

Efficiency of olaparib in colorectal cancer patients with an alteration of the homologous repair protein

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Abstract

Precision medicine is defined by the administration of drugs based on the tumor's particular genetic characteristics. It is developing quickly in the field of cancer therapy. For example, *KRAS*, *NRAS* and *BRAF* genetic testing demonstrates its efficiency for precision medicine in colorectal cancer (CRC). Besides for these well-known mutations, the purpose of performing larger genetic testing in this pathology is unknown. Recent reports have shown that using the poly ADP ribose polymerase (PARP) inhibitor olaparib in patients with homologous repair enzyme deficiency gave positive clinical results in breast, ovarian and prostate cancers. We have reported here the cases of 2 patients with multi-treated metastatic CRC who underwent somatic and constitutional exome analyses. The analyses revealed a loss of function mutation in a homologous repair enzyme resulting in the loss of heterozygosity for both patients (Check2 for the first patient and RAD51C for the second one). Both patients were treated with off-label usage of olaparib. While the first patient showed clinical benefit, reduction of carcinoembryonic antigen tumor marker and radiologic response, the second patient quickly presented a progression of the tumor. Additional genetic analyses revealed a frameshift truncating mutation of the *TP53BP1* gene in the patient who progressed. Interestingly, deficiency in TP53BP1 was previously described to confer resistance to olaparib in mice breast cancer models. Our findings suggest that exome analysis may be a helpful tool to

highlight targetable mutations in CRC and that olaparib may be efficient in patients with a homologous repair deficiency.

Key words: Colorectal cancer; Exome analysis; Genetic aberrations; Homologous repair deficiency; Precision medicine

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Core tip: The role of genetic profiling in metastatic colorectal cancer for precision medicine is currently under investigation. This case report underlines for the first time, that olaparib may have some clinical efficiency in patients with homologous repair deficiency in colorectal tumor.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide with about 1 million new cases and over 500000 deaths every year^[1]. Approximately 30% of patients with CRC develop an overt metastatic disease. Meanwhile, 40% to 50% of newly diagnosed patients already present a metastatic disease. For patients with non-operable metastatic CRC (mCRC), there are no curative options, but the use of palliative systemic chemotherapy dramatically enhances response rates, progression-free survival (PFS) and overall survival (OS)^[2-4]. Currently, few drugs have demonstrated effectiveness in the treatment of metastatic colorectal disease and patients are treated based on the use of three cytotoxic chemotherapies: fluoropyrimidine, oxaliplatin and irinotecan, associated with targeted therapies [anti-EGFR (panitumumab and cetuximab) or anti-VEGF (bevacizumab) monoclonal antibodies].

In consequence, at the end of their treatment sequence, many patients still have a good performance status and would still be able to undergo treatment; unfortunately, we do not have any approved and efficient therapies to offer. Cancer cells are characterized by multiple genomic alterations. This finding has led to the development of molecularly targeted agents that inhibit mutated proteins. Such drugs are theoretically more specific for cancer cells bearing specific mutations. While such targeted agents have followed clinical development based on tumor location, most genetic molecular alterations exist across tumor types and histologies. This observation raises the possibility

of shifting towards the administration of drugs based on molecular pattern rather than on histological status. Improvements in genetic sequencing have made possible the identification of multiple genomic molecular alterations in a timeframe compatible with clinical practice. Many retrospective and prospective trials have shown the usage and efficiency of off-label molecularly targeting agents. We report here the usage of exome testing in 2 patients with metastatic CRC and show for the first time that homologous repair deficiency could be targeted by poly ADP ribose polymerase (PARP) inhibitor in this pathology.

Sample preparation

Formalin-fixed paraffin-embedded (FFPE) tumors were characterized by a pathologist to determine the tumor cell content and sent to the molecular biology platform for DNA extraction. Tumor cell content was 85% for Case 1 and 60% for Case 2. Seven 15- μ m slices were extracted using the Maxwell 16 FFPE Plus LEV DNA purification kit (Promega) according to the manufacturer's protocol. Corresponding normal DNA was extracted from 500 μ L ethylenediaminetetraacetic acid blood samples with the Maxwell 16 Blood DNA Purification System (Promega) according to the manufacturer's instructions. DNA quality was assessed by spectrophotometry with absorbance at 230, 260 and 280 nm. DNA was quantified using a fluorimetric assay with a Qubit device.

Two-hundred nanogram of genomic DNA from normal and cancer cells were fragmented with a Covaris device to obtain fragments around 180-200 bp. Then, libraries were constructed and captured by using SureSelect Human All Exon v5 kit (Agilent), following the manufacturer's protocol. Paired-end (2×151 bases) sequencing was performed on a NextSeq500 device (Illumina). Obtained sequences were aligned and annotated with the human Hg19 genome based on the SureSelect Human All Exon v5 manifest by using Burrows-Wheeler Aligner (BWA) and Genome Analysis toolkit (GATK) algorithms. Only sequences with a read depth of $10 \times$ and a mutation allele frequency superior to 5% were conserved for the analysis. The analysis is fostered on 137 clinically relevant genes related to biological pathways linked to cancer predisposition or available targeted therapies (Supplementary Table 1). Copy number variations were studied by using Control-FREEC software as described^[5,6].

CASE REPORT

Patient 1

A 58-year-old Caucasian male initially presented with abdominal pain. A CT scan, carried out in June 2011, revealed a metastatic sigmoid cancer with the following metastatic locations: mediastinal and lomboartic lymph nodes, lungs. A lymph node biopsy was performed

Table 1 Alterations observed for Case 1 in the short list of clinically relevant genes

Gene	Nucleotide variation	Protein variation	Origin	Impact
<i>AKT1</i>	c.235C>A	Gln79Lys	Somatic	Activating
<i>CCNE1</i>	c.1022C>T	Thr341Met	Somatic	Unknown
<i>CHEK2</i>	c.478A>G	Arg117Gly	Constitutive	Likely pathogenic
<i>CUL2</i>	c.70C>T	Pro24Ser	Somatic	Unknown
<i>ERCC6</i>	c.4179G>A	Met1393Ile	Somatic	Unknown
<i>PMS2</i>	c.1531A>G	Thr511Ala	Constitutive	Benign
<i>SMAD4</i>	c.1091T>A	Leu364X	Somatic	Loss of function
<i>SUFU</i>	c.1211T>C	Met404Thr	Constitutive	Unknown

and the diagnosis of wild-type KRAS, NRAS and BRAF, moderately differentiated Lieberkühn adenocarcinoma was made. From 2011 to 2015, the patient received different chemotherapeutic regimens. In July 2015, the patient's lung metastases progressed and he started to show symptoms such as breathlessness and a permanent dry cough. As no approved chemotherapy or targeted therapy could be proposed, we performed somatic and constitutional exome analyses. We observed 479 somatic mutations. For clinical use, we analyzed a short list of 137 genes. It was interesting to see that among the 8 altered genes (Table 1), we observed a SMAD4 stop mutation, which is frequently found in CRC. An activating mutation of *AKT1* was observed (Q79K). It could be targetable by protein kinase B (AKT)/mTor inhibitors. Surprisingly, we observed a constitutive Chek2 mutation (R117G), a gene involved in the homologous repair process. This mutation is cited in the public database for conferring a predisposition to cancer. Moreover, the analysis of copy number variation showed a loss of heterozygosity in chromosome 22 (from 29091114 to 29130709) (Figure 1A). This analysis suggested a complete deletion of Check2 function in tumor cells. After discussion of the case at the molecular tumor board, the patient was proposed to receive off-label PARP inhibitor olaparib which previously showed efficiency in patients with Chek2 mutation in metastatic prostate cancer^[7]. One mo after beginning the therapy by PARP inhibitor, the patient declared reduction of cough and disappearance of breathlessness. After 3 mo we observed a reduction in carcinoembryonic antigen serum level (57 ng/mL to 25 ng/mL) and a tumor size reduction upon CT scan (Figure 2). No hematological toxicity was mentioned. Patient weight increased from 62 kg to 68 kg. However, despite this response, the patient died suddenly at home 4 mo after introduction of the therapy.

Patient 2

A 49-year-old woman presented with rectal bleeding and diarrhea in March 2015. She underwent a colonoscopy with biopsies that revealed a KRAS mutated, well differentiated Lieberkühn rectal adenocarcinoma. The patient did not present any family history of CRC. The genetic testing did not show microsatellite instability. CT scan showed multiple, bilobar liver metastases. The

patient was treated with FOLFIRINOX combination plus bevacizumab for 12 cycles. The CT scan showed major response in the liver and the rectum but no curative option could be proposed for the liver disease. Despite efficacy, the therapy had major toxicity with grade 3 peripheral neuropathy which precluded further usage of oxaliplatin. A therapeutic pause was proposed. The patient refused and asked for additional therapy. We performed somatic and constitutional exome analyses. We observed 905 somatic mutations. For clinical use, we analyzed a short list of 137 genes and interestingly, among the 13 altered genes (Table 2), we observed a potentially pathogenic APC mutation, which could predispose to CRC. Moreover, a KRAS activating mutation (G12D), commonly found in CRC, was observed. What was even more interesting is that we observed a somatic mutation of the homologous repair in RAD51C (T287A) previously reported to be associated with a loss of function^[8]. Analysis of copy number variable showed a loss of heterozygosity in chromosome 17 from 56770004 to 56801461 (Figure 1B). This analysis suggested a complete deletion of RAD51C function in tumor cells. After discussion of the case at the molecular tumor board, the patient was proposed to receive off-label PARP inhibitor olaparib which previously showed efficacy in patients with RAD51 mutation in metastatic prostate cancer^[7]. The patient received 3 mo of olaparib therapy without toxicity. Despite the absence of toxicity, the magnetic resonance imaging (Figure 2) showed tumor progression. Olaparib was stopped and the patient was included in a phase I clinical trial.

As loss of TP53BP1 was previously described to be involved in PARP inhibitor resistance in homologous repair deficient breast cancer models in mice^[9], we searched for the mutation of this gene in both patients. While patient 1 had a wild-type *TP53BP1* gene, patient 2 had a frameshift truncating insertion in *TP53BP1* (AG insertion at chromosomal position 17:43766919) (Figure 1C), thus suggesting a loss of function of the protein.

DISCUSSION

The use of exome sequencing in cancer has largely taken place in the setting of research studies, such

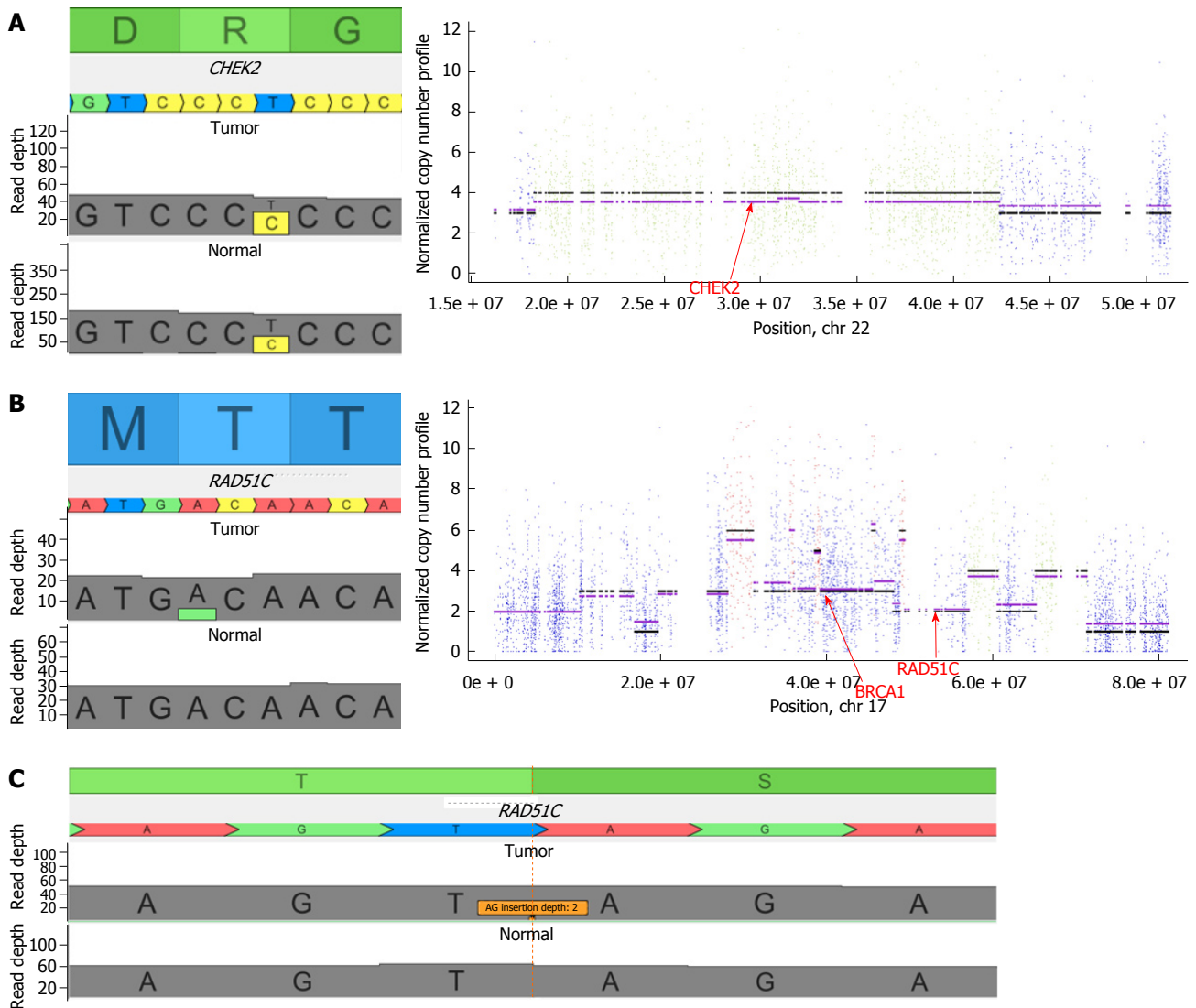


Figure 1 Genetic data of targeted alterations. A: Patient 1 presented a T>C variation in the *CHEK2* gene inducing a constitutive deleterious R117G mutation (left panel). At the chromosomal level, it appeared that chromosome 22 harbored a loss of heterozygosity inducing (right panel) a complete inactivation of *CHEK2*; B: Patient 2 presented a A>G variation in the *RAD51C* gene inducing a somatic loss of function T287A mutation (left panel). At the chromosomal level, it appeared that chromosome 17 harbored an important loss of heterozygosity at the *RAD51C* locus inducing a complete inactivation of *RAD51C*; C: Patient 2 also harbored an AG insertion resulting in a frameshift truncating mutation in the *TP53BP1* gene.

as The Cancer Genome Atlas. However, integration of exome sequencing into precision cancer care remains a challenging issue because samples issued from formalin-fixed tissues (*i.e.*, FFPE) are difficult to analyze (due to small size and poor quality). Furthermore, bioinformatics approaches require detection of the wide-spectrum of mutations with the capacity to identify actionable mutations at an acceptable sensitivity and it remains an issue. This case report is the first to suggest efficacy of olaparib in CRC with homologous repair deficiency and to demonstrate that exome sequencing could be used to help drug repositioning. Accordingly, single-agent olaparib as well as combinations with irinotecan were previously tested in unselected CRC that is resistant to standard therapy without any clinical efficacy^[10,11]. Such data raises the hypothesis that olaparib activity also requires molecular testing of

homologous repair deficiency for CRC as requested for ovarian cancer.

Homologous repair is an enzymatic complex aimed at repairing DNA double-strand breaks. *CHEK2* and *RAD51* play a central role in the repair of DNA double-strand breaks performed by homologous repair^[12]. After the detection of DNA double-strand breaks by ATM and *CHEK2*, *BRCA1* is phosphorylated by these proteins. *Rad52* binds recombinase polymerase amplification and displaces it to allow *Rad51* binding. *BRCA2* binds to *Rad51* until *BRCA2* becomes phosphorylated, releasing *Rad51* and allowing it to localize to the double strand break with *Rad52*. Homologous repair-mediated repair goes on; *Rad51* then forms a nucleoprotein filament that invades a homologous sequence and activates strand exchange to generate a crossover between the juxtaposed DNA^[13]. Several studies have shown that

Table 2 Alterations observed for Case 2 in the short list of clinically relevant genes

Gene	Nucleotide variation	Protein variation	Origin	Impact
APC	c.3949G>C	Glu1317Gln	Constitutive	Potentially Pathogenic
BRCA1	c.5180G>C	Gly1727Ala	Somatic	Unknown
BRCA1	c.3119G>A	Ser1040Asn	Constitutive	SNP
BRCA1	c.2521C>T	Arg841Trp	Somatic	Neutral
FGFR4	c.1676G>A	Arg559Gln	Somatic	Unknown
GLI2	c.1418G>A	Arg473His	Constitutive	Unknown
JAK2	c.195A>C	Glu65Asp	Constitutive	Unknown
JAK3	c.2164G>A	Val722Ile	Constitutive	Activating
KDR	c.2159G>A	Arg720Gln	Somatic	Unknown
KRAS	c.35G>A	Gly12Asp	Somatic	Activating
MET	c.2572G>A	Val858Met	Constitutive	Unknown
RAD51C	c.859A>G	Thr287Ala	Somatic	Loss of function
SLC28A1	c.568G>T	Ala190Ser	Constitutive	SNP
SLC28A1	c.1152delG	Val385Ser fsX16	Constitutive	Loss of function
THRA	c.454C>T	Arg152X	Somatic	Loss of function
UIMC1	c.43C>T	Arg15Trp	Constitutive	Unknown

SNP: Single nucleotide polymorphism.

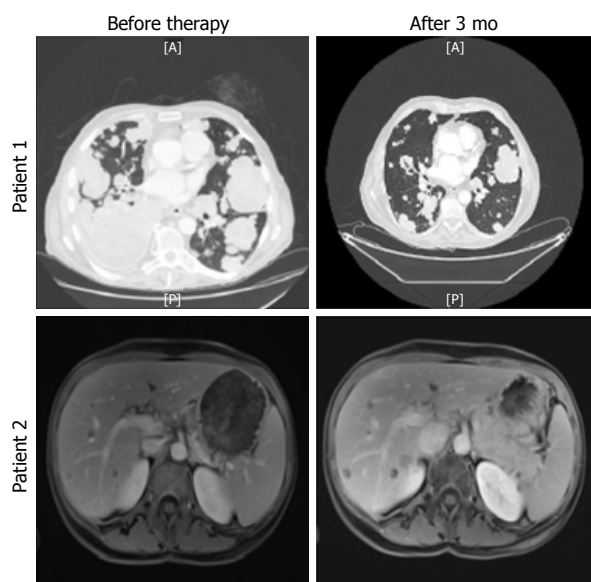


Figure 2 Computed tomography scan of patient 1 before and after 3 mo of olaparib (upper panel), and magnetic resonance imaging of liver metastasis of patient 2 before and after 3 mo of olaparib (lower panel).

the level of RAD51 protein expression is elevated in immortalized cells as well as in a wide variety of human cancer cell lines^[14,15]. It is generally suggested that RAD51 overexpression results in an increased cellular resistance to radiation and some chemotherapeutic drugs, such as topoisomerase inhibitors or crosslinking agents^[15-17]. In CRC, high expression of RAD51 is associated with poor prognosis^[18]. Several *in vitro* studies have shown that an increase in RAD51 expression stimulates homologous repair, resulting in greater cellular resistance to treatment with crosslinking agents, etoposide or irradiation^[15-17]. High numbers of RAD51 foci in tumor biopsies were also positively associated with greater chemoresistance in

breast cancer patients^[19]. Chek2 is also involved in the colorectal oncogenesis and protein truncating mutations in *CHEK2* have been reported to confer higher risks of cancer of the breast and the prostate but also CRC^[20].

Biallelic invalidation of homologous repair enzymes are still described to be a predictive marker of response to PARP inhibitor like olaparib in different diseases such as breast, ovarian and prostate cancer^[7,21-23]. Our report is the first one that researched biallelic deficiency of homologous repair enzyme in metastatic CRC patients and underlines that such events could also occur in this pathology and could be targeted.

Resistance to PARP inhibitors is a key question and determining a predictive biomarker is important for the future design of clinical trials. Three mechanisms of resistance have been described: restoration of BRCA function by additional mutations^[24-26], increased *Mdr1* gene expression^[27] or loss of TP53BP1^[9]. Interestingly, TP53BP1 loss also induces resistance to the topoisomerase I inhibitor while tumor cells remain sensitive to DNA crosslinking agents like platinum, may thus explain the good response to FOLFIRINOX.

To conclude, we believe that this case report supports that large genetic characterization of metastatic CRC patients could be useful to find molecular hits that could be targeted by off-label targeted therapy. PARP inhibitors could be particularly useful in this context. Nevertheless, biallelic deficiency of homologous repair enzyme is a prerequisite to benefit from a PARP inhibitor therapy, but is not always associated to a PARP inhibitor response. Additional resistance pathways like TP53BP1 loss must be determined before prescribing PARP inhibitors.

COMMENTS

Case characteristics

Two case of multitrated metastatic colorectal cancer patients that benefit from

genetic testing.

Clinical diagnosis

metastatic colorectal cancer.

Laboratory diagnosis

Whole exome sequencing revealed inactivating mutation in the homologous repair gene with genetic deficiency in RAD51C or Check2.

Treatment

Patients were treated with the poly ADP ribose polymerase inhibitor olaparib.

Experiences and lessons

One out the 2 patients gained clinical benefit from olaparib usage, thus suggesting that genetic testing could also be used in colorectal cancer to predict response to olaparib.

Peer-review

This case report highlighting the importance of the exome sequencing analysis before administering targeted therapy.

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