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The Clinical Trials Analysis of Active Ingredient in Mutations of BRCA1 and BRCA2 Genes in Patients with Breast Cancer

Mikołaj Bartoszkiewicz[1]
https://orcid.org/0000-0002-8728-5998

[1] Department of Biology of Lipid Disorders, Poznan University of Medical Sciences, Poland

Address for correspondence

Mikołaj Bartoszkiewicz
Department of Biology of Lipid Disorders
Poznan University of Medical Sciences
Rokietnicka 7 Str., 60-806 Poznan, Poland
e-mail: m.bartoszkiewicz@ump.edu.pl

Abstract

Background: *Breast cancer is the most commonly diagnosed cancer in women all around the world. In 2018 alone, this type of cancer has been diagnosed in 2 million cases. Women who are transmitters of the BRCA mutation are more likely to get breast and ovarian cancer at their young age than women who do not possess this kind of genetic mutation.*

Objectives: *This project aims to analyze clinical studies in the mutation of genes BRCA1 and BRCA2 in breast cancer. Specifying the active substances allows the approximation of which substances are being examined at the moment as innovations.*

Material and methods: *The web database www.clinicaltrials.gov was used for the analysis of clinical studies related to BRCA1 and BRCA2 mutations. The analysis covered research conducted in the European Union and the United States.*

Results: *The most clinical trials of BRCA1 and BRCA2 gene mutations in breast cancer are conducted in the USA – 9 studies, which indicates a 56.2% share in the entire market of research in medicinal products in this indication. Of the EU countries, the majority of research is conducted in Spain – 6 (37.5%). Most of the clinical studies are conducted in an active substance Talazoparib – 6 types of research.*

Conclusion: *Clinical studies in breast cancer in the BRCA1 and BRCA2 gene mutations give hope to many patients waiting for innovative treatments. The United States is conducting more clinical trials in this disease than the European Union.*

Key words: *clinical trials, cancer, BRCA1 gene, BRCA2 gene, mutation.*

Introduction

Breast cancer is the most commonly diagnosed cancer in women all around the world. In 2018 alone, this type of cancer has been diagnosed in 2 million cases. It is estimated that around 5-10% of breast cancer has a genetic origin [1]. One of the genetic factors, which may cause breast and ovarian cancer is the mutation of genes BRCA1 and BRCA2. BRCA1 and BRCA2 are tumor suppressor genes. Their main role is to fix damaged fragments of the DNA, playing an important role in providing stability to the varying genetic material of the cell. When any of these genes are mutated or are not modified in a way that protein end product is not created or does not function correctly, the damaged DNA cannot be fixed. As a result, these types of cells are at risk of genetic changes, which may lead to malignant transformations. Patrimonial BRCA1 and BRCA2 mutations increase the risk of breast and ovarian cancer in women, in addition to increasing the possibility of developing other cancers. Women who are transmitters of the BRCA mutation are more likely to get breast and ovarian cancer at their young age than women who do not possess this kind of genetic mutation. This mutation may be inherited from mother or father, every child of a parent who has the variation of this gene has a 50% chance to inherit this mutation [2]. Women inheriting the BRCA1 or BRCA2 mutation have an approximately 50% to 80% chance of developing breast cancer in their lifetime, as well as a 40% chance of developing ovarian cancer [3]. The average age of getting breast cancer in BRCA1 mutation is forty years old. This mutation very often redounds to medullary carcinoma of the breast in cases of low expression of the estrogen receptor. The oncology clinical studies are a huge chance to access innovative medications for patients; therefore, the development of research of the product is significantly essential. The enormous number of clinical studies conducted on breast cancer allows the oncologist to fit adequate treatments and to present access to innovative therapies. The analysis of studies in breast cancer of BRCA1 and BRCA2 genes allows approximating the amount of research, their stages, and the best treatments accessible on the market.

Material and methods

The web database www.clinicaltrials.gov was used for the clinical study analysis, which relates to mutation BRCA1 and BRCA2. It is a database of international clinical studies that are either private or founded by public resources. The information is provided by the US National Library of Medicine, in which the analysis of the amount of research associated with mutation BRCA1 and BRCA2, stages of research, and tested treatment schemes was made. The data covers the period from the 1st of January to the 25th of January 2020. The analysis covered the research conducted in the European Union and the United States.

Aim

This project aims to analyze clinical studies in the mutation of genes BRCA1 and BRCA2 in breast cancer. Specifying the active substances allows the approximation of which substances are being examined at the moment as innovations. The analysis will also determine the country where the most significant amount of clinical studies in BRCA1 and BRCA2 mutation was conducted, divided into the phases of the research.

Results

During the analysis period, there are 16 clinical studies associated with mutation of BRCA1 and BRCA2 gene in breast cancer, where 9 of them are in the US, and seven are in the EU. There are six clinical trials in the recruitment stage, and ten are in the active stage. Figure 1 shows the number of clinical trials divided into phases.

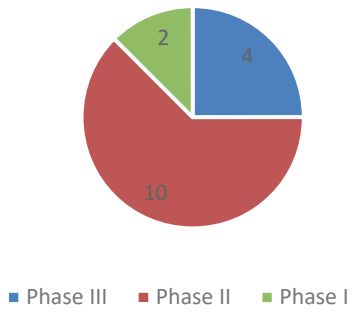

Figure 1. Division by the phase of gene mutation studies BRCA1 and BRCA2 in breast cancer

Analyzing the following diagram (figure 1) we can notice that most of those studies with BRCA1 and BRCA2 gene mutation in breast cancer are conducted in the second phase – 10 studies, then the third phase – 4 trials, and in the third place is phase number one – 2 studies.

Table 1 presents all the countries included in the analysis. The most clinical trials of BRCA1 and BRCA2 gene mutations in breast cancer are conducted in the USA – 9 studies, which indicates a 56.2% share in the entire market of research in medicinal products in this indication. Of the EU countries, the majority of research is conducted in Spain – 6 (37.5%), followed by France, Poland, and the UK – 5 (31.2%), the third places are Hungary and Italy – 4 (25%). Furthermore, EU countries do not exceed 19% market share in the clinical trials of BRCA1 and BRCA2 gene mutation in breast cancer in the EU and the US. Nine of the EU countries do not conduct any medical research in this diagnosis.

Table 2 presents clinical experiments by NCT numbers (clinical trials number from the clinicaltrials.gov database): the active substance being tested and the countries that participate in the project. When analyzing the active substance, which during the analysis period was most often studied in clinical trial projects in the EU and the US, Talazoparib comes first – 6 studies (37.5%). Olaparib is second – 3 studies (19%), Niraparib, and Veliparib are in the third place – 2 (12.5%). The fourth place take

active substances: ABT-888, Temozolomide, Denosumab, and Pembrolizumab after 1 study (6.2%).

Table 1. The countries participating in the analysis

Country	Number of clinical trials
US	9
Spain	6
France	5
Poland	5
UK	5
Hungary	4
Italy	4
Belgium	3
Germany	3
Sweden	3
Czechia	2
Netherlands	2
Romania	2
Bulgaria	1
Denmark	1
Greece	1
Finland	1
Ireland	1
Portugal	1
Austria	0
Cyprus	0
Estonia	0
Latvia	0
Lithunia	0
Luxembourg	0
Malta	0
Slovakia	0
Slovenia	0

Table 2. The clinical experiments by NCT numbers, divided in to:
active substance, phase, country and status

NCT number	Active substance	Phase	Country	Status
NCT 0200622	Olaparib	3	Bulgaria, Czechia, France, Germany, Hungary, Italy, Spain, Sweden, Poland, Romania, UK, US	Active
NCT 01945775	Talazoparib	3	Belgium, France, Germany, Ireland, Italy, Spain, Poland, UK, US	Active
NCT 01905592	Niraparib	3	Belgium, France, Greece, Hungary, Italy, Netherlands, Spain, Portugal, Poland, UK, US	Active
NCT 01506609	Veliparib	2	Belgium, Czechia, Denmark, Finland, France, Hungary, Netherlands, Spain, Sweden, Poland, Romania, US	Active
NCT 03286842	Olaparib	3	Hungary, Itlay, France, Germany, Spain, Poland, UK, US	Active
NCT 01078622	Olaparib	2	Spain, US	Active
NCT 02034916	Talazoparib	2	UK	Active
NCT 01009788	ABT-888, Temozolomide	2	US	Active
NCT 02282345	Talazoparib	2	US	Active
NCT 02286687	Talazoparib	2	US	Recruitment
NCT 03382574	Denosumab	1	US	Recruitment
NCT 03428802	Pembrolizumab	2	US	Recruitment
NCT 03329937	Niraparib	1	US	Recruitment
NCT 01149083	Veliparib	2	US	Active
NCT 02401347	Talazoparib	2	US	Recruitment
NCT 03499353	Talazoparib	2	US	Recruitment

Discussion

During the analyzed period, seven active substances were tested in the BRCA1 and BRCA2 gene mutations in breast cancer. Most of the clinical studies are conducted in an active substance Talazoparib – 6 types of research, which from the 16th of October 2018 is officially approved by the FDA as medicine in advanced treatment of breast cancer in BRCA positive patients [4]. The second place is Olaparib – 3 trials, which is registered in Europe and the United States in the treatment of ovarian cancer in further line therapy [5]. The use of this medicine may not reach the full potential; therefore, there are conducted other clinical studies in differential diagnosis and treatment lines, which gives hopes to ill patients. Another active substance is Veliparib – 4 types of research, which from 2014 is in the third stage of ovarian cancer recognition, triple-negative breast cancer, and non-small-cell lung carcinoma [6]. Niraparib also 2 trials; it was approved for treating ovarian cancer on 27th of March 2017 in the US and in Europe on 16th of November 2017 [7,8]. Another active substance, which is tested in the event of BRCA mutation, is the Tremelimumab – 1 trial, which was unsuccessfully tested in the recognition of malignant melanoma, mesothelioma, and non-small-cell lung cancer [9]. Temozolomide – 1 trial is registered as a medicine for patients with newly diagnosed glioblastoma multiforme in a combination of x-ray therapy, and next with monotherapy [10]. The last two active substances that have proven effects are Pembrolizumab and Denosumab. Pembrolizumab is a humanized antibody used in cancer immunotherapy. Pembrolizumab is approved by the FDA for several different cancers [11]. Denosumab is a human monoclonal antibody for the treatment of osteoporosis, treatment-induced bone loss, metastases to bone, and giant cell tumor of bone [12,13]. In the United States, more research is being carried out in this diagnosis than in the European Union. The United States also dominate in terms of clinical trials during recruitment. About 58% of clinical trials in breast cancer worldwide are conducted in the United States. The clinical trials market in the United States has more significant development potential than the

European Union market. One EU concept for improving the situation of clinical trials is a Regulation (EU) No 536/2014 of the European Parliament and of the Council of the 16th of April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. The primary purpose of the Regulation is to streamline and shorten the procedure for obtaining permits for clinical trials of medicinal products. It provides for the submission of one central application (via the Internet portal), which will allow sponsors to avoid the preparation of various documentation and international application forms for global clinical trials. Due to delays in creating the portal, the application of this Regulation has been postponed several times. According to unofficial information, it is planned until the end of the first quarter of 2020 [14]. Oncologist engagement in clinical trials has an effect on patient recruitment, which in turn can affect trial success. Encouraging primary care physicians to a patient participant in clinical trials should be the next step in improving the EU clinical trial market. A survey conducted in Canada on 127 physicians by Bylund L. et al, shows that primary care physicians may be an important group to target in trying to improve cancer clinical trial participation among minority patients. Future work should explore methods of an educational intervention for such interested providers [15]. A survey conducted on 221 oncologists by Somkin CP. et al shows that to increase trial participation, there is a critical need for infrastructure to support trials, especially additional support staff and research nurses. In addition, there is a need for better intra-organizational communication and consideration of the impact of trial design on internal health plan resources. This research supports the need to continue a national dialogue about the broadly defined benefits and costs of clinical trials to patients, physicians, and health plans [16].

Conclusion

Clinical studies in breast cancer in the BRCA1 and BRCA2 gene mutations give hope to many patients waiting for innovative treatments. The

United States is conducting more clinical trials in this disease than the European Union. The most commonly studied drug substance is Talazoparib. Most studies are conducted in phase III. Of the European Union countries, Spain is the country where the largest number of studies on medicinal products in the BRCA1 and BRCA2 gene mutations are carried out in breast cancer.

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