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Title: Incidence of Unlicensed and Off-Label Prescription in Urologic Cancers Therapy in Turkey: Assessment of Legislative and Regulatory Policy

Turkish Title: Türkiye'de Ürolojik Kanserlerin Tedavisinde Ruhsatsız ve Endikasyon Dışı Reçetelemenin Sıklığı: Yasama ve Yasal Politikaların Değerlendirilmesi

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Öz

Amaç: Endikasyon dışı ilaç kullanımı, TC Sağlık Bakanlığı tarafından, onaylanmış endikasyonun dışındaki dozlarda ruhsatlı farmasötik ürünlerin kullanımı ve kişisel tedavi amacıyla ithal edilen ruhsatsız tıbbi ürünlerin kullanımı olarak tanımlanmaktadır. Çalışmanın amacı, sağlık hizmetleri hükümleri çerçevesinde Türkiye'nin perspektifini anlamak için ürolojik kanserlerde endikasyon dışı veya ruhsatsız ilaçların kullanımını değerlendirmektir.

Yöntemler: Bu çalışma Türkiye'deki paklitaksel veya diğer endikasyon dışı ilaç kullanan metastatik mesane kanseri olan hastaları (n=105), sorafenib, sunitinib veya diğer endikasyon dışı uygulamaları kullanan metastatic böbrek hücreli kanser olan hastaları (n=194) ve paklitaksel, gemsitabin veya diğer endikasyon dışı ilaç kullanan metastatik testis kanseri olan hastaları (n=44) kapsamaktadır. TITCK 'nun hasta bazlı veri tabanı kullanılarak arama yapıldı.

Bulgular: TITCK veri tabanından elde edilen verilere göre; metastatik mesane CA, metastatik renal hücreli CA ve metastatik testis CA endikasyon dışı ilaç kullanım başvuru sayıları sırasıyla 86, 136 ve 44dür. Metastatik mesane CA endikasyon dışı ilaç kullanım başvurularının %90,47'si, metastatik renal hücreli CA için 122 (%62,88)si ve metastatik testis CA için 39 (%88,63)i onaylandı. Metastatik mesane CA'sı için başvuruların büyük çoğunluğu (%79,89), metastatik renal hücreli CA için (%64,76)'sı ve metastatik testis CA için (%79,89)'unu üniversite hastaneleri tarafından oluşturuldu. Mesane CA, renal CA ve testis CA için en çok tercih edilen endikasyon dışı ilaçlar sırasıyla paklitaksel (%84,04), sorafenib (%68,42) ve paklitaksel (%43,24) idi.

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Sonuç: Türkiye'de ürolojik kanserlerde endikasyon dışı ilaç kullanımı artmaktadır. Endikasyon dışı ilaç kullanımı, endikasyon dışı üroloji ilaçlarına paralel olarak artarsa, uygulamaları değerlendirmede yeni yollar tanımlamak gerekir.

Anahtar Kelimeler: Endikasyon dışı reçeteleme, testis kanseri, renal hücreli kanser, mesane kanseri

Abstract

Objective: "Off-label" is defined by the Turkish Ministry of Health as the use of licensed pharmaceutical products in doses outside the scope of the registered indication and the use of unlicensed medicinal products that are imported for the purpose of individual treatment. The aim of the study is to evaluate the usage of off-label or unlicensed medicines in urologic cancers for understanding of Turkey's perspective within this area of healthcare provisions.

Methods: This study involved patients (n=105) with metastatic bladder cancer who received paclitaxel or other off-label medicine application, (n=194) with metastatic renal cell cancer who received sorafenib, sunitinib or other off-label medicine application, (n=44) with metastatic testis cancer who received paclitaxel, gemcitabine or other off-label medicine application in Turkey. A computer search was performed using the TITCK's database (patient based).

Results: Data obtained from TITCK's database showed 86, 136, and 44 applications for off-label metastatic bladder cancer medicine, metastatic renal cell cancer and metastatic testis

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cancer medicine usage, respectively. 90.47% of all off-label medicine usage applications for metastatic bladder cancer, 62.88% for metastatic renal cell CA and 88.63% for metastatic testis cancer were approved. University hospitals were created the vast majority of applications (79.89%) for metastatic bladder CA, (64.76%) for metastatic renal cell cancer and (79.89%) for metastatic testis cancer. The most preferable off-label drug medications for bladder, renal and testis cancer were paclitaxel (84.04%), sorafenib (68.42%) and paclitaxel (43.24%), respectively.

Conclusion: Off-label drug use in urological cancers increase in Turkey. If off-label drug use increasing parallel to the off-label urology medicines, it is needed to define new pathways to evaluate the applications.

Keywords: Off-label prescription, testis cancer, renal cell cancer, bladder cancer

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).

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). The TITCK evaluates off-label and unlicensed medication use for each patient through off-label

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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).

The aim of this study is to evaluate the use of off-label or unlicensed medicines in urologic cancers 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 urologic cancers as metastatic bladder cancer, renal cell cancer and testis cancer.

METHODS

This study involved patients (n=105) with metastatic bladder cancer who received paklitaxel or other medicine application off-label, (n=194) with metastatic renal cell cancer who received sorafenib, sunitinib or other medicine application off-label, (n=44) with metastatic testis cancer who received paklitaxel, gemsitabin or other medicine application off-label in Turkey during 1st May 2008 to 1st May 2011. Informed consent was obtained from these patients in accordance with the legislation on the use of off-label drugs. These are available in the records of our Ministry of Health.

Database of TITCK was used to examine off-label medicine use for the treatment of urologic cancers. In the analysis, the off-label use of medicines during the urologic cancers 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

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aimed to help update the guidelines and determine pharmaceuticals and off-label indications for no-need to approve process off-label indications in urologic cancers pharmaceuticals. Discriminative analysis was conducted with Microsoft Office Excel 2011 program.

RESULTS

The data obtained from TITCK's database between 1st May 2008 to 1st May 2011 showed that 86 applications were submitted for off-label metastatic bladder cancer medicine use, 136 applications were submitted for off-label metastatic renal cell cancer medicine use and 44 applications were submitted for off-label metastatic testis cancer medicine use. Average age was 64.62±19.42 for metastatic bladder cancer, 60.52±19.22 for metastatic renal cell cancer and 39.77±34.66 for testis cancer, shown in Figure 1.

Ninety five (90.47%) of all off-label medicine usage applications for metastatic bladder cancer, one hundred twenty two (62.88%) for metastatic renal cell cancer and thirty nine (88.63 %) for metastatic testis cancer were approved as seen at Figure 2. Also, these applications are concluded at the 12 weeks time period for metastatic bladder cancer, metastatic renal cell cancer and metastatic testis cancer. However, the procedure can be longer, if the application requirements are acceptable.

University hospitals were created the vast majority of applications (79.89%) for metastatic bladder cancer. Other part of all the applications were received from education & research hospitals (28.57%) and private hospitals (6.66%). This distribution is similar for renal and testis cancers also were shown in Figure 3.

The most preferable off-label drug medications for bladder CA, renal CA and testis CA were paklitaxel (84.04%), sorafenib (68.42%) and paklitaxel (43.24%), respectively were shown in table 1 (Table 1).

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DISCUSSION

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 (1).

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 (4, 5). 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 (6). 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 (7).

When an unlicensed medicine is approved by the TITCK, the Turkish Pharmacy Association is then responsible for importing it (3). 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 use of off-label drugs in oncology has been estimated to reach 50%, or even more (8, 2, 3). In paediatrics, the off-label issue is particularly widespread, all the more in paediatric oncology (8, 3). Often, these uses of drugs, although off-label, are fully 'evidence based' and therefore fall within the state of the art. In spite of this, off-label uses of drugs might in a

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sense be viewed as illegal. In practice, off-label uses are often 'tolerated' under restrictions, in spite of the size of the phenomenon, especially in some medical areas (9, 3).

Unlicensed or off-label medicine use is controlled by the Ministry of Health in Turkey. Oncology medicines are imported for these types of uses. It was reported that unlicensed or off-label medicine use has been rising over the past few years in Turkey (3). On the other hand, off-label medicine use is a rising topic in medicine. It could be seen from a search in PubMed with "off-label drug use" keywords that the majority of published articles are in last years (10-14). While the number of published articles was 35 in 2000, it was 368 in 2014 (14).

In conclusion, off-label urology medicine use is rising in Turkey as other oncologic medicines` off-label useage (3). Debates about the use of expensive cancer medicines should consider postmarketing assessments. The longer duration of off label drug use in clinical practice and the high rates of off label use provide incentive for new clinical trials. If off-label use increasing paralel to off-label urology medicines, it is needed to define new pathways to evaluate the applications.

REFERENCES

1. Mesgarpoura B, Müller M., Herknerbb H. Search strategies identified reports on ''off-label'' drug use in MEDLINE. Journal of Clinical Epidemiology 2012;65:827-834.

2. Stafford RS. Regulating Off-Label Pharmaceutical Use - Rethinking the Role of the FDA. N Engl J Med 2008;358:1427-9.

3. Kockaya G, Polat M, Vural İM, Akbulat A, Dedeoglu BD. Off-label and unlicensed oncology medicine use in Turkey: a retrospective analysis of computer records of the Turkish Ministry of Health Journal of Pharmaceutical Health Services Research. 2011; 2-1:53–7.

4. De Mario MD, Ratain MJ. Oral chemotherapy rationale and future directions. J Clin. Oncol 1998;16:2557-67.

5. Batlle JF, Arranz EE, de Castro Carpeno J, Saez EC, Aunon PZ. Oral chemotherapy potential benefits and limitations. Clin Transl Oncol. 2004;6:335-40

6. Conroy S, Newman C, Gudka S. Non-licensed and off-label pharmaceutical use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol. 2003;14: 42–7.

7. General Directorate of Pharmaceuticals and Pharmacy, Guideline of Off-label Medicine Use. 2011[onlinepublication]:Ankara2009.http://www.iegm.gov.tr

8. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. JAMA 2003; 290: 905–11.

9. Casali PG. Executive Committee of ESMO, The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). Ann Oncol 2007; 18:1923–25.

10. Radley DC, Finkelstein SN, Stafford RS.Off-label prescribing among office-based physicians. Arch Intern Med 2006;166:1021–26.

11. Borner M, Scheithauer W, Twelves C, Maroun J, Wilke H. Answering patients needs: oral alternatives to intravenous therapy Oncologist. 2000;6:12-6.

12. Sharma S, Saltz IB. Oral chemotherapeutic agents for colorectal cancer Oncologist 2000;5:99-107.

13. O'Neill VJ, Twelves CJ. Oral cancer treatment:developments in chemotherapy and beyond Br J Cancer 2000;87:933-7.

14. Soares M. Off-Label' indications for oncology pharmaceutical use and pharmaceutical compendia: history and current status. J Oncol Pract 2000;1:10–105.

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Table 1. The most preferable off-label drug medications

CA	Medication	%
Bladder CA	Paclitaxel	84.04%
	Docetaxel	6.38%
	Irinotecan	4.25%
	Vinblastine	2.12%
	IVIG	2.12%
	Topotecan	1.06%
Renal CA	Sorafenib	68.42%
	Sunitinib	21.92%
	Temsirolimus	2.63%
	Bevacizumab	1.75%
	Ibandronic Acid	1.75%
	Everolimus	1.75%
	Paklitaxel	0.87%
	Gemcitabin	0.87%
Testis CA	Paklitaxel	43.24%
	Gemcitabin	37.83%
	Paklitaxel+Gemcitabin	16.21%
	Gemcitabin+Dosetaxel	2.70%

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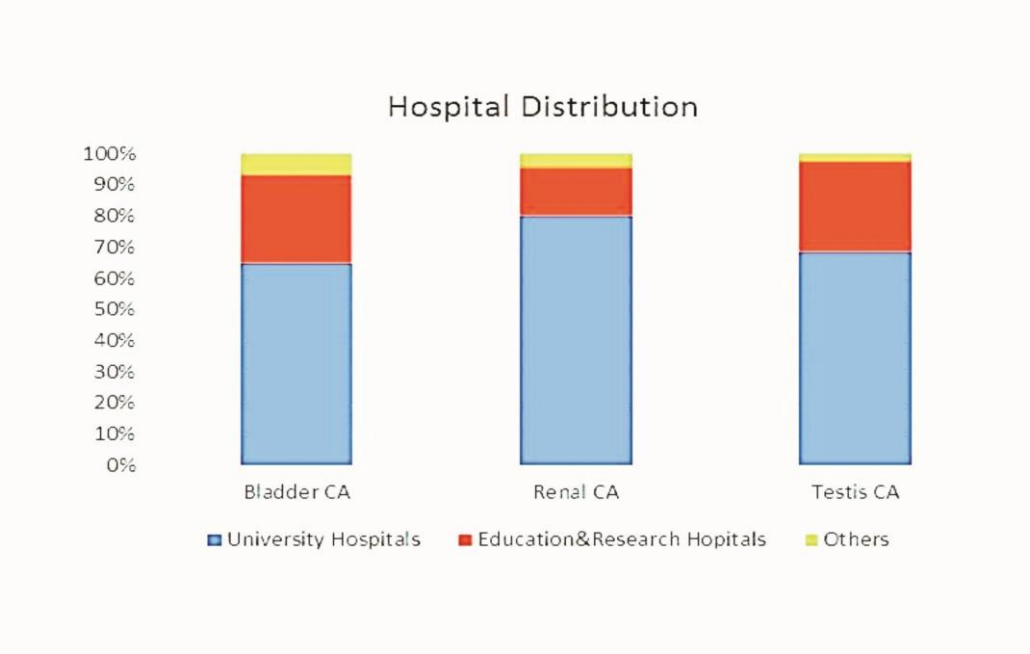

Figure 1. Hospital distribution

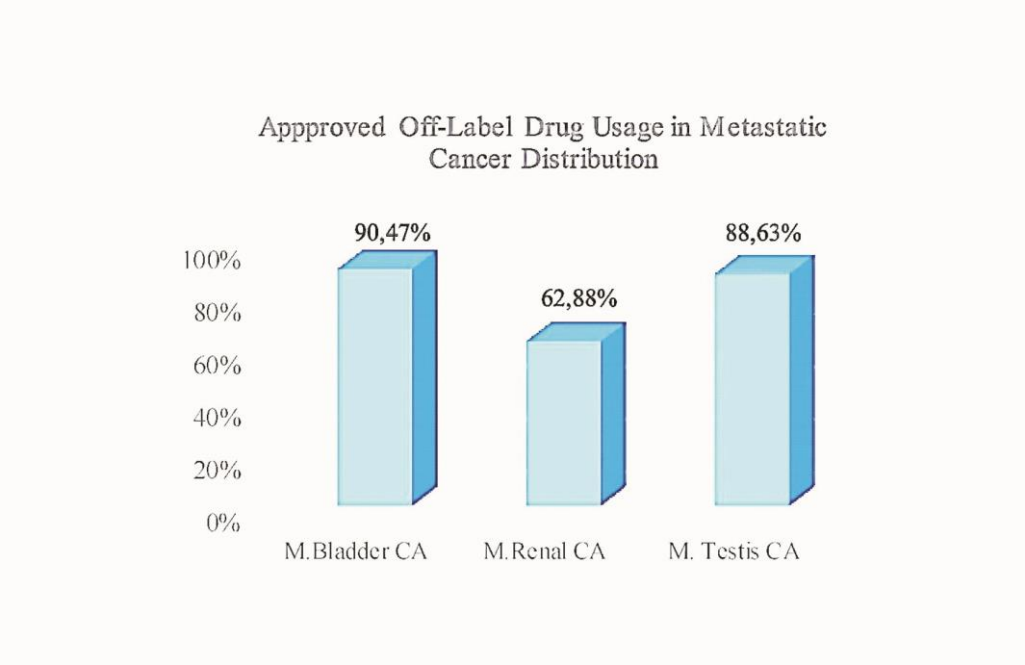

Figure 2. Approved off-label drug usage in metastatic cancer distribution

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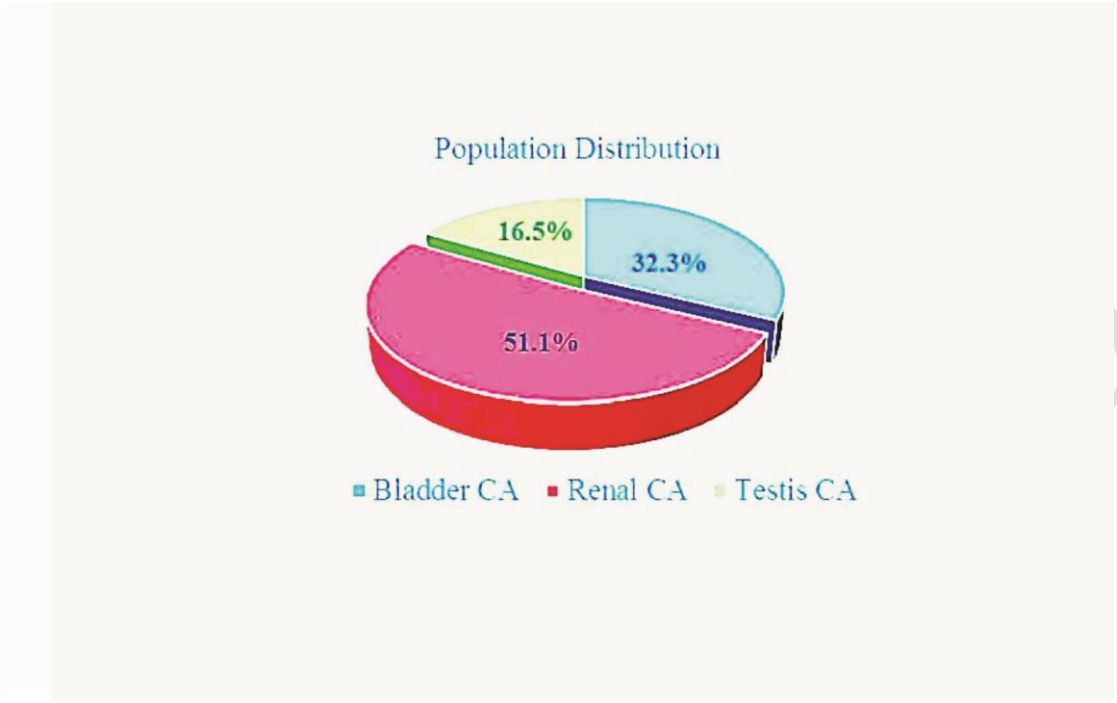

Figure 3. Population distribution

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