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ANALYSIS OF PERSONALIZED TREATMENT IN PATIENTS WITH COLORECTAL LIVER METASTASES IN PAKISTAN

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Abstract:

Colorectal cancer (CRC) is the second most common cancer type in the Western world, accounting for approximately 450,000 new cases in Europe each year. The basic aim of the study is to find the personalized treatment in patients with colorectal liver metastases in Pakistan. This cross-sectional study was conducted at Punjab Health Department during June 2019 to December 2019. This study was done basically due to analysis of personalized treatment of colorectal liver metastases in Pakistan. We collected the data through pubmed and literature review analysis. It is concluded that personalized medicine has made some major advances in CRC, with KRAS testing now part of routine clinical practice. However, KRAS has some limitations as a biomarker and despite extensive research into other biomarkers for antiangiogenic drugs, chemotherapy and other targeted agents, these are not yet established in clinical practice.

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INTRODUCTION:

Colorectal cancer (CRC) is the second most common cancer type in the Western world, accounting for approximately 450,000 new cases in Europe each year. More than 200,000 patients die of the disease each year, which makes CRC still the second leading cause of cancer death in the Western world. Over the past decade the treatment of CRC has changed markedly, in particular in metastatic disease, mostly through the introduction of combination chemotherapy with targeted agents, leading to more curative resections and also prolonging survival in patients with unresectable disease [1].

CRC develops along distinct pathways involving various genetic and epigenetic alterations. Two major pathways of CRC development are presently known. One, called the classical adenoma-carcinoma sequence, is through chromosomal instability (CIN), and one through microsatellite instability (MSI), which is caused by a defective mismatch repair (dMMR) gene system following the so-called serrated pathway [2]. Beyond the division into these two major pathways, colon cancers are further grouped into five subtypes through their genetic and epigenetic alterations and prognosis [3].

Personalized medicine is defined by the US National Cancer Institute as 'a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease'. The potential benefits of this treatment approach include increased response rates and survival, as well as reduced toxicity. In addition, the cost effectiveness of oncology treatment may be improved as expensive drugs can be given to the patients most likely to benefit. Biomarkers are characteristics that indicate a normal or pathogenic process or a response to a specific therapeutic intervention [4]. Biomarkers may have prognostic and/or predictive value. Prognostic biomarkers provide information on the natural history of the patient's disease independent of treatment, whereas predictive biomarkers provide information on the likelihood of response to a particular treatment [5]. There are many challenges to overcome in personalizing medicine. These include the cost of developing biomarker-related drugs and biomarker testing, standardization of testing (including specimen type, collection and storage), ethical issues occurring as a result of genetic testing, regulatory hurdles for biomarkers and the need to establish the benefit of targeted drugs over alternative approaches [6].

Aims and objectives

The basic aim of the study is to find the personalized treatment in patients with colorectal liver metastases in Pakistan.

MATERIAL AND METHODS:

This cross-sectional study was conducted at Punjab Health Department during June 2019 to December 2019. This study was done basically due to analysis of personalized treatment of colorectal liver metastases in Pakistan. We collected the data through pubmed and literature review analysis.

Epigenetic markers

Beyond single markers, some have found that the combination of genetic and epigenetic markers seems to improve the prediction of survival in patients with resected colon cancer. There in particular, presence or absence of BRAF mutations separate survival in patients with microsatellite-stable cancers, with BRAF-mutant MSS (proficient mismatch repair) patients having the worst prognosis. Most recently, analysis of mismatch repair in combination with mutation detection of KRAS and BRAF and hypermethylation of MLH1 (methylator phenotype) in patients with stage III colon cancer under adjuvant FOLFOX therapy identified significant differences in survival. Thus, the prognosis in this patient population can be better predicted using the combination of these markers. Here again, the analysis did not identify markers indicating benefit from adjuvant therapy (predictive marker) [7].

Anti-epidermal growth factor receptor therapies

One of the major advances in the treatment of CRC has been the development of targeted therapies. Amongst the most well-established of these are the monoclonal antibodies cetuximab and panitumumab, which target the EGFR. Cetuximab has been shown to have efficacy both as monotherapy and in combination with chemotherapy for patients with pretreated metastatic CRC. However, the situation is less clear in the first-line setting [6]. However, not all patients respond to anti-EGFR therapies and a variety of molecular characteristics have been evaluated to see if they have a predictive role. The most established biomarker is the presence or absence of *KRAS* mutations. Mutations in KRAS, PIK3CA or BRAF result in the downstream activation of the RAS-mitogen-activated protein kinase (MAPK) or PI3K pathways irrespective of EGFR activation [8].

Outcomes of a personalized medicine

The hypothesis underpinning a personalized medicine approach is that this will lead to improvements in clinical outcomes. Apart from the use of anti-EGFR therapies in patients who are *KRAS* wild type, initial results from clinical

trials have been mixed. For example, in a nonrandomized phase I trial, 175 patients with one molecular aberration were treated with matched targeted therapy and 116 patients had unmatched therapy. The patients receiving matched therapy had a higher overall response rate (27% *versus* 5%), longer time to treatment failure (median 5.2 *versus*2.2 months) and longer survival [9]. However, a phase I trial showed no benefit in patients with advanced CRC in matching treatment to their current molecular profile. However, this study had important limitations. For example, some of the biomarkers were exploratory (e.g. many patients were treated with PI3K inhibitors based on PTEN expression levels), the targeted agents had different mechanisms of action, archival tumor specimens may not have reflected the patients' current molecular characteristics and because this was a phase I study patients may have been treated at non-biologically active doses [10].

CONCLUSION:

It is concluded that personalized medicine has made some major advances in CRC, with KRAS testing now part of routine clinical practice. However, KRAS has some limitations as a biomarker and despite extensive research into other biomarkers for antiangiogenic drugs, chemotherapy and other targeted agents, these are not yet established in clinical practice. Therefore, truly personalized medicine in CRC currently remains an aspiration for the future rather than a clinical reality. However, it is likely that a molecular screening approach to treatment will become increasingly used in the future to fully characterize tumors and identify patients who are most likely to benefit from targeted treatments.

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