RESEARCH ARTICLE / Araştırma Makalesi

Incidence of Unlicensed And Off-Label Drug Use in Breast Cancer Therapy İn Turkey: Assessment of Legislative and Regulatory Policy

Türkiye'de Meme Kanseri Tedavisinde Ruhsatsız ve Endikasyon Dışı İlaç Kullanım Sıklığı: Yasama Ve Düzenleme Politikasının Değerlendirilmesi

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Abstract

Objective The aim of the study is to evaluate the use of off-label or unlicensed medicines in breast cancer for understanding of Turkey's perspective. **(Sakarya Med J 2018, 8(4):847-853)**

Materials and Methods This study involved patients (n=1317) with metastatic breast cancer with tumors ErbB-2 positive who received trastuzumab or other medicine application off-label use.

Results It was seen the Marmara Region had the highest application percentage (33.26 %) and it was continued the Central Anatolia Region (27.79 %). Evaluated on the base of cities Istanbul, Ankara and Izmir had the most applications with 29.6 %, 19.2 % and 15.7 % respectively. University hospitals were created the most of the applications, other applications were from education and research hospitals and private hospitals

Conclusion This may be caused from the fact that university hospitals accept severe patients who may need off-label medicines.

Keywords Off-label drug use; Breast Cancer; Trastuzumab

Öz

Amaç Bu çalışmanın amacı, Türkiye'de meme kanseri tedavisinde ruhsatsız ve endikasyon dışı ilaç kullanımını değerlendirmektir. **(Sakarya Tıp Dergisi 2018, 8(4):847-853).**

Gereç ve Yöntem Bu çalışmaya trastuzumab veya diğer endikasyon dışı ilaç kullanımı için başvuruda bulunmuş ve ErbB-2 pozitif tümörleri olan metastatik meme kanseri hastaları (n = 1317) alındı.

Bulgular Marmara Bölgesi en yüksek başvuru yüzdesine (% 33,26) sahipdi bunu İç Anadolu Bölgesi (% 27,79) izledi. En fazla başvuru sırasıyla İstanbul (% 29,6) Ankara (% 19,2) ve İzmir (% 15,7) illerinden yapıldı. En çok üniversite hastanelerinden başvurular vardı, diğer başvurular ise eğitim ve araştırma hastaneleri ve özel hastanelerden geliyordu.

Sonuç Bu durum, üniversite hastanelerinin endikasyon-dışı ilaç kullanımına ihtiyaç duyabilecek hastaları daha fazla kabul etmesinden kaynaklanabilir.

Anahtar Kelimeler Endikasyon-dışı ilaç kullanımı; Meme Kanseri; Trastuzumab

Introduction

A large number of licensed medications are used routinely for unapproved indications or dosages, routes of administration, or age groups which are not described in their package insert are called ''off-label usage''. This term contains unlicensed, unregistered or ''compassionate use'' medicines.[1] Off-label use is the practice of prescribing pharmaceuticals for an unapproved indication for use or in an age group outside of an approved indication for use, dose, or method of administration.[2] The principles underlying the use of unlicensed medicines are the same as those of off-label medicines. Generally, off- label use is not recommended but still has legal procedures in many countries' laws and regulations, after all normal treatment protocols are applied. Situations may occur in which a physician has used all normal treatment options and off-label and/or unlicensed medicinal products may be the last options.[3] Off-label drug usage is very preferable in many countries. One of the studies reported that 55 % of prescriptions were licensed, 19% were unlicensed, and 26% were licensed pharmaceuticals used through off-label policies. In fact, unlicensed preparations were used in pediatric patients.[4]

Off-label drug use is also public policy in Turkey in such that off-label use may lead to reimbursement restrictions. Off-label drug use is defined by the Turkish Ministry of Health (MoHT) as the use of licensed pharmaceutical products in doses outside of or exceeding the scope of the registered indication and the use of unlicensed medicinal products that are imported for the purpose of individual treatment. Hence, off-label use covers both licensed and unlicensed products.[5]

In Turkey, physicians can prescribe medications off-label or unlicensed drugs under the control of the Ministry of Health Medicines and Medical Device Agency (TITCK) (http:// www.titck.gov.tr). The TITCK evaluates off-label and unlicensed medication use for each patient through off-label application procedures. A physician who wants to prescribe an off-label or unlicensed pharmaceutical has to apply to the TITCK for patient-based approval. The TITCK evaluates each application based published scientific evidence and academic consultants. If the TITCK approves the off-label or unlicensed prescriptions, the cost of medication subject to these prescriptions shall be reimbursed by the Turkish Social Security Institution (SGK) (http://www.sgk.gov.tr). When an unlicensed medicine is approved by the TITCK, the Turkish Pharmacy Association is then responsible for importing it.[5] The TITCK also publishes guidelines for using pharmaceuticals without the patient base approval process. If a pharmaceutical is mentioned in these guidelines for use in an off-label indication not yet approved, physicians can prescribe it. The pharmaceutical will then be reimbursed by the SGK in the off-label indication without approval process. This indication is mentioned as "no-need to approval process off-label indications" in the guideline. No-need to approve process helps to increase the efficiency of off-label use decrease the workload of the TITCK.

The aim of this study is to evaluate the use of off-label or unlicensed medicines in breast cancer for understanding of Turkey's perspective within this area of healthcare provisions. In addition, we hope that result of this study will help to update the guidelines and determine pharmaceuticals and off-label indications in breast cancer.

Materials and Methods

This descriptive study involved patients (n=1317) with metastatic breast cancer (human epidermal growth factor receptor 2; ErbB-2 positive) who received trastuzumab or other medicine applicati-

on off-label in Turkey. During 1st January 2008 to 1st January 2011, trastuzumab was licensed only for 9 weeks, not for 52 weeks in Turkey.

Database of TITCK was used to examine off-label medicine use for the treatment of metastatic breast cancer. In the analysis, the off-label use of medicines during the breast cancer therapy were evaluated to provide an understanding of Turkey's perspective within this area of healthcare provisions. Outcomes were evaluated based on the application status, approval period, locational applications, hospital category and medication status. In addition, it was aimed to help update the guidelines and determine pharmaceuticals and off-label indications for no-need to approve process off-label indications in breast cancer pharmaceuticals.

Results

The data obtained from TITCK's database between 1st January 2008 to 1st January 2011 showed that 1317 applications were submitted for off-label metastatic breast cancer medicine use. Average age was 49.02 ± 10.46. One thousand one hundred twenty two (85 %) of all off-label medicine usage applications for breast cancer were approved as seen at Figure 1. Also, these applications are concluded at the 8 to 16 weeks time period (Figure 2). In general, the application period consists 8 or 9 weeks. However, the procedure can be longer, if the application forms are adequate.

Figure 1: Status of Application Results

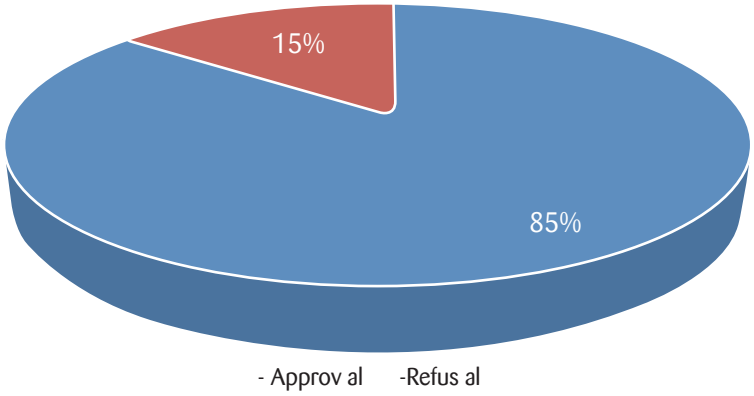
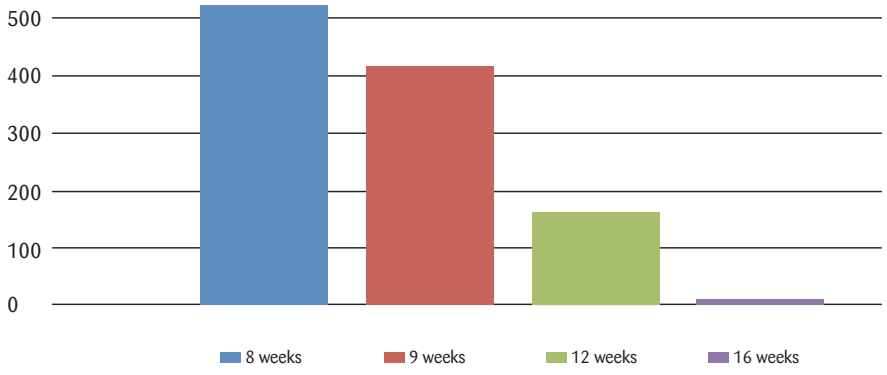


Figure 2: Approval Period



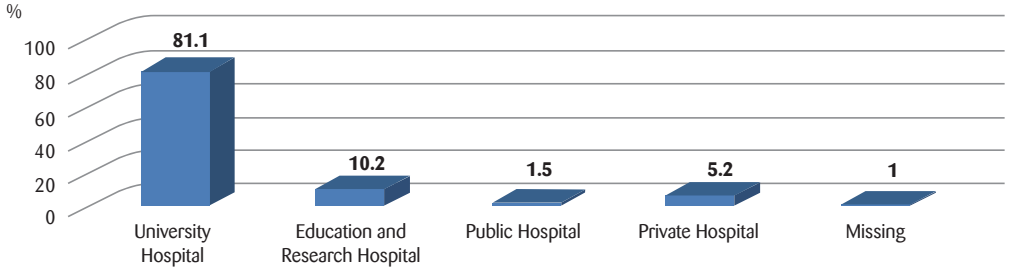
It was seen the Marmara Region had the highest application percentage (33.26 %) and it was continued the Central Anatolia Region (27.79 %). Evaluated on the base of cities Istanbul, Ankara and Izmir had the most applications with 29.6 %, 19.2 % and 15.7 % respectively (Table 1).

Table 1: Region, applications, regional applications, percentage of regional applications (off-label)

Region	Location	Application	Regional Application	Percentage of regional application
Mediterranean Region	Adana	47	174	13.21
	Antalya	98		
	Mersin	21		
	Isparta	8		
Central Anatolian Region	Ankara	254	366	27.79
	Eskişehir	23		
	Kayseri	42		
	Konya	45		
	Sivas	2		
Aegean Region	Bursa	22	438	33.26
	Edirne	8		
	İstanbul	391		
	İzmit	17		
East Anatolian Region	Elazığ	5	34	2.58
	Malatya	15		
	Erzurum	14		
South East Anatolian Region	Gaziantep	27	28	2.13
	Şanlıurfa	1		
Black Sea Region	Trabzon	27	32	2.43
	Samsun	4		
	Zonguldak	1		
Not Specified		15	15	1.14

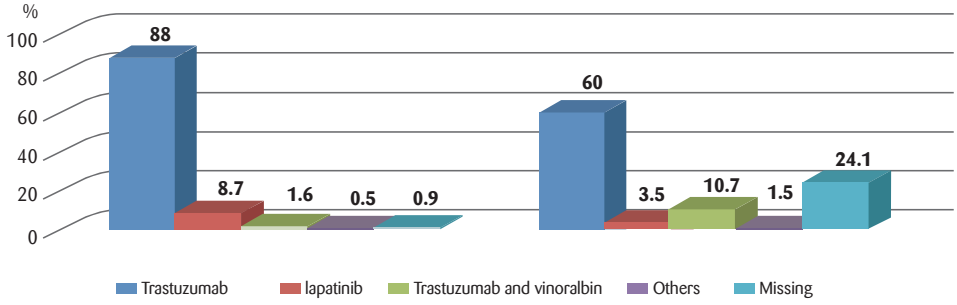
University hospitals were created the vast majority of applications (81.1%). Other part of all the applications were received from education & research hospitals (10.2 %) and private hospitals (5.9 %) (Figure 3).

Figure 3: Applications by Hospital Category



The most of applications for breast cancer medication were trastuzumab. As you can see at Figure 4, trastuzumab and trastuzumab+vinoralbin medication were preferred by physicians. The next choice was Lapatinib for off-label medication usage in the breast cancer.

Figure 4: Applications by Medication



Discussion

The recombinant antibody trastuzumab exemplifies the new generation of targeted anticancer therapies. Trastuzumab inhibits the growth of breast cancer cells by binding to human epidermal growth factor receptor 2 (HER-2).6 Overexpression of this receptor is found in approximately 25 % of breast cancers and occurs as a consequence of amplification of the HER2/neu gene.[7-8] Clinical trials demonstrated trastuzumab, used alone or in combination with chemotherapy slowed the progression of HER-2–positive metastatic breast cancer.9 In patients failing prior chemotherapy for metastatic breast cancer, trastuzumab used as a single agent reduced tumor size in 15% of patients.[10] Adjuvant therapy with trastuzumab for 6 months resulted in a clinical benefit in patients with HER2 positive breast cancer.[11] More recently, studies have shown that trastuzumab prevents disease recurrence, at least in the short term, in women with early-stage breast cancer.[10,12]

In comparison with chemotherapy, trastuzumab is well tolerated and has few side effects. In a recent study the addition of trastuzumab to chemoteraphy is effective and tolerated for metastatic breast cancer with HER2+ patients, on the other hand especially cardiac toxicity will occur followed the use of trastuzumab.[13] The most significant side effect of trastuzumab is cardiotoxicity, which is manifested in most cases by an asymptomatic decrease of the left ventricular ejection fraction in 2.3-17.3% of patients, although in most cases this has no clinical significance. Symptomatic heart failure is a rare event in trastuzumab treated patients, occur in 0-4 % of patients and it is generally reversible with trastuzumab discontinuation.1 In contrast to metastatic breast cancer studies, trastuzumab trials in early breast cancer have excluded individuals with preexisting heart disease and incorporated compulsory cardiac monitoring in their design.[10,12]

Trastuzumab had the highest percentage in all off-label medicine applications for breast cancer usage. On the other hand, 85 % of all trastuzumab off-label usage applications were approved. The reason of 15 % of trastuzumab applications is needed to be investigated further. From the perspective of cities Istanbul had the highest application percentage in all applications depending on the population. In additional, university hospitals had the highest percentage. This may be cause from

university hospitals accept severe patients who may need off-label medicines.

In conclusion, off-label oncology medicine use is rising in Turkey.3 If trastuzumab off-label use increasing parallel to off-label oncology medicines, it is needed to define new pathways to evaluate the applications.

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