors[27,45]. However, the authors of the original article, as well as those of the two accompanying editorials[52,53], were extremely careful in the interpretation of the results and did not suggest that stage Ⅲ MSI CRC patients should thereafter be excluded from standard 5-FU-based chemotherapy. Nevertheless this issue was still evident.

Interestingly, in a 2011 article by Sinicrope *et al*[28] concerning 2141 CRC patients, a benefit of 5-FU treatment for stage Ⅲ MSI CRC patients was observed, contrary to what was previously reported[27,39]. In addition, the authors went further, and added the germline *vs* sporadic MSI origin parameter, stating that the beneficial treatment outcome in stage Ⅲ MSI CRC patients seemed to be restricted to tumors where MSI originated from a germline defect[28]. Unfortunately, Sinicrope *et al*[32] did not formally compare the predictive value of MSI status for DFS or survival in patients treated in adjuvant 5-FU-based clinical trials compared to untreated control groups in the available cohorts, nor did they perform a formal analysis of the treatment effect in stage Ⅱ MSI CRC patients[45].

Another pending question open for debate is "which kind of adjuvant chemotherapy should be used in MSI CRC patients?" A trial by Bertagnolli *et al*[54] was suggestive of a positive effect of irinotecan-based adjuvant chemotherapy (CALGB 89803) in favor of MSI patients[54], which became only marginally significant in the updated trial[26] and was not replicated in PETACC-3[31].

CONCLUSION: ISSUES FOR FUTURE ELABORATION

We believe the prognostic value of MSI to be clearer than its predictive value. According to our opinion, MSI status should be evaluated in all stage Ⅱ CRC patients in order to contribute in treatment decision-making regarding chemotherapy administration; indeed MSI-H patients can be spared adjuvant chemotherapy.

Although undoubtedly much progress has been made, pending questions, such as the differential impact of MSI status between stage Ⅱ and stage Ⅲ CRC patients and the potential harm of 5-FU treatment in stage Ⅱ CRC MSI patients, still exist and remain largely unanswered[45].

A possible method of moving forward and resolving

the prognostic and predictive validity of such an easy to perform and relatively cheap biomarker in the controversial area of stage Ⅱ colon cancer disease is to combine efforts. Patient series from large databases from Europe and the United States analyzed together and preferably having in their included trials patients randomized between treatment and no treatment, could allow a per stage stratification and open the field for strong and unambiguous answers regarding prognosis and prediction[30,45].

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