DIFFERENCE IN RESPONSE TO ORDINARY CHEMOTHERAPY IN PATIENT WITH MSI STABLE AND INSTABLE DISEASE AMONG COLON CANCER CASES

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Abstract
Colonic carcinoma is the most commonly diagnosed cancer-related morbidity and mortality worldwide with high mortality. Colorectal cancer (CRC) can be classified according to the chromosomal-instability pathway (a microsatellite-stable (MSS) pathway) and the microsatellite-instability (MSI) pathway, MSI-H CRCs have better stage-adjusted survival. A prospective study , 28 patient with colon cancer enrolled in the study, for each patient the Microsatellite Instability (MSI) was tested, and the patient were followed for 36 months to detect the survival rate. Patients referred to the Salahadeen Cancer Management Center in Iraq underwent testing for Microsatellite Instability (MSI). The MSI stable found among 11(61.1%) and MSI instable found among 7(38.9%). the MSI instable was non significantly higher among male patients 5(41.7%), common in younger age group < 50 years. Most of the nod negative were significantly had MSI instable characteristics 5(83.3%), most of the T2 staging were non significantly had MSI stable characteristics 8(80.0%), while MSI instable commonly found among T4 stage 3(60%). Most of the MSI instable commonly found among grade III and IV 3(75%), and 2(100%) respectively. The patient with MSI instable characteristics significantly had longer relapse free survival time 26.8 ± 4.5 months than those with MSI stable character 21.36 ± 1.01. The patient with MSI characteristics had better prognosis and longer time of relapse free survival than those with MSS patient. A study with larger sample size and longer follow up time was needed to relate the stage of the disease with the prognosis of the treatment
Key words: MSI, MSS, colorectal cancer, colon cancer, chemotherapy.

Introduction

Colorectal cancer (CRC) is third in terms of recognition (6.1%) and second in terms of mortality (9.2%) Colorectal cancer (CRC) is the third most common cancer overall, after lung and breast cancer, and the second leading cause of cancer-related deaths (9.2%), It is estimated that by the year 2035, the total number of deaths from rectal and colon cancer will increase by 60% and 71.5%, respectively [1]. Usually caused by external variables, like environmental and dietary agents, and internal factors, like somatic or genetic factors, can interact in complex ways to cause colorectal cancer to develop in patients [2]. Colorectal cancer is the third most popular occurring cancer in men and the second most commonly occurring cancer in women [3]. Developed nations account for two-thirds of all CRC cases, the risk of developing colorectal cancer begins to rise around the age of 40 and continues to rise steadily beyond the age of 50. Among those aged 50 and up, over 90% of colorectal cancer cases occurred; among those aged 60–79, the incidence is over 50 times higher than among those younger than 40 [4].

The detection of MSI, due to DNA mismatch repair (MMR) defects as currently assessed by immune-histochemistry, was first proposed as the method of choice for the molecular screening aimed at identifying the patients with Lynch syndrome [5]. Over time, MSI progressively emerged as the biomarker of a disease subtype marked by a low metastatic potential. This notion stemmed from the stage of distribution at diagnosis of MSI colon cancers, more frequently detected at an early stage (i.e., mainly stage II), conveying the idea of a mild, slow-progressing disease [6].

Approximately 85% of colorectal cancer cases are attributed to the chromosomal-instability pathway, while the remaining 15% are attributed to the microsatellite-instability (MSI) pathway. These two pathways have been widely used to describe the molecular architecture of colorectal cancer. The MSI pathway is associated with MMR defects in DNA. Repairing base substitutions and insertion-deletion errors that occur during DNA replication is controlled by the DNA MMR repair system. [7]

The chance of survival for patients diagnosed with MSI tumors is better than that of patients diagnosed with MSS. The effects of 5-FU on MSI tumors have been the subject of conflicting reports. There was a benefit in the early, small, non-randomized studies, but later research found no benefit and even a negative effect [8].

This study aimed to identify how MSI status response to ordinary Chemotherapy in patient with MSI stable and instable disease among colon cancer cases

Patient and Method

A prospective study done in Salahadeen cancer management canter during the period of 1st January of 2021 to the 1st January 2024. About 28 patient with colon cancer enrolled in the study, for each patient the Microsatellite Instability (MSI) was tested, and the patient were followed for 36 months to detect the survival rate.

Patients referred to the Salahadeen Cancer Management Center in Iraq underwent testing for Microsatellite Instability (MSI). This test is developed to identify microsatellite instability through the use of multiplex High Resolution Melting (HRM) REAL TIME PCR. Each marker is evaluated for stability or instability based on the comparison of normal and tumor genotype patterns. If a tumor does not have microsatellite instability, it is called microsatellite instability-stable (MSI-Stable). When one of the markers being studied shows instability, it indicates that the tumor is MSI-Intermediate. Tumors with unstable microsatellite markers are identified by an MSI-High status. It is present in 90% of Lynch Syndrome colorectal cancer cases.

Results

The MSI stable found among 11(61.1%) and MSI instable found among 7(38.9%). The patient distribution according to tumor status of MSI show that MSI instable was non significantly (P value > 0.05) higher among male patients 5(41.7%) while SI stable was higher in female patients. 4(66.7%). The MSI instable were common in younger age group < 50years than those with MSI stable > 50 years, this relation was not statistically significant (P value > 0.05). Most of the nod negative were had MSI instable characteristics 5(83.3%), while MSI stable commonly found among N2 6(100%), this relation was statistically significant (p value < 0.05). Most of the T2 staging were had MSI stable characteristics 8(80.0%), while MSI instable commonly found among T4 3(60%), this relation was statistically non-significant (p value > 0.05). Most of the Grade II staging were had MSI stable characteristics 10(83.3%), while MSI instable commonly found among grade III and IV 3(75%), and 2(100%) respectively, this relation was statistically significant (p value< 0.05), as shown in table 1.

Table 1: The general characteristics of patients with colorectal cancer

Variables	MSI stable		MSI Instable		P value
	Frequency	%	Frequency	%	
Sex					0.7
Male	7	58.3%	5	41.7%	
female	4	66.7%	2	33.3%	
Job					0.1
Employer	3	50.0%	3	50.0%	
Housewife	4	80.0%	1	20.0%	
hand worker	3	100.0%	0	0.0%	
Retired	1	25.0%	3	75.0%	
Age					0.4
< 40 years	1	50.0%	1	50.0%	
40-49 years	0	0.0%	1	100.0%	
50-59 years	5	71.4%	2	28.6%	
60-69 years	1	33.3%	2	66.7%	
> 70 years	4	80.0%	1	20.0%	
N					0.02
N0	1	16.7%	5	83.3%	
N1	1	50.0%	1	50.0%	
N2	6	100.0%	0	0.0%	
N3	3	75.0%	1	25.0%	
T					0.1
T2	8	80.0%	2	20.0%	
T3	1	33.3%	2	66.7%	
T4	2	40.0%	3	60.0%	
Grade					0.02
Grade II	10	83.3%	2	16.7%	
Grade III	1	25.0%	3	75.0%	
Grade IV	0	0.0%	2	100.0%	
Total	11	61.1%	7	38.9%	

Regarding the relapse free survival rate the patient with MSI instable characteristics had longer time 26.8 ± 4.5 months than those with MSI stable character 21.36 ± 1.01, this relation was statistically significant (P value < 0.05), as shown in table 2.

Table 2. The mean relapse free survival duration

MSI	N	Mean	Std. Deviation	P value
MSI stable	11	21.36	1.01	0.009
MSI Instable	7	26.8	4.5	

Discussion

The MSI stable found among 11(61.1%) and MSI instable found among 7(38.9%). This goes with Koenig JL, eta l [9] found it (87.9%) and 12.1% respectively. Kruhøffer M etal [10] found that among 65 patients with Stage III tumors receiving adjuvant chemotherapy, 16 were classified as MSI tumors and 49 as MSS tumors

Most of the nod negative were had MSI instable characteristics 5(83.3%), while MSI stable commonly found among N2 6(100%), this goes with Klingbiel D et al [11] found that the MSI-H frequency was almost twice as high in node-negative, compared with node-positive, patients.

Most of the T2 staging were had MSI stable characteristics 8(80.0%), while MSI instable commonly found among T4 3(60%), this goes with Klingbiel D et al [11] found that the proportion of MSI-H tumors was higher with higher T-stage.

Our results show that the relapse free survival rate the patient with MSI instable characteristics had longer time 26.8 ± 4.5 months than those with MSI stable character 21.36 ± 1.01. this goes with Kruhøffer M etal [10] found that among 65 patients with Stage III tumors receiving adjuvant chemotherapy, 16 were classified as MSI tumors and 49 as MSS tumors. As six MSI and 30 MSS patients died within five years of follow-up, there was no significant difference in overall survival between these groups (P ¼ 0.55).

Klingbiel D et al [11] found that the follow-up of 69.1 months for colon cancer patient, the RFS (HR 0.48, 95% CI 0.34–0.69, P < 0.001) as well as OS (HR 0.47, 95% CI 0.31– 0.72, P < 0.001) were better for patients with MSI-H than with MSI-L/S CC.

Bertagnolli et al. [12] reported, in a larger patient cohort, an only marginally significant increase in RFS for 5-FU-/irinotecantreated MSI-H patients, when all other risk factors were taken into account.

Recently a meta-analysis study done by Aggarwal N et al [13], found that the MSI status does not alter 5-year survival of patients with CRC patients treated with adjuvant 5-FU, however there is significant heterogeneity in the design of individual studies in the data synthesis. More studies are necessary to clarify whether CRC patients with MSI CRC, in particular early stage, should be offered 5-FU based adjuvant chemotherapy.

Although BRAF mutation in early diseases was associated with a good prognosis for MSI-H colorectal cancer, the prognosis for MSS and MSI-L CRC was poor. Despite this, BRAF mutation is a negative factor; a study by Goldstein et al. [14] found that MSI-H is associated with BRAF mutation in metastatic CRC patients with advanced BRAF mutation. A higher risk of MSI-H colon cancer is linked to moderate to heavy alcohol consumption, and lifestyle factors can influence the molecular pathological subtypes of colorectal cancer [15]. MSI has the potential to be a powerful molecular indicator for CRC adjuvant treatment and prognosis [16]. At various points in time, MSI affects lymph nodes and distant metastasis of colorectal cancer (CRC) in different ways, and it also affects patients' prognoses. In contrast to patients with stage III MSI colorectal cancer, those with stages I and II have a good prognosis, high 5-year survival rate, low recurrence rate, and deterioration rate, according to other studies [17].

Conclusion

The patient with MSI characteristics had better prognosis and longer time of relapse free survival than those with MSS patient. A study with larger sample size and longer follow up time was needed to relate the stage of the disease with the prognosis of the treatment.

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