Utilization Trends of Endocrine Therapies for Breast Cancer in Albania During 2004-2014

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Abstract

Aim: To evaluate the patterns of use of the out-of-hospital endocrine therapies for breast cancer in Albania during the period 2004-2014. Methods: The study was retrospective and we analyzed the prescription and consumption of these drug classes in the primary health care in Albania during 2004-2014. All data were collected from Health Insurance Institute (HII)(1) and analysed reflecting the ambulatory and outpatient use for the period 2004-2014. The data about the consumption of drugs were expressed as a number of Defined Daily Dose (DDDs) /1000 inhabitants/day. Utilization was measured in DDD/1000 inhabitants/day and was also compared with breast cancer morbidity/1000 inhabitants, to understand the covering of the population from the reimbursement scheme. For all the period under study 2004-2014, there were collected and analysed the data of import and domestic production of drugs, which altogether represent the real consumption of drugs in the country. These data were subsequently included in a comparative analysis with the utilization data according to the HII. Results: The drug with the highest values of consumption is Letrozole 0.05-0.37 DDD/1000 inhabitants/day2004-2014). Anastrazole was introduced to the scheme in 2008. Its consumption in2014 was 0.26 DDD/1000 inhabitants/day. The consumtion of Tamoxifen is reduced through these years with values 0.32-0.17 DDD/1000 inhabitants/day respectively 2004-2014. Breast cancer morbidity data indicate that there does exist a correlation statistically significant between this disease and the trend of consumption of endocrine therapies drugs (p = 0,0009) Conclusions: It is evident that a non-small part of the patients remain untreated under the scheme. There is noted a shift in use of endocrine therapy from tamoxifen to aromatase inhibitors. This trend is consistent with major international clinical guidelines that recomend preferential use of aromatase inhibitors in post-menopausal women.

Keywords: Drug utilization, DDD, endocrine therapies, breast cancer

Introduction

Breast cancer is the leading cause of cancer deaths in women around the world, with approximately 522 000 women dying of the disease in 2012.(2)

Hormonal therapy, also called endocrine therapy, is an effective treatment for most tumors that test positive for either estrogen or progesterone receptors (called ER-positive or PR-positive), in both early-stage and metastatic breast cancer. This type of tumor uses hormones to fuel its growth. Blocking the hormones can help prevent a cancer recurrence and death from breast cancer when used for early-stage disease either by itself or after adjuvant or neoadjuvant chemotherapy.

Tamoxifen. Tamoxifen is a drug that blocks estrogen from binding to breast cancer cells. It is effective for lowering the risk of recurrence in the breast that had cancer, the risk of developing cancer in the other breast, and the risk of distant recurrence. Tamoxifen is also an effective treatment for metastatic hormone receptor-positive breast cancer. **Aromatase inhibitors (AIs).** AIs decrease the amount of estrogen made by tissues other than the ovaries in postmenopausal women by blocking the aromatase enzyme, which changes weak male hormones called androgens into estrogen when the ovaries

have stopped making estrogen during menopause. These drugs include anastrozole, letrozole, and exemestane. All of the AIs are pills taken daily by mouth. Treatment with AIs, either alone or following tamoxifen, is more effective than tamoxifen alone at reducing the risk of recurrence in post-menopausal women. AIs are also an effective treatment for metastatic hormone receptor positive breast cancer. Women who have gone through menopause and are prescribed hormonal therapy have several options: start therapy with an AI for up to 5 years, begin treatment with tamoxifen for 2 to 3 years and then switch to an AI for 2 to 3 years, or take tamoxifen for 5 years then switch to an AI for up to 5 years, in what is called extended hormonal therapy. Recent research has shown that taking tamoxifen for up to 10 years can further reduce the risk of recurrence following a diagnosis of early-stage breast cancer, although side effects are also increased with longer duration of therapy.

Premenopausal women should not take AIs, as they are not effective. Options for adjuvant hormonal therapy for premenopausal women include the following:

Five or more years of tamoxifen, with switching to an AI after menopause begins

Either tamoxifen or an AI combined with suppression of ovarian function.

Objective, Materials and Methods

Objective:

To assess the out-of-hospital endocrine therapiesfor breast cancer use in Albania during the period 2004-2014.

Materials and Methods:

The data were obtained from the HII. All data were collected for the period 2004-2014 and analyzed.

The analysis included, the total number of prescriptions made, and quantities of drugs used.

The data about the population were obtained from the Institute of Statistics (INSTAT)(3). The data about the consumption of drugs were expressed as a number of Defined Daily Dose (DDDs)/1000 inhabitants/day. All drugs were classified by groups of Anatomic Therapeutic Chemical Classification (ATC).

Data on the levels of morbidity

From the database of HII there were extracted the general number of patients reported for each diagnose, for each year. Following, there were calculated the respective levels of annual morbidity (based on the respective code-diagnoses) for 1000 inhabitants.

Data on real consumption (import and domestic production)

For all the period under study 2004-2014 there were collected and analysed data from the import and domestic production of the drugs,(4) which represent the real consumption of drugs in the country. It was noted that the increase in consumption from one year to another was small, e.g. the consumption from 2010 to 2014 (i.e. 4 years) was increased by only 2.98%. Consequently, in order to obtain an updated study, there were chosen the data of import and domestic consumption only for the last three years, 2012, 2013, 2014, and those were involved in a comparative analysis with the equivalent consumption data according to HII. In order to minimize the effect of variations between consumption and stock inventory balances from one year to another, it was calculated and put to analysis the annual average value of the three chosen years (on one hand that of the import and domestic consumption, and on the other hand that of HII).

Presentation of the results and statistical elaboration. The database of HII was modified in Microsoft Office Excel 2007, whereas the statistical elaboration of the obtained results was conducted with the statistical package StatsDirect (version 2.7.2.). A descriptive statistics was used to report all data on drugs consumption and the results obtained were displayed in tabular form as well as through the histogram method.

Average annual values of consumption in the country level and for each district were used as a basis to generate the overviews and the graphics that illustrate the trends of consumption for each class of drugs during the 8-years period 2004-2014. The linear regression model was used to evaluate the trends of consumption of drugs relative to the time. A value of $p \leq 0.05$ was considered as significant.

In order to asses if there exists a correlation statistically significant between the level of consumption of drugs and the level of morbidity, it was applied the Spearman correlation (with a significance level of ≤ 0.05).

Results

The drug with the highest values of consumption is Letrozole 0.05-0.37 DDD/1000 inhabitants/day2004-2014). Anastrazole was introduced to the scheme in 2008. Its consumption in2014 was 0.26 DDD/1000 inhabitants/day.

The consumtion of Tamoxifen is reduced through these years with values 0.32-0.17 DDD/1000 inhabitants/day respectively 2004-2014.

Breast cancer morbidity data indicate that there does exist a correlation statistically significant between this disease and the trend of consumption of endocrine therapies drugs (p = 0,0009) (Figure 1).

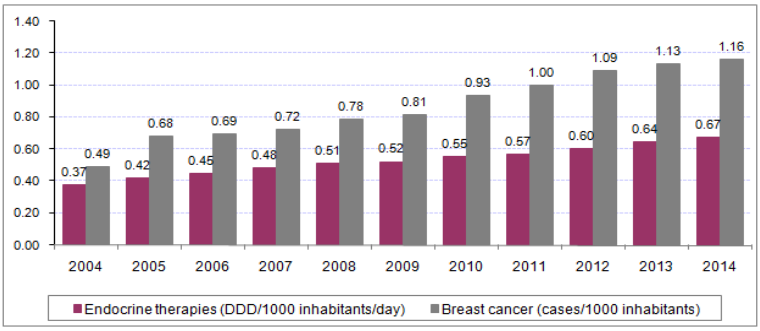

Figure 1 Consumption of Endocrine therapies drugs at the national level (DDD/1000 inhabitants/day) versus breast cancer morbidity (cases/1000 inhabitants);

(p = 0,0009; correlation coeficient is statistically significant)

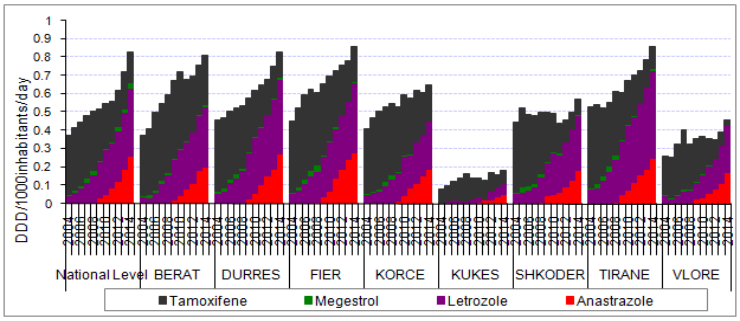

Figure 2 Consumption of endocrine therapies drugs in different regions and at the national level (DDD/1000 inhabitants/day).

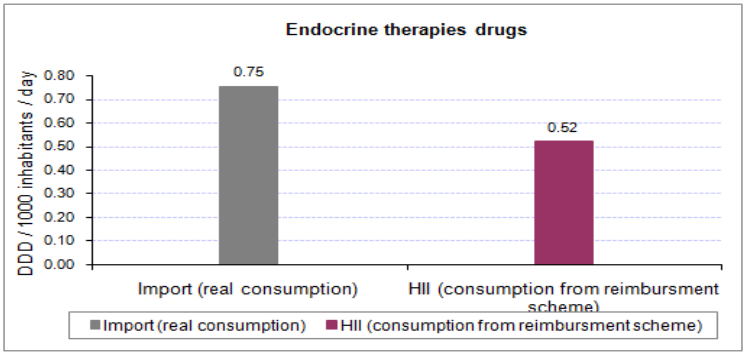

Figure 3Annual average value of consumption of total Endocrine therapies drugs: consumption based on import (real consumption) [*] versus consumption based on HII.

[*] The "Import" item includes the consumption based on import data as well as the consumption based on domestic production: this represents the factual consumption.

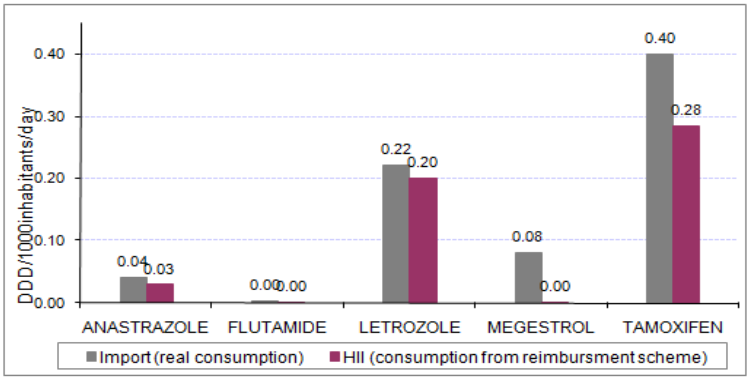

Figure 4 Annual average value of consumption of each Endocrine therapie drug: consumption based on import (real consumption) [*] versus consumption based on HII.

[*] The "Import" item includes the consumption based on import data as well as the consumption based on domestic production: this represents the factual consumption.

Discussion

It results that the increase in consumption of the anti-tumour drugs goes in line with the data on breast cancer morbidity, but in lower values. Particularly in recent years, the difference has become deeper, indicating that a non-small part of the patients remain un-treated.

One possible reason for this situation may be the delayed diagnosis of the disease, in an advanced phase. This phase may coincide with the passage from the hormonal therapy to classic cytostatic drugs, or with the preliminary termination of the treatment due to lethal complications of the base disease.Another reason may be the delayed inclusion of anastrazole under the scheme (only after 2008).

The breast cancer at females consists in a major public health problem due to the number of patients affected by this disease. The incidence of breast cancer increases with aging and around 80% of the cases with breast cancer appear at women of over 50 years old (5). Around 30% of all malignant tumours at females pertain to breast cancer, thereby causing

a more frequent tumoural diagnosis (6). After determination of the diagnosis, the prognosis and the choice of the protocol treatment depend on the progress level of the disease. Approximately 2/3 of the women with this diagnosis have positive tumour receptors to oestrogens. The aim of the therapy is to deter the growth of tumour cells by inhibiting the estrogenic proliferative stimulus. The ovarian inhibition and the treatment with tamoxifen has demonstrated an improvement of the 5-year survival rate even in cases where the condition or type of the estrogenic receptors is not known (7). Tamoxifen is indicated for the treatment of breast cancer at the preliminary and ER+ advanced phase (with 'oestrogen receptor-positive' invasive breast cancers) in the females at pre- and post-menopause (8). Differently from the females in pre-menopause, in which oestrogen is produced in ovaries, in women in post-menopause it is produced as a result of the action of aromatase enzyme in peripheral tissues of the body. Given that in the majority of cases breast cancer responds to estrogenic stimulation, the decrease of its production in the tumour tissue (e.g. breast adipose tissue) through inhibitors of aromatase enzyme (anastrazole, letrozol, exemestan) has been proved effective in the treatment of hormone-sensitive tumours at women in post-menopause(9).

With the aim to obtain a better understanding of the situation, the consumption data based on import were included in the analysis by comparing them with the consumption data based on HII. As a general rule, this group of drugs get reimbursed 100%, hence it is expected that the import data are in line with the consumption data based on HII (Figure 3, Figure 4). However, as it can be understood from the analysis obtained, a significant part of the patients are treated outside of the scheme. Around 30% of the consumption of anastrazole, tamoxifen and the whole class in its entirety occurs outside of the scheme. We can obtain the expected matching between the real consumption of anti-cancer drugs and the morbidity data, only by including these values.

The consumption of anti-tumoural medicaments has increased, although in minor values, in all the regions under study within the period 2004-2014 (Figure 2). The minimum values of consumption of these medicaments appear in Kukes, and then Vlora and Shkodra. Whereas, the maximum consumption values are noticed in Berat, followed by Fier, and then Tirana and Durres. In the majority of regions, we note the progressive decrease in the consumption of tamoxifen, against the increase in consumption of and anastrazole, which is in line with the recommendations of therapeutic guides and the literature. The regions of Berat, Kukes and Vlora represent an exception, thereby indicating the lack of adherence of doctors to therapeutic guides and reflecting probable lack of update of information and therapeutic knowledge. Other reasons may be the poor social-economic standard of the women-patients in these regions, the low level of access of these patients to the medical system, the poor coverage by specialist doctors, as well as reduced diagnostic skills.

At the national level, the consumption of these medicaments shows an increase of 79,37% (0,37-0,67 DDD/1000 inhabitants/day, 2004-2014). Nevertheless, this increase results low, as it does not match with the data of morbidity of breast cancer, which show an increase of the disease of 137,78% (0,49-1,16 cases/1000 inhabitants).

As regards the prescription tendency (DDD%), there can be noted that the medicament most described is tamoxifen, which however, incurs a decrease in the period under study: from 85,92% in 2004 to 35,23% in 2014. The decrease in prescription of tamoxifen is in line with the literature and clinical studies conducted, which indicate a reduced efficacy of tamoxifen versus an increased risk from its usage after 5 years of therapy.

Meanwhile, we find an increase of prescription in enzymatic inhibitors: anastrazole and letrozole. Anastrazole included in the list of 2008, occupies the first place as regards the increase in prescription: 1,05%-9,20%, 2008-2014. Whereas, letrozole, which appears in the list since 2004, is characterised by a prescription in higher amounts but with a lower increase: 12,61%-44,38%, 2004-2014.

This increase in the prescription of aromatase inhibitors goes in line with therapeutic guides, according to which:

For women in post-menopause with breast cancer, tamoxifen remains the treatment chosen as adjuvant initial therapy. In case of presence of counter-indications relative to its consumption (high risk for thromboembolic, or endometrial disorders), or in case of intolerance, the medicament needs to be substituted with an aromatase inhibitor;

For patients in post-menopause, it should be considered the change of therapy towards an aromatase inhibitor after 2, 3 or 5 years of treatment with tamoxifen.

For women in post-menopause at an advanced phase of the disease, it should be considered right at the beginning the initiation of treatment with medicaments of the III-d generation of aromatase inhibitors, before the usage of tamoxifen, or of megestrol acetat(10).

Conclusions

As a result, the increase in consumption of anti-tumoral drugs goes in line with the breast cancer morbidity data, but in lower values. Particularly in recent years, the difference becomes deeper and it is evident that a non-small part of the patients remain un-treated under the scheme.

There is noted a shift in use of endocrine therapy from tamoxifen to aromatase inhibitors. This trend is consistent with major international clinical guidelines that recommend preferential use of aromatase inhibitors in post-menopausal women.

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Declaration of authorship: Laerta Kakariqi contributed to the data acquisition, study conception

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The Authors declare that there is no conflict of interest.

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