Extended Abstract
Volume 5:5, 2021

Hepatology and Pancreatic Science

Open Access

How can clinician be precise in era of precision medicine? Case of colon cancer

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Abstract

Colorectal cancer is the second cause of death in the world and genomic alteration plays an important role in this disease. Much of the underlying genetic ???Cancer Driver??? mutations/variants in sporadic colorectal cancer (CRC) have not been characterized by race. Here, we report the identification of distinct novel variants from CRC patients in mismatch repair (MMR) genes MSH2, MHS3, MSH6 and APC. We developed a panel of 20 frequently altered colon cancer genes for targeted sequencing in 138 colon tissues using next generation sequencing to examine 98.8% of the targeted exons and splice junctions at a depth of sequencing that allowed for high confidence variant calling. After alignment and variant calling, we annotated the variants with information from the 1000 Genomes Project, Catalogue of Somatic Mutations in Cancer (COSMIC), Polymorphism Phenotyping v2 (PolyPhen-2) and PFAM domain and transcription factor motifs. Excluding synonymous SNVs, 212 deleterious variants in adenoma, 760 in advanced adenoma and 2624 variants in tumors were detected. Novel variants (1591 and 1363) were found in MMR genes (MSH6 and MSH3) and APC gene, respectively. These findings further highlight the relevance of APC gene in CRC onset but also the potential underestimation of the MSI-H in sporadic CRC as many of the novel mutations so called ???uncertain significance??? in MMR genes detected here were of a deleterious nature with a therapeutic interest.

Precision cancer medicine involves the detection of tumor-specific somatic mutations, including insertions/deletions (indels), single nucleotide variants, translocations, and copy number alterations, followed by treatment with therapeutics that specifically target identified actionable alterations. This approach using precision medicine has largely been hampered by the high cost of testing and the extended turnaround times associated with in-depth genomic diagnostic analysis. However, advances in genomic technologies, including next-generation sequencing (NGS) and droplet digital polymerase chain reaction, have now rendered extended genomic analyses of human malignancies technologically and financially feasible for use in the clinic.Concomitant with these advances in genomic technologies, there have been significant advances in two overlapping areas of cancer research, each with major clinical ramifications; the first is a greater understanding of the underlying genomic alterations and molecular mechanisms of cancer, and the second is development of novel therapeutic agents and biomolecules that exploit specific genomic aberrations in tumors.These advances are the underpinnings of the new precision cancer medicine clinical paradigm.In the precision medicine approach to cancer, the physician and patient use the identification of specific genetic aberrations that affect cancer-related genes to better inform treatment decisions. The underlying rationale is that this personalized diagnostic approach will lead to a clinical recommendation for targeted cancer therapies that will ultimately result in improved clinical outcomes.

This approach has been successfully applied to single tumor types with predetermined genomic variants such as EGFR-positive non–small-cell lung cancer (NSCLC) and BRAF-positive melanoma, whereas previous studies revealed that precision medicine can improve survival in a single cancer type. Earlier studies indicated that targeted therapies given to patients whose tumors harbored specific alterations may improve outcomes as measured by tumor responsiveness. However, the impact of precision medicine compared with standard therapies on survival and the effect of implementing sophisticated diagnostic technologies such as NGS on the costs of cancer care, remain unknown.

Our precision cancer medicine program was clinically established in a single region of the Intermountain Healthcare delivery system. Patients with advanced, refractory cancer were referred to the precision medicine clinic where they received genomic testing, an in-depth interpretation of the genomic results from a multi-institutional molecular tumor board, and a list of treatment options for implementation at the discretion of the treating oncologist.

We report here the progression-free survival (PFS), total costs, and cost per week of survival associated with the initial cohort of patients who received targeted treatment in the precision cancer medicine program compared with control patients who received standard chemotherapy or best supportive care.

In calculating patient costs, a payer perspective was adopted. Patient costs were estimated by using standard Intermountain Healthcare payer charges. Only charges incurred between the treatment line start and end dates were included in the total charge estimates for each patient. Patient costs included all

amounts for patient treatment, toxicity, patient sequencing, and targeted drug therapy. Treatment costs for both targeted and control patients included all facility-based and clinic-based charges associated with treatment, including chemotherapy, drug, radiology, and laboratory costs. Palliative care costs were limited to daily reimbursement charge rates determined by the Centers for Medicare and Medicaid Services. Toxicity costs included all patient charges associated with treating the adverse effects resulting from treatment. Sequencing costs for target patients were obtained from the test provider and were based upon estimated payer reimbursement rates.

Drug cost data were drawn from local specialty pharmacies and drug manufacturers and were based upon estimated payer reimbursement rates, including estimates of any out-of-pocket costs for the patient. A discount rate was not applied to costs to adjust for the time value of money. Given the limited availability of quality-of-life data for control patients, PFS weeks were not quality adjusted. The mean per patient cost per PFS week was calculated by adding the costs per PFS week for each patient and dividing by the total number of patients. Statistical comparisons of costs between precision medicine and control groups were performed by using a two-sided rank sum test.

This work is partly presented at 14th Euro-Global Gastroenterology Conference