Review article

Off-label drug use in breast cancer therapy

Tomasz Jankowski, MD, PhD[1], Monika Urbaniak, MD, PhD[2]

[1] Oncology Ward, John of Dukla Oncology Centre in Lublin, Poland

[2] Department of Healthcare Organization and Management, The Karol Marcinkowski Poznan University of Medical Sciences, Poland

ABSTRACT

Breast cancer is one of the most common malignancies across the world, including Poland. Chemotherapy plays an important part in the treatment of the disease. Most of the available chemotherapy drugs and regimens have undergone randomized clinical studies and have been registered for that specific indication. However, a number of drugs are used in an off-label manner, i.e. outside the officially approved product specifications.

The paper discusses the use of several off-label therapies in breast cancer in order to demonstrate that such treatment may be well-grounded and indeed turns out beneficial in many cases. It describes the use of liposomal doxorubicin in pre- and post-operative treatment, capecitabine for incomplete efficacy of preoperative treatment, and the administration of metronomic vinorelbine. Moreover, the paper is aimed at demonstrating the legal basis and the principles of marketing authorization of off-label drug use.

Key words: breast cancer, off-label, chemotherapy, metronomic vinorelbine, liposomal doxorubicin, capecitabine

Correspondence:
Tomasz Jankowski, MD, PhD
Oncology Ward, John of Dukla Oncology Centre in Lublin
20-090 Lublin
ul. dr K. Jaczewskiego 7
e-mail: yankitom@wp.pl

Received:
7.06.2017.
Accepted:
12.06.2017.

DOI: 10.24292/01.OR.300617.5

INTRODUCTION

Breast cancer is one of the most common malignancies across the world, including Poland [1]. Chemotherapy plays an important part in the treatment of the disease, administered both as radical and palliative treatment, at the pre- and post-operative stage, and used to manage remote metastases as well [2]. Most of the available chemotherapy drugs and regimens have undergone randomized clinical studies and have been registered for that specific indication. However, a number of drugs are used in an off-label manner, i.e. outside the officially approved product specifications.

It is worth observing that the practice resembles that of a therapeutic experiment. In a medical experiment, a physician introduces new or only partially tested diagnostic, therapeutic or prophylactic methods in order to accomplish direct benefits for the person undergoing treatment. Such an experiment may be conducted if the previously applied methods prove ineffective or if their efficacy is insufficient (Article 21 section 2 of the Polish Act on the Professions of Physician and Dentist). It should be recognized, though, that prescribing an off-label therapy by a doctor does not constitute a medical experiment due to the absence of the innovation premise.

In 2015, Hamel et al. published the results of studies involving the population of American women treated for breast cancer in the years 2000–2009. The analysis involved 2663 women in total, suffering from different stages of breast cancer, and undergoing different therapeutic modalities. 55.4% out of the 65 regimens identified involved off-label drug use. The most commonly administered off-label drugs included vinorelbine, carboplatin, bevacizumab, leuprorelin, liposomal doxocycline, cisplatin and gemcitabine. It was observed that the off-label use of most of the above mentioned drugs was associated with a number of specific factors, including patient insurance, younger age, race other than Caucasian, smaller medical centres, and a low number of clinical studies for drugs available on the market for a long time. In most cases, the efficacy of off-label therapies had been confirmed in medical literature, even though they had not been included in the registered product specifications [5].

EXAMPLES OF OFF-LABEL BREAST CANCER THERAPIES

Liposomal doxorubicin in breast cancer adjuvant therapy

Based on many clinical experiences, it appears that pegylated liposomal doxorubicin (PLD) may be administered in operable stage I–III breast cancer.

Lu et al. analysed the use of PLD in 180 patients undergoing post-operative treatment for stage I–III breast cancer. The treatment was offered in 6 different centres, using different regimens including PLD. 5-year disease-free survival was accomplished in 76.3% of the patients, with 10-year survival reported for 72.6% of them. Toxicity was acceptable and comparable with conventional treatment, mostly involving haematological complications. Grade 3 and 4 haematological events affected around 7% of the patients [3].

Another interesting study was dedicated to adjunctive treatment in the HER2-negative and HR-negative breast cancer patients. A group of 162 triple-negative breast cancer patients was treated with chemotherapy based on PLD (30% of the patients) and without PLD (70% of the patients, most of whom received doxorubicin or epirubicin). Analysis of the study results indicated no significant differences in terms of progression-free survival and overall survival. In the group of patients treated with PLD, haematological toxicity was statistically significantly lower, while the hand–foot syndrome was reported more frequently [4].

The use of PLD in adjuvant breast cancer therapy is an alternative method, with respect to the conventionally administered anthracyclines, to be considered in a group of patients at risk of cardiovascular complications, and in particular in older patients or those with other contraindications for doxorubicin or epirubicin.

Capecitabine in breast cancer adjuvant therapy

Treatment involving capecitabine prolongs progression-free survival and overall survival in breast cancer patients, in whom complete response has not been achieved following conventional neoadjuvant chemotherapy. In December 2015, during the San Antonio Breast Cancer Symposium, results of the CREATE-X multi-centre study were announced. It involved 910 HER2-negative breast cancer patients with residual invasive carcinoma following pre-operative treatment (patients with pCR in the breast and lymph nodes had been excluded). Most of the study subjects had received anthracyclines as neoadjuvant treatment, followed by taxanes (80% of the patients). 60% of the patients had also been started on 5-fluorouracil. Hormone therapy had been offered to 40% of pre-menopausal patients and 25% of post-menopausal patients.

455 patients were randomized to oral capecitabine dosed at 1250 mg/m^2 twice daily for 14 days every 21 days. 58% of the patients received 6 treatment cycles, and 38% of the patients completed therapy, having undergone 8 cycles of capecitabine treatment. The control group was subject to close follow-up. Oestrogen or progesterone receptor-positive patients received hormone therapy in accordance with the binding standards.

After the 5-year follow-up, the percentage of progression-free patients amounted to 74.1% in the capecitabine arm, and in the control arm it was 67.7%, with the risk reduction totalling 30% and being statistically significant ($p = 0.00524$). Overall survival was 89.2% and 83.9%, respectively, with a statistically significant risk reduction of 40% ($p < 0.01$). Therapeutic benefits were achieved in all of the analysed subgroups, with the greatest benefits reported for the triple-negative breast cancer patients [6].

Treatment tolerance was relatively good, and the most common complications included the hand–foot syndrome (72.3% of the capecitabine patients, with grade 3 events affecting ca. 11% of the patients), grade ≥ 3 neutropenia (6.6% of the capecitabine patients, and 1.6% in the control arm), and grade ≥ 3 diarrhoea (3% of the capecitabine patients, and 0.4% of those in the control arm).

Postoperative capecitabine treatment may be considered in the HER2-negative, ER-negative and PR-negative patients in whose case complete response has not been accomplished following preoperative treatment, even though previous studies failed to demonstrate the drug's efficacy in the adjuvant setting. Additional arguments in favour of the use of capecitabine include: high availability of the drug, low price, relatively low toxicity, and no cross-resistance to anthracyclines and taxanes [7].

Metronomic vinorelbine in the treatment of metastatic breast cancer

Metronomic chemotherapy (MCT) is a novel and promising treatment strategy for patients suffering from malignant neoplasms. The underlying principle is to administer low doses of drugs at short time intervals. The main goal of metronomic therapy is to inhibit angiogenesis, a process which is indispensable for tumour growth. Neoangiogenesis involves the development of blood vessels from the endothelium of the already existing ones. It has been proven that those blood vessels are highly sensitive to low doses of cytostatic drugs [8]. Thanks to such management, one can achieve significant clinical benefits, while maintaining treatment-related toxicity at a minimum level [9, 10].

The VICTOR-1 and VICTOR-2 studies demonstrated that oral metronomic chemotherapy involving vinorelbine + capecitabine has a high efficacy and low toxicity in the patients with advanced HER2-negative and HR-positive breast cancer.

The study looked into the use of oral vinorelbine dosed at 40 mg three times a week, and capecitabine dosed at 500 mg three times a day. 31 patients were observed in the VICTOR-1 study, 18 (58%) out of which were reported to have benefitted from the treatment (complete and partial response was achieved in 5 patients, and stable disease was observed in 9 of them). The regimen was especially efficacious in patients over the age of 70. In that subgroup, 39% of the patients responded to treatment, with median time to progression totalling 10.5 months. Treatment tolerance was satisfactory. The main problem was grade 3 and 4 neutropenia, diagnosed in 6% of the patients, with only 2.2% of them coming from the 70+ subgroup [13]. The above mentioned results were later confirmed in the VICTOR-2 study, involving a larger population of patients [11]. In other phase II clinical studies, metronomic vinorelbine was administered as monotherapy, e.g. at the dose of 30 mg/m^2 every other day [12].

The ABC guidelines (Advanced Breast Cancer Third International Consensus Conference on the diagnosis and treatment of advanced breast cancer), published in the wake of the Lisbon conference in 2015, recommend metronomic vinorelbine chemotherapy as a valuable option for patients with metastatic HER2-negative and HR-positive breast cancer, in whose case it is not necessary to induce immediate remission. We are still waiting for the results of on-going studies comparing metronomic chemotherapy with the conventional one. They are currently at the stage of patient recruitment or treatment.

LEGAL ASPECTS OF THE OFF-LABEL DRUG USE

Issues related to the off-label drug use are regulated by a number of different legal acts, including in particular the Act of 5 December 1996 on the professions of physician and dentist, Act of 6 September 2001 "Pharmaceutical Law," and the Act of 12 May 2011 on the reimbursement of medicines, food products of special nutritional purpose and medicinal products [14].

One should start by pointing out that the legislator has not included a direct ban on the off-label drug use in the provisions of mandatory legislation. Therefore, we may assume that such a solution is admissible. Moreover, following the publication of Luty, it should be noted that there are no statutory regulations that would impose the obligation to prescribe on-label drugs only on physicians [15]. In accordance with Article 23 section 2 of the Pharmaceutical Law Act, issuing a marketing authorization is tantamount to the approval of product characteristics, leaflet and packaging, including its labelling, quality requirements and quality test methods both for the medicinal product and its packaging. The summary of product characteristics is the summary of knowledge acquired in the course of clinical studies dedicated to the medicinal product in question [16]. It is also a point of reference with respect to conventional use of the product.

It seems fitting here to ask about the legal nature of the summary of product characteristics. It does not constitute a legal act which would be binding for all or only for the persons it is addressed to (physicians). It would also be difficult to accept that the indications included in the summary of product characteristics should be treated as binding for the physicians from the point of view of the current medical knowledge. Instead, it should be understood as containing the basic information on the drug's characteristic features, and every decision on drug use lies in the hands of the medical doctor involved, and requires detailed assessment of each individual medical case. Still, one should certainly admit that the summary of product characteristics (SmPC) is a set of guidelines for medical practitioners on how to administer specific drugs.

There are such situations in clinical practice, when a physician decides to go beyond the indications included in SmPC, i.e. they go beyond the circumstances in which a given drug has been licensed for use, e.g. when a drug is prescribed to patients from a different age bracket than the one officially indicated for [17]. A setting that is conducive to off-label drug use is paediatric and geriatric treatment, where there is a shortage of medicinal products due to the heavy restrictions with respect to clinical studies carried out by pharmaceutical concerns in those populations of patients [18]. Reasons for off-label drug use include, inter alia, the need to offer a lifesaving therapy or one which saves the patient's health, and inefficacy of the existing therapies. In every case, off-label drug use will be regarded as an exception from the rule of initiating or continuing treatment in line with SmPC [19].

It is one of the doctor's duties to undertake treatment which is determined by the patient's clinical condition. In the context of the off-label drug use, one should take into consideration the content of Article 4 of the Act on the professions of physician and dentist, which stipulates that a physician is obliged to perform his profession in compliance with the current medical findings, using the available therapeutic and preventative methods, to diagnose and treat diseases in accordance with the principles of medical ethics, and to do so with due diligence. Based on that legal provision, one might conclude that a physician is allowed to prescribe an off-label therapy to a patient on condition that such management follows from the current medical knowledge. Such an approach was confirmed by the Supreme Court in the judgement of 10 February 2010 [20], in which the court decided that medical practitioners were obliged to undertake such management as required in order to guarantee, with due diligence and adherence to the current medical knowledge, a predictable effect in the form of patient recovery, and first and foremost in order not to put patients at risk of exacerbation. On the other hand, Article 6 of the Code of Medical Ethics stipulates that a physician has the freedom to choose the therapeutic methods he believes to be the most efficacious. The principle of an autonomous therapeutic decision-making process reinforces the physician's position with respect to the patient, providing the medical doctor with the freedom to choose a specific treatment method based solely on his decision. A condition for taking such a decision is that the medical activities undertaken by the doctor should be limited to the ones that are truly indispensable [21]. It should also be noted here that a doctor's decision that goes against the patient's will delegalizes all the actions undertaken by the physician, and therefore a lack of consent on the part of the patient should be treated as binding for the doctor. It appears fitting to invoke the content of Article 31 section 1 of the Polish Act on the professions of physician and dentist, which stipulates that a physician is obliged to provide comprehensible information to the patient or to the patient's statutory representative with respect to the patient's health condition, diagnosis, proposed and possible diagnostic and therapeutic methods, their predictable sequelae as well as the consequences of failure to apply those methods, treatment results and further prognosis. It follows from the article that it is a physician's duty to inform the patient about the possible treatment methods, including off-label therapies. Certainly, off-label drug use is more difficult for the physician in terms of the decision-making process than the use of drugs in accordance with their SmPC, as off-label drug use entails the need to reproduce the content of a medical standard on one's own, and thus to assess the validity of the standard in so doing.

In line with Article 40 of the Act of 12 May 2011 on the reimbursement of drugs, food products of special nutritional purpose and medicinal products, reimbursement of a drug administered in a different clinical condition than the ones included in the product's SmPC is possible. That legal provision is a legal basis for the reimbursement of a drug outside of its official specifications [15]. According to the above mentioned article, if it is indispensable to save the lives and health of patients (beneficiaries), and in light of the absence of other available medical procedures financed from the public funds, the minister competent for health matters, having consulted the Transparency Board and the national consultant responsible for the medical field in question, may issue, ex officio and having taken into consideration:

1. the criteria mentioned in Article 12, items 4-6, 9, 10, 12 and 13
2. the cost–effectiveness ratio

– an administrative decision to reimburse a drug whose clinical use goes beyond the official summary of product characteristics within the meaning of the Pharmaceutical Law Act (in terms of

the drug's indications for use, dosing schedule or route of administration). If the legislator did not allow for off-label drug use, reimbursement of a drug administered outside of the official specifications, based on individual therapeutic decisions, would clearly not be possible.

CONCLUSIONS

To conclude the above deliberations, one should quote the content of Article 35 section 4 of the Pharmaceutical Law Act, which stipulates that a responsible entity, manufacturer or company authorized to carry out wholesale or retail trade, a physician or other persons entitled to prescribe and dispense medicinal products based on separate legal provisions are not subject to civil or disciplinary liability for the effects of off-label drug use or for the effects of an unlicensed medicinal product, if such non-standard drug use stems from a temporary marketing authorization granted by the minister competent for healthcare.

In summary, it should be observed here that prescribing an off-label therapy does not constitute a violation of the binding legal regulations on condition that such management has been chosen with due diligence and in keeping with the requirements of the current medical knowledge. It is of utmost importance for the process that the patient involved gives his informed consent to a specific therapy, including an off-label one.

References

1. Wojciechowska U, Didkowska J, Zatoński W. Nowotwory złośliwe w Polsce w 2010 rok. Centrum Onkologii – Instytut, Warsaw 2012.
2. Krzakowski M. Nowe możliwości w uzupełniającym leczeniu systemowym chorych na raka piersi. Onkologia w Praktyce Klinicznej 2007; 3(1): 8-15.
3. Lu YC, Ou-Yang F, Hsieh CM et al. Pegylated liposomal doxorubicin as adjuvant therapy for stage I-III operable breast cancer. In Vivo 2016; 32(2): 159-163.
4. Lien MY, Liu LC, Wang HC et al. Safety and efficacy of pegylated liposomal doxorubicin-based adjuvant chemotherapy in patients with stage I-III triple-negative breast cancer. Anticancer Res 2014; 34(12): 7319-7326.
5. Hamel S, McNair DS, Birkett NJ. Off-label use of cancer therapies in women diagnosed with breast cancer in the United States. Springerplus 2015; 4: 209.
6. Lee SJ, Toi M, Lee ES et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04). 2015 San Antonio Breast Cancer Symposium. Abstract S1-07. Presented December 9, 2015.
7. von Minckwitz G, Reimer T, Potenberg J et al. The phase III ICE study: Adjuvant ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. 2014 San Antonio Breast Cancer Symposium. Abstract S3-04. Presented December 11, 2014.
8. Bujak A, Kałas W. Chemioterapia metronomiczna jako nowa strategia leczenia chorób nowotworowych. Postępy Hig Med Dośw 2008; 62: 364-371.
9. Su WH, Ho TY, Li YT et al. Metronomic therapy for gynecologic cancers. Taiwan J Obstet Gynecol 2012; 51: 167-178.
10. Munoz R, Shaked Y, Bertolini F et al. Anti-angiogenic treatment of breast cancer using metronomic low-dose chemotherapy. Breast 2005; 14: 466-479.
11. Cazzaniga ME on behalf of the VICTOR-2 Study. Poster presentation at 10th European Breast Cancer Conference (abstract 375). Amsterdam, The Netherlands. 09-11 March 2016.
12. De Iuliis F, Salerno G, Taglieri L et al. On and off metronomic oral vinorelbine in elderly women with advanced breast cancer. Tumori 2015; 101(1): 30-35.
13. Cazzaniga ME, Torri V, Villa F et al. Efficacy and safety of the all-oral schedule of metronomic vinorelbine and capecitabine in locally advanced or metastatic breast cancer patients: the Phase I-II VICTOR-1 study. Int J Breast Cancer 2014; 769790. DOI: 10.1155/2014/769790.
14. Ustawa z dnia 12 maja 2011 r. o refundacji leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych. Official Journal of Laws 2016, item 1536.
15. Luty O. Zaniechanie zlecenia produktu leczniczego poza zarejestrowanymi wskazaniami a odpowiedzialność cywilnoprawna lekarza. Cz. II. Obowiązek zlecenia leku off label i konsekwencje jego niewykonania. Prawo i Medycyna 2014; 2: 132-150.
16. Szafrański T, Szafrańska A. Przechadzki po polu minowym – uwagi dotyczące stosowania leków niezgodnie z charakterystyką produktu leczniczego. Postępy w Psychiatrii i Neurologii 2012; 2: 108.
17. Gałęska-Śliwka A. Pozarejestrowe stosowanie leków (*off label* use). Serwis Prawniczy Prawo i Zdrowie [Access: 31 May 2017].
18. Polaczuk P. Przeciwdziałanie off label use w prawie europejskim. Zarys wybranych problemów. Studia Prawno – Ekonomiczne 2016; t. C: 155.
19. Zajdel J. Stosowanie produktów leczniczych „off label use" w populacji pediatrycznej – działanie na granicy ryzyka, czy dołożenie należytej staranności? Przegląd Lekarski 2011; 68(1): 35.
20. Decision of the Supreme Court of 10 February 2010, case file reference number V CSK 287/09.
21. Urbaniak M, Cofta S. Zasady postępowania lekarza wobec pacjenta – komentarz do art. 6 i art. 7 KEL. Medyczna Wokanda 2015; 7: 54.

Authors' contributions:
Tomasz Jankowski: 50%; Monika Urbaniak: 50%.
Conflict of interests:
None.
Financial support:
None.
Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.