фоне иммунотерапии Евразийский онкологический журнал. 2018. Т. 6. № 2. С. 563-576.

Камышов С.В., Юлдашева Н.Ш., Салимова Л.Р. Изучение методов экстракорпоральной иммунофармакотерапии в качестве сопровождения химиотерапии у больных раком яичников Онкология и радиология Казахстана. 2010. № 3-4 (16-17). С. 96.

Юлдашева Н.Ш., Наврузова В.С., Ахмедов О.М., Умарова Н.А., Камышов С.В. Особенности лечебного патоморфоза опухоли при рентгенэндоваскулярной полихимиотерапии в комплексном лечении рака шейки матки Онкология и радиология Казахстана. 2010. № 3-4 (16-17). С. 96-97.

Le Tourneau C, Delord JP, Gonçalves A, et al: Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 16:1324-1334, 2015

McNeil C: NCI-MATCH launch highlights new trial design in precision-medicine era. J Natl Cancer Inst 107:djv193, 2015

Sholl LM, Do K, Shivdasani P, et al: Institutional implementation of clinical tumor profiling on an unselected cancer population. JCI Insight 1:e87062, 2016

Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:703-713, 2017 [Erratum: Nat Med 23:1004, 2017]

Jones S, Anagnostou V, Lytle K, et al: Personalized genomic analyses for cancer mutation discovery and interpretation. Sci Transl Med 7:283ra53, 2015

Schrader KA, Cheng DT, Joseph V, et al: Germline variants in targeted tumor sequencing using matched normal DNA. JAMA Oncol 2:104-111, 2016

Mandelker D, Zhang L, Kemel Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 318:825-835, 2017

Dumbrava EI, Brusco L, Daniels MS, et al: Expanded analysis of secondary germline findings from matched tumor/normal sequencing identifies additional clinically significant mutations. JCO Precis Oncol doi:10.1200/PO.18.00143

Kalia SS, Adelman K, Bale SJ, et al: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics. Genet Med 19:249-255, 2017 [Erratum: Genet Med 19:484, 2017]

Meric-Bernstam F, Brusco L, Daniels M, et al: Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. Ann Oncol 27:795-800, 2016

National Comprehensive Cancer Network (NCCN): Familial and Genetic High-Risk Assessment: Breast and Ovarian. 2019. Version 3.2019, 112. https://www.
nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf

National Comprehensive Cancer Network (NCCN): Familial and Genetic High-Risk Assessment: Colorectal. 2018. Version 1.2018, 97. https://www.nccn.org/
professionals/physician_gls/pdf/genetics_colon.pdf

UDC: 618.11-006

REVERSION MUTATIONS IN BRCA1 AND BRCA2 AND RESISTANCE TO PARP INHIBITORS AND PLATINUM

DOI: 10.31618/ESU.2413-9335.2019.2.69.483

Islamov Khurshid Djamshidovich
MD, PhD. Head of coloproctology Department of Republican specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan, Tashkent

ABSTRACT
This article discusses mutations in the BRCA1 and BRCA2 genes and resistance to PARP inhibitors.

АННОТАЦИЯ
В статье рассматриваются мутации в генах BRCA1 AND BRCA2 и резистентность к ингибиторам PARP.

Key words: PARP inhibitors, BRCA1 and BRCA2 genes, resistance.
Ключевые слова: ингибиторы PARP, гены BRCA1 и BRCA2, резистентность.

Germline pathogenic mutations in BRCA1 and BRCA2 are associated with an increased lifetime risk of breast and ovarian cancers [1]. The tumors that arise in mutation carriers have almost always undergone loss of the wild-type allele, leading to loss of BRCA1/2 function. This, in turn, leads to a profound defect in homology-mediated DNA repair and inappropriate use of error-prone repair pathways, which result in gross genomic instability that contributes to tumorigenesis [2]. This DNA-repair defect in BRCA1/2-mutant cancers renders them exquisitely vulnerable to certain kinds of DNA damage, including those caused by poly (ADP-ribose) polymerase (PARP) inhibitors and certain classic chemotherapy agents, including

platinum.[3] The vulnerabilities of BRCA1/2-mutant cancers to these agents have been translated successfully into treatment approaches. PARP inhibitors are now approved by the US Food and Drug Administration for treatment of BRCA1/2- mutant ovarian cancers [4], and data are accumulating that suggest that PARP inhibitors are likely active in BRCA1/2-mutant cancer regardless of the tissue of origin. PARP inhibitors are thought to be toxic to BRCA1/2-mutant cancers not only because of their catalytic inhibition of PARP but by their ability to trap PARP-1 enzyme on DNA.[5,6] The most potent PARP inhibitors that induce cell death in BRCA1/2-mutant cells are those that most efficiently trap PARP protein on DNA, creating a bulky protein DNA adduct [7]. In this sense, PARP inhibitors work similarly to topoisomerase inhibitors, which trap topoisomerases to create a bulky protein DNA adduct. Thus, in many ways, PARP inhibitors function similarly to classic DNA-damaging agents in the treatment of BRCA1/2-mutant cancers. Other DNA-damaging agents including platinum, mitomycin C, and topoisomerase inhibitors, that also induce DNA adducts, are also effective in the treatment of BRCA1/2-mutant cancers in animal models and clinically.

Given the widespread use of germline and tumor sequencing, and recent US Food and Drug Administration approval of PARP inhibitors, more patients who have tumors with pathogenic BRCA1/2 mutations are being treated with PARP inhibitors and/or platinum agents. However, this has led to more clinicians confronting the problem of acquired resistance to PARP inhibitors and platinum agents in these cancers. One important mechanism of acquired resistance is reversion mutations in BRCA1 or BRCA2 that partly restore wild-type gene function. [8,9] The three reports [10-12] of reversion mutations in BRCA2 in breast and prostate cancers that accompany this editorial highlight the importance and increasing awareness of this mechanism of resistance. The presence of reversion mutations in BRCA1/2 also reveals some insights about the role of BRCA1/2 function in tumorigenesis and chemosensitivity.

Most pathogenic mutations in BRCA1 and BRCA2 are small insertion/deletions that result in a frameshift. A frameshift will introduce a premature stop codon, which leads to a truncated, nonfunctional protein product. Often, frameshift mutations lead to effective null mutations, because RNA transcripts harboring premature stop codons can be recognized and degraded by the nonsense-mediated decay pathway [13]. Reversion mutations are secondary mutations, often small deletions, in a mutant BRCA1/2 allele that convert the initial frameshift mutation into an in-frame internal deletion that still produces a partly functional protein product. Splice-site mutations that induce exon skipping can also result in in-frame reversions, as can

large deletions that encompass multiple exons. Complex rearrangements or abnormal use of alternative start sites that bypass the frameshift mutation may also occur[14]. Rarely, there is full reversion of the pathogenic mutation with restoration of the full wild-type sequence [10]. Reversion mutations can occur in the setting of either germline or somatic BRCA1/2 mutations, [12] and can lead to acquired resistance not only to PARP inhibitors but to other classes of DNA-damaging agents, such as platinum [11].

Intriguingly, the mechanism underlying many reversion mutations is inappropriate use of the nonhomologous end-joining pathway, resulting in small deletions, as seen by presence of microhomology at junction sequences [15]. Longer deletions associated with single-strand annealing may also be present but more difficult to detect. Thus, the DNA-repair defect associated with BRCA1/2 loss may predispose these cells to the kind of mutation that leads to reversion. It is not clear whether treatment with DNA-damaging agents, including PARP inhibitors, contributes to the generation of reversion mutations. It is possible that reversion mutations may already be present in a small population of cells, especially if there is high tumor burden as seen, for example, in ovarian cancer, and are simply selected with ongoing treatment.

Reversion mutations can be difficult to detect by standard sequencing methods. Large deletions may be completely missed by short-read sequencing, and even small deletions have to be carefully curated to determine in which allele they originate, and the effect on the final reading frame. Some full reversions to wild-type sequence may only be detected by careful analysis of tumor purity and mutant allele frequencies in serial samples over time, as demonstrated by Banda et al. Heterogeneity of reversion mutations may also hinder detection. Different tumor sites within one patient may harbor different reversion mutations; this is an example of convergent tumor evolution under selection pressure of therapy. Analysis of circulating-cell free DNA, such as reported by Cheng et al and Carneiro et al, can detect multiple reversion mutations simultaneously at the time of clinical resistance to PARP inhibitors or platinum, each restoring the reading frame and arising from a different small tumor-cell population [16]. It is possible that only a fraction of reversion mutations in BRCA1/2 are being identified by current sequencing methods. New technologies, such as long-read sequencing, and higher depth sequencing may allow more robust detection of reversion mutations and better define their frequency.

The selection for reversion mutations in BRCA1/2 under certain treatments does give us some insights into the biology of BRCA1. The induction of reversion mutations by platinum is clear genetic evidence that this agent acts on the DNA-repair defect associated with BRCA1/2 loss and exerts direct selection pressure to restore BRCA1/2 function. Thus, platinum agents, and possibly some other classes of DNA-damaging agents, are targeted therapy for BRCA1/2-mutant cancers. This finding also suggests that perhaps, in general, DNA-damaging chemotherapies function not as gross metabolic poisons but as targeted therapies for cancers with underlying defects in DNA repair and/or checkpoint control. If this is true, we may need to reconsider how to optimally dose and schedule platinum and other chemotherapy agents, especially in the setting of cancers with underlying DNA-repair defects.

The presence of reversion mutations demonstrates that loss of BRCA1 or BRCA2 function and the associated DNA-repair defect is only required for initiation of tumorigenesis and is not required for maintenance of the cancer phenotype. Thus, one cannot treat BRCA1/2-deficient cancers by restoring BRCA1/2 function. Thus, BRCA1 and BRCA2 are not like p53. Restoration of p53 function kills p53-mutant cancers. Restoration of BRCA1 in BRCA1-mutant cancers will likely make these cancers more fit, not less fit. This feature can be labeled "tumor-suppressor tolerance" to place it in contrast to oncogene addiction.

Tumor-suppressor tolerance may operate in cancers that have underlying mutations in genes critical for genomic stability. Loss of tumor-suppressor function of these genes may only be required for initial tumorigenesis; once the tumor is established, there may be selection pressure to restore the tumor-suppressor function and reestablish DNA-repair function. Thus, reversion mutations are seen in other tumor suppressors associated with DNA repair, such as Fanconi anemia genes including PALB2, as well as RAD51C and RAD51D [17-20]. Selection for other mechanisms to restore tumor-suppressor function can also occur. In BRCA1-mutant cancers, resistance to PARP inhibitors can occur not only by reversion mutations that directly restore BRCA1 function but also by compensating mutations in other genes such as 53BP1 and its downstream factors such as RIF1, PTIP and REV7, which also can restore homology- mediated repair pathways independent of functional BRCA1 [21-25]. Similarly, loss of PTIP and CHD4 may allow BRCA2-mutant cells to reestablish replication fork stability and become resistant to cisplatin and PARP inhibitors [26]. These findings suggest that to better predict sensitivity to PARP inhibitors and platinum, we will need to develop assays capable of distinguishing a cancer with ongoing genomic instability from a cancer with just a history of genomic instability followed by functional reversion of a DNA-repair defect.

With increasing use of PARP inhibitors and platinum for targeted therapy of BRCA1/2-mutant cancers, we will likely see increased incidence of acquired resistance that exploits tumor-suppressor tolerance and restores BRCA1/2 function. This mechanism of resistance is hard to target therapeutically, because it restores DNA-repair function. It is possible that some hypomorphic alleles of BRCA1 and BRCA2 that arise by reversion mutation may still have some targetable vulnerability. Alternatively, PARP inhibitors, or other DNA-damaging agents such as platinum, will need to be combined with other drugs that target a different vulnerability in these cancers. Combination approaches with immunotherapy or with targeted therapy against other oncogenic drivers may lead to combined selection pressure, reduced likelihood of acquired resistance, and overcoming of tumor- suppressor tolerance.

REFERENCES

Камышов С.В., Пулатов Д.А., Юлдашева Н.Ш. Изучение роли молекулярно-биологических маркеров опухоли в выборе метода иммунотерапии в сопроводительном лечении рака яичников и рака шейки матки Евразийский онкологический журнал. 2015. № 2 (5). С. 53-60.

Камышов С.В., Пулатов Д.А., Юлдашева Н.Ш. Изучение роли экстракорпоральной иммунофармакотерапии в снижении токсических эффектов химиолучевой терапии у пациентов с раком шейки матки Евразийский онкологический журнал. 2015. № 4 (7). С. 28-34.

Камышов С.В., Пулатов Д.А., Ахмедов О.М., Саидова К.А., Алиева Д.А., Гильдиева М.С., Нишанов Д.А. Влияние экстракорпоральной иммунофармакотерапии на внутриклеточный метаболизм у пациентов с раком шейки матки Евразийский онкологический журнал. 2018. Т. 6. № 2. С. 551-562.

Камышов С.В. Механизмы иммунных нарушенийу пациентов с раком яичников, получающих химиотерапию, и их динамика на фоне иммунотерапии Евразийский онкологический журнал. 2018. Т. 6. № 2. С. 563-576.

Камышов С.В., Юлдашева Н.Ш., Салимова Л.Р. Изучение методов экстракорпоральной иммунофармакотерапии в качестве сопровождения химиотерапии у больных раком яичников Онкология и радиология Казахстана. 2010. № 3-4 (16-17). С. 96.

Юлдашева Н.Ш., Наврузова В.С., Ахмедов О.М., Умарова Н.А., Камышов С.В. Особенности лечебного патоморфоза опухоли при рентгенэндоваскулярной полихимиотерапии в комплексном лечении рака шейки матки Онкология и радиология Казахстана. 2010. № 3-4 (16-17). С. 96-97.

Venkitaraman AR: Linking the cellular functions of BRCA genes to cancer pathogenesis and treatment. Annu Rev Pathol 4:461-487, 2009

Silver DP, Livingston DM: Mechanisms of BRCA1 tumor suppression. Cancer Discov 2:679684, 2012

Turner N, Tutt A, Ashworth A: Targeting the DNA repair defect of BRCA tumours. Curr Opin Pharmacol 5:388-393, 2005

Evans T, Matulonis U: PARP inhibitors in ovarian cancer: Evidence, experience and clinical potential. Ther Adv Med Oncol 9:253-267, 2017

Pommier Y, O'Connor MJ, de Bono J: Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med 8:362ps17, 2016

Helleday T: The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Mol Oncol 5:387-393, 2011

Murai J, Huang SY, Renaud A, et al: Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 13:433-443, 2014

Ashworth A: Drug resistance caused by reversion mutation. Cancer Res 68:10021-10023, 2008

Sakai W, Swisher EM, Karlan BY, et al: Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 451:1116-1120, 2008

Banda K, et al: Somatic reversion of germline BRCA2 mutation confers resistance to PARP inhibitor therapy. JCO Precis Oncol http://doi.org/10.1200/PO.17.00044

Cheng HH, et al: Polyclonal BRCA2 reversion mutations detected in circulating tumor DNA after platinum chemotherapy in a patient with metastatic prostate cancer. JCO Precis Oncol https://doi.org/10.1200/PO.17.00169

Carneiro B, et al: Acquired resistance to the PARP inhibitor olaparib in BRCA2-associated prostate cancer due to biallelic BRCA2 reversion mutations restoring both germline and somatic loss of function mutations. JCO Precis Oncol http://doi.org/10.1200/PO.17.00176

Perrin-Vidoz L, Sinilnikova OM, Stoppa-Lyonnet D, et al: The nonsense-mediated mRNA decay pathway triggers degradation of most BRCA1 mRNAs bearing premature termination codons. Hum Mol Genet 11:2805-2814, 2002

Wang Y, Krais JJ, Bernhardy AJ, et al: RING domain-deficient BRCA1 promotes PARP inhibitor and platinum resistance. J Clin Invest 126:3145-3157, 2016

Edwards SL, Brough R, Lord CJ, et al: Resistance to therapy caused by intragenic deletion in BRCA2. Nature 451:1111-1115, 2008

Quigley D, Alumkal JJ, Wyatt AW, et al: Analysis of circulating cell-free DNA identifies multiclonal heterogeneity of BRCA2 reversion mutations associated with resistance to PARP inhibitors. Cancer Discov 7:999-1005, 2017

Kondrashova O, Nguyen M, Shield-Artin K, et al: Secondary somatic mutations restoring RAD51C and RAD51D associated with acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov 7:984-998, 2017

Gregory JJ, Jr., Wagner JE, Verlander PC, et al: Somatic mosaicism in Fanconi anemia: Evidence of genotypic reversion in lymphohematopoietic stem cells. Proc Natl Acad Sci USA 98:2532-2537, 2001

Xia B, Dorsman JC, Ameziane N, et al: Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. Nat Genet 39:159-161, 2007

Escribano-Díaz C, Orthwein A, Fradet-Turcotte A, et al: A cell cycle-dependent regulatory circuit composed of 53BP1-RIF1 and BRCA1-CtIP controls DNA repair pathway choice. Mol Cell 49:872-883, 2013

МОНИТОРИНГ ФИЗИЧЕСКОГО РАЗВИТИЯ ДЕТЕЙ ДО ГОДА Г. ЕРЕВАНА

DOI: 10.31618/ESU.2413-9335.2019.2.69.480

Арустамян М.А.
ЕГМУ

Актуальность

Обеспечение охраны здоровья детей является одной из важнейших целей государственной политики в Республике Армения, а принцип профилактической медицины является приоритетом в области детской медицины. Цель профилактической педиатрии - обеспечить гармоничное развитие и достижение оптимального состояния здоровья ребенка. Здоровье будущих поколений определяется состоянием здоровья детского населения. [1].

Физическое развитие детей является одним из ведущих критериев оценки здоровья растущего организма , который является чувствительным индикатором различных внешних факторов окружающей среды [4].

Для каждой детской возрастной группы характерны специфические особенности роста и развития, которые способствуют нормальному течению морфофункционального развития организма на более поздней стадии (если искусственно не ингибировать или не активировать его естественное течение) [2,3].

В первый год жизни (он включает в себя два периода - новорожденности и грудной) решаются задачи подготовки к реализации антигравитационных реакций , первичному овладению микросоциальной средой его существования; формированию предпосылок дальнейшего физического, нервно-психического развития и соматического здоровья. Ребенку до первого года жизни характерны особенности, не встречающиеся в более старшем возрасте: быстрый темп физического развития, взаимозависимость нервно-психического и физического развития; низкая резистентность к метео- и экологическим условиям, дефектам ухода и вскармливания [3,5]

Материалы и методы

Были обследованы 520 новорожденных, из которых 260 мальчиков.

В соответствии с классификацией Ю.А. Князева (1993) антропометрические данные детей разделили по морфотипу [2]

Нормосомия, при которой масса и длина тела находится в промежутке от 25 до 75 центиля и соответсвует среднестатистической норме

Пахисомия – длина тела в пределах 25-75 центилей, масса тела превышает 75 центиля

Лептосомия- длина тела в пределах 25-75 центилей, масса тела менее 25 центиля

Гиперсомия – длина и масса тела превышает 75 центиля

Макросомия –длина тела превышает 75 центиля, масса тела в пределах нормы

Макролептосомия – длина тела превышает 75 центиля, а масса тела менее 25 центиля

Микросомия – длина тела менее 25 центиля, масса в пределах нормы

Микропахисомия – длина тела менее 25 центиля, масса более 75 центиля

Микролептосомия – длина и масса тела находятся ниже нижней границы нормы(менее 25 центиля).