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ORIGINAL ARTICLE

Association of Metastatic Colorectal Cancer and its Treatment

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ABSTRACT

Objective: The purpose of this study is to diagnose metastatic colorectal cancer and its treatment.
Study Design: Retrospective/observational study
Place and Duration: Department of Gastroenterology, HITEC-IMS Taxila Cantt. 1st July, 2021 To 31 December, 2021
Methods: There 150 patients of both genders were presented in this study. Included patients were aged between 25-85 years. All the presented patients had confirmed metastatic colorectal cancer diagnosed by using CT scan. Informed permission was obtained prior to obtaining detailed demographics, including age, sex and BMI, for all enrolled patients. Mutation of metastatic CRC were recorded and treated in terms of three line treatments by combination of biological and chemotherapy. SPSS 22.0 was used to analyze all data.
Results: Males were higher in numbers 90 (60%) than females 60 (40%). Mean age of the patients was 62.16±22.56 years and had mean BMI 9.12 ± 11.45 kg/m^2. Most common symptoms were pain in bones, constipation, diarrhea, rectal bleeding and difficulty in breathing among all cases. Frequency of RAS mutation was found in 100 (66.7%) cases, BRAF mutation in 20 (13.3%) cases and MSI-H/dMMR was found in 12 (8%) cases. According to mutational status as first line therpay, frequency of biological targeted therapies in combination with fluoropyrimidine/based combination chemotherapy was 105 (70%), and frequency of combination chemotherapy alone was among 45 (30%) cases. We found 80 (53.3%) patients received biological targeted therapies in combination with chemotherapy, frequency of immunotherapy was 35 (23.3%), combination chemotherapy in 20 (13.3%) and biological targeted therapies in 15 (10%) cases at second line while at third line, combination chemotherapy was received in 90 (60%) cases, frequency of biological targeted therapies was 40 (26.7%), biological targeted therapies in combination with chemotherapy in 13 (8.7%) cases and immunotherapy in 7 (4.7%) cases.
Conclusion: This research found that mCRC is a social problem for healthcare systems since therapy is longer but increases patient survival. RAS mutations were frequent. Advances in molecular profiling of metastatic CRC help tailor therapy to particular patient subgroups. Despite few treatments, patients might expect longer longevity. Genomic profiling helps choose treatments so more patients benefit and fewer are exposed to harm.
Keywords: Metastatic Colorectal Cancer, Immunotherapy, Chemotherpy, Biological Therapy, Mutation

INTRODUCTION

According to the World Cancer Research Fund International, 1.4 million cases of colorectal cancer were discovered in 2012, making it the third most common tumour in the world. In 2002, CRC was responsible for 19.05 fatalities per 100,000 people, but in 2006, 8240 new instances of the illness were found. [1-3] Being over 50, abusing alcohol, not exercising enough, being overweight, eating a poor diet heavy in fat rather than fibre, having had polyps in the past, and having an inflammatory disease of the gut are all risk factors for colorectal cancer (CRC). Colorectal adenocarcinomas account for the vast majority of cases (3 out of 95). One-fifth of patients come with metastatic disease (mCRC), and 30 to 50 percent of patients develop metastasis following surgery for initially localised illness [4,5].

Metastatic illness affecting the liver, peritoneum, lungs, bone, and brain is unusual, thus organ order is critical (ovary, pancreas etc.). CEA, 18q, aggressive cellularity, and advanced stage upon diagnosis are risk factors for metastatic illness [6]. For patients with minimal metastases in a single organ, the median survival span is less than eight months. Those with more widespread disease have longer intervals (the liver). Chemotherapy (alone or in combination with biological therapies) is the only non-surgical treatment for metastatic disease (most cases with mCRC). Pharmacological research has reduced MCC deaths. Systemic treatment improves survival and quality of life. [7] Adjuvant treatment for mCRC includes 5-FU, oxaliplatin, irinotecan, capecitabine, and the biological agents bevacizumab, panitoumumab, and cetuximab, which inhibit angiogenesis or reduce EGFR (panitumumab, cetuximab). Survival rates depend on the patient's overall health, tumour histology and immunohistochemical features, and treatment availability [8,9].

RAS mutations activate downstream pathways without EGFR and create primary resistance to EGFR therapy in mCRC patients. [10,11] One-third of CRC patients had the KRAS p.G12C mutation, which affects the KRAS protein at DNA position 12 and has a poor prognosis. RAS-mutant cancer therapies haven't progressed sufficiently, but new drugs could assist. [12] AMG510, a new KRAS G12C inhibitor, showed anti-cancer advantages for KRAS G12C-mutant solid tumours, including mCRC. [13]

According to studies, BRAFV600E-mutant mCRC patients had a poorer prognosis. [14] Anti-EGFR antibodies show inconsistent outcomes in BRAF and KRAS-mutant tumours. Certuximab (an anti-EGFR antibody) proved superior to standard therapy in the BEACON CRC study and is currently routine for 2nd and later-line treatment. Encorafenib and cetuximab both outperformed standard treatment. [15].

MSI-H and mismatch repair deficiency affect CRC therapy (dMMR). Immune checkpoint inhibitors are the usual treatment for people with these variables [12]. These inhibitors are effective.

The present study's goals include a review of mCRC's diagnostic nuances, therapy choices, and clinical progression.

MATERIAL AND METHODS

This Retrospective/observational study was conducted at Department of Gastroenterology, HITEC-IMS Taxila Cantt and comprised of 150 patients. Informed permission was obtained prior to obtaining detailed demographics, including age, sex and BMI, for all enrolled patients. Patients with severe other medical illness and those did not give any written consent were excluded from this study.

Advanced colorectal cancer recurrence patients were excluded. RAS/BRAFV600E mutations were tested in primary or metastatic tumour tissues. Age, gender, original tumour location, histological differentiation, stage, TNM grade, number of metastatic locations, first-line systemic chemotherapy regimen, duration, and efficacy were gathered.

A CT scan was used every 8–2 weeks to monitor the patient's health (CT). The response was rated using radiological pictures and the solid tumours version 1.1 response grading criteria. After accounting for all deaths, we estimated our total survival (OS). Patients who were still living were censored at the last checkup. PFS is the period from treatment commencement to disease progression or death. Complete or partial responses were considered in the CT response rate. Statistical significance was determined using SPSS statistics version 22.0 and p 0.05. It compared patients' traits. Kaplan–Meier employed this method for OS and PFS analysis.

RESULTS

We found that males were higher in numbers 90 (60%) than females 60 (40%).(fig 1)

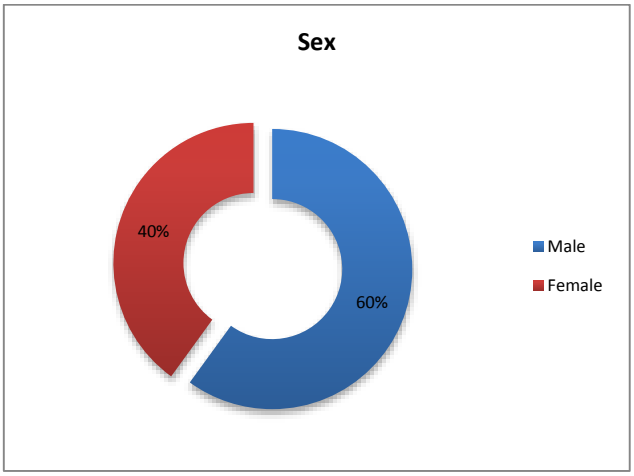

Figure-1: The distribution of cases by gender

Mean age of the patients was 62.16±22.56 years and had mean BMI 9.12 ± 11.45 kg/m^2. Most common symptoms were pain in bones, constipation, diarrhea, rectal bleeding and difficulty in breathing among all cases.(table 1)

Table-1: Age and symptoms of enrolled cases

Variables	Frequency	Percentage
Mean age (years)		
Mean BMI (kg/m^2)		
Symptoms		
pain in bones	50	33.3
constipation	40	26.7
diarrhea	35	23.3
rectal bleeding	17	11.3
difficulty in breathing	8	5.3

Frequency of RAS mutation was found in 100 (66.7%) cases in which (RAS/BRAF WT Right was 16.7 and RAS/BRAF WT Left was 40%), BRAF mutation in 20 (13.3%) cases and MSI-H/dMMR was found in 12 (8%) cases.(table 2)

Table-2: Association of mutation among all cases

Variables	Frequency	Percentage
Mutation		
RAS	100	66.7
RAS/BRAF WT Left	75	40
RAS/BRAF WT Right	25	26.7
BRAF	20	13.3
MSI-H/dMMR	12	8

According to mutational status as first line therapy, frequency of biological targeted therapies in combination with fluoropyrimidine/based combination chemotherapy was 105 (70%), and frequency of combination chemotherapy alone was among 45 (30%) cases. We found 80 (53.3%) patients received biological targeted therapies in combination with chemotherapy, frequency of immunotherapy was 35 (23.3%), combination chemotherapy in 20 (13.3%) and biological targeted therapies in 15 (10%) cases at second line while at third line, combination chemotherapy was received in 90 (60%) cases, frequency of biological targeted therapies was 40 (26.7%), biological targeted therapies in combination with chemotherapy in 13 (8.7%) cases and immunotherapy in 7 (4.7%) cases.(table 3)

Table-3: Treatments/therapy according to mutational status

Variables	Frequency	Percentage
First Line Therapy		
biological comb. With fluoropyrimidine/based chemotherapy	105	70
combination chemotherapy alone	45	30
Second Line Therapy		
biological targeted therapies in combination with chemotherapy	80	53.3
immunotherapy	35	23.3
combination chemotherapy	20	13.3
biological targeted therapies	15	10
Third Line Therapy		
combination chemotherapy	90	60
biological targeted therapies	40	26.7
biological targeted therapies in combination with chemotherapy	13	8.7
immunotherapy	7	4.7

DISCUSSION

People who have treatable stage I-III tumours are still dying from colorectal cancer despite recent advances in treatment. Stage IV CRC patients have a 5-year survival rate of 13.8%-14.7 percent [16]. Therefore, healthcare decision-makers need to prioritise new treatments that improve survival rates. It's important to keep in mind that even though the cost of treating mCRC appears to be high, recent pharmacological advances have given mCRC patients better survival rates and a better quality of life.

Patients with metastatic colorectal cancer can now live for months or even years with improved quality of life thanks to the availability of new targeted medicines. Treatment of mCRC with irinotecan and oxaliplatin, instead of 5-FU-based chemotherapy regimens, has increased median overall survival time to 18 months in the last decade [17]. Combining chemotherapy with cetuximab, panitumumab, and bevacizumab has increased overall survival (OS) for mCRC to over 24 months [18,19]. Health care costs are negatively impacted by these treatments, which are expensive.

In current study 150 patients had metastatic colorectal cancer were presented. Males were higher in numbers 90 (60%) than females 60 (40%). Mean age of the patients was 62.16±22.56 years and had mean BMI 9.12 ± 11.45 kg/m^2. Most common symptoms were pain in bones, constipation, diarrhea, rectal bleeding and difficulty in breathing among all cases. These results were comparable to the previous studies.[20,21] According to mutational status as first line therapy, frequency of biological targeted therapies in combination with fluoropyrimidine/based combination chemotherapy was 105 (70%), and frequency of combination chemotherapy alone was among 45 (30%) cases. We found 80 (53.3%) patients received biological targeted therapies in combination with chemotherapy, frequency of immunotherapy was 35 (23.3%), combination chemotherapy in 20 (13.3%) and biological targeted therapies in 15 (10%) cases at second line while at third line, combination chemotherapy was received in 90 (60%) cases, frequency of biological targeted therapies was 40 (26.7%), biological targeted therapies in combination with chemotherapy in 13 (8.7%) cases and immunotherapy in 7 (4.7%) cases.[22,23]

Most patients in the first, second, and third lines of treatment are receiving biological targeted treatments in conjunction with chemotherapy, according to our data. – (70 percent, 53.3 percent, and 60 percent, respectively). As a component of patient

management resource use, it is critical to identify the cost of illness. Medical oncologists, cancer nurses, and day hospital visits are the most typical sources of resource use while cancer is in remission (pre-progression). In addition, patients visit 17.3 oncologists and hospitals year throughout progression and 13 oncologists and hospitals annually following the third line. 8–10 percent of the cost is spread across all lines and mutations. For every additional line of illness progression, the cost to the health care system approximately triples in contrast to monthly resource utilisation. [20]

Prevention of CRC is undoubtedly the best approach for both individuals and society as a whole, notwithstanding recent advances in therapy. Endoscopic procedures such as flexible sigmoidoscopy or colonoscopy should be used to screen for CRC, according to European Union recommendations issued in 2012 [24]. In light of the high success rate of effective therapy for early-stage CRC [25], formal population screening may be able to dramatically lower the death rate from this illness.

CONCLUSION

This research found that mCRC is a social problem for healthcare systems since therapy is longer but increases patient survival. RAS mutations were frequent. Advances in molecular profiling of metastatic CRC help tailor therapy to particular patient subgroups. Despite few treatments, patients might expect longer longevity. Genomic profiling helps choose treatments so more patients benefit and fewer are exposed to harm.

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