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Availability of the Drugs for Malignant Diseases Treatment: Comparison between Developing and Developed Countries

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Authors' contributions

This work was carried out in collaboration between all authors. Author AJ designed the study, managed the analyses of the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript and the literature searches. Authors MR, IP and DR contributed to the section Results and Discussion, as well to the literature searches. Author BB designed the study and managed the analyses of the study. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: The financial burden of malignant diseases treatment has increased remarkably over the years. This is due to, among many reasons, the costs of drugs, especially those of the new classes. Thus, it is of interest to assess the availability and differential cost of anti-cancer drugs in developing countries compared to developed countries.
Study Design: The study was designed to determine the anti-cancer drugs availability in the world, in the United States of America (USA), the United Kingdom (UK) and the Republic of Serbia (RS), with the aim to get insights into the similarities and differences between developed and developing countries toward anti-cancer drugs availability, as well as the prices of these drugs. This analysis was based on three drug data bases for anti-

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cancer drugs that were available during 2011 and 2012 year in the world, USA, UK, and RS.
Results: About 37% of anti-cancer drugs that were present in the world market in 2011 year were also present in the RS (the drugs that were reimbursed by the state health insurance), compared to 74.8 and 67.4% that were available in the USA and the UK, respectively. Furthermore, out of all drugs registered in 2012 in the UK, 62.8% were present in the RS and almost all pharmacological groups were represented with some drugs, including very expensive ones like the biological agents. Most of the drugs in the RS were cheaper, regardless of whether they belonged to nonproprietary or brand-name drugs. These findings could be the result of the very low national gross domestic product in the RS and thus, the small funds earmarked for the health care.
Conclusion: The Republic of Serbia, which belongs to developing countries, face some difficulties in taking care of patients with malignant diseases where the prominent place have drugs for malignant diseases treatment, especially the newer classes, which are usually more expensive and generally do not provide the first-line treatment.

Keywords: Anti-malignant drugs; developing country; health care funds; pharmaco epidemiology.

1. INTRODUCTION

Pharmacological treatments of malignant diseases have had a great transformation over time.

This refers to the curative field, prolonging life without curing the disease, or to the palliative field. A new wave of antineoplastic agents has been introduced in the recent years. The novel treatment approaches brought a significant progress in the treatment of malignant diseases.

Unlike earlier generations of chemotherapeutic agents with systemic, nonspecific targets, the new generation of anti-cancer drugs called 'targeted therapies', has been created to target specific types of cells, enzymes and receptors. Furthermore, the new generations brought expansion of the individualized therapy of malignant disease due to a personalized pharmacotherapy tailoring approach [1], which gives a great opportunity for improvement of the disease outcome. Administered either solely or in combination with already established chemotherapeutic agents, apart from improved clinical responses and outcomes, i.e. survival benefit, such treatments are thought to bring better tolerability and safety that promote improved quality of the patient's life. Furthermore, modern pharmacotherapy offers oral administration of antineoplastic drugs which facilitate treatment, improve the quality of life and reduce the number of hospital days. Thus, introduction of new generations of chemotherapeutic agents like monoclonal antibodies [2], protein kinase inhibitors [3], and other biological agents, could lead to reduction of pharmacotherapeutic side effects, survival benefit and increased drug adherence and compliance. Biological therapy (synonyms: immunotherapy, biotherapy, or biological response modifier therapy) can boost or restore natural defenses against diseases, including malignant. This is obtained via the host's (sufferer's) immune system, either directly (active immunity) or indirectly (passive immunity), and also via antiproliferative, antiangiogenic, and direct cytotoxic action.

However, high prices of anti-cancer drugs, particularly novel, are a growing concern to payers and patients that could blunt a number of their good characteristics. Thus, in spite of great improvement in pharmacological treatment, it is not clear in which range these drugs can be worldwide applicable especially whether poor and developing country are in a same position to apply such drugs in their clinical practice [4,5]. Thus, the aim of this study was to highlight the availability of drugs for the treatment of malignant diseases in rich and poor countries. In an effort to address the evidence of potential gaps between these countries, in the present research we included the Republic of Serbia (RS), which belongs to the developing countries, and the United Kingdom (UK) and the United States of America (USA) as developed countries. In addition, the UK and the USA are leaders in the field of drug regulation, as well as in clinical pharmacology that is extensively applied in clinical practice in general, including malignant diseases.

2. METHODS

This analysis was based on three drug databases of anti-cancer drugs in the world, US, UK, and RS that were present at the market during 2011 and 2012 year. The Serbian official data are been taken from the Republic Fund for Health Insurance (RFHI; Lists of drugs A, B, C and D) [6]. The source of data on anti-cancer drugs for the world and the United States were the list of drugs given in Martindale: The complete Drug Reference [7], and the British National Formulary (BNF) for the UK [8]. RFHI source was used because the government regulates reimbursement of medications, including those for the treatment of malignant diseases for all the patients who have state health insurance. The health insurance in Serbia is obligatory to almost all citizens. The RFHI drug data provide the product name (International Nonproprietary Name: INN, and brand name: ®), the producers, the pharmaceutical formulation, the amount of the drug in the pharmaceutical formulation, and the price of the drug. Instead of INN, NP abbreviation is used in the BNF.

When we compared the anti-cancer drugs that were available in the world, with those medicaments which were available in the USA, UK and RS, the drugs were listed alphabetically by their generic names (Appendix 1). However, the comparison between the RS and the UK was carried out in the framework of pharmacological classes of anti-cancer drugs given in the BNF, within which generic names of drugs were listed alphabetically. We analyzed the participation of drugs according to their INN and brand-names, as well as to their prices Table 1-5. However, the comparison of drugs given in the BNF and that in the RS was sometimes complicated, and very difficult by the fact that certain drugs/combinations/pharmaceutical formulations were unavailable or did not exist in the RS drug marked and *vice versa*.

The prices of drugs have been obtained from the BNF and the RFHI lists of drugs. They were expressed in the UK pounds sterling (GBP). The retail prices were given in the BNF, while in the RFHI the wholesale, which are lower than the retail prices for about 20%. For the conversion of RS dinars (RSD) into GBP, the middle exchange rate determined by the National Bank of the Republic Serbia as of December 31, 2011 has been regarded as 1 GBP equaled to 124.

Drug availability was compared between countries. It was expressed in percentages. The difference between the two percentages was calculated. Values of $P < .05$ were considered significant.

3. RESULTS

Sub-optimal treatment of malignant diseases inevitably demands a search for drugs that provide better results [10]. Therefore, with some new anti-cancer drugs, since they preferentially target tumor cells and do not harm the other, nonmalignant cells, it became possible to obtain desirable action. The consequences of such treatments could be the reduction of anti-cancer treatment modification, the decrease of drug's side effects including life-threatening events or, even more, the reduction of specific treatments toward adverse events. When considering the new anti-cancer drugs, however, data obtained by Niraula and coworkers about increased toxicity of these new drugs in advanced or metastatic solid malignancies in adults have to be taken into account [11]. In fact, it is questionable whether all these drugs are available to the patients throughout the world, as well as those drugs that belong to the older generation of anti-cancer drugs.

According to the study we are presenting, in the year 2011 there were 135 anti-cancer drugs at the world market (Appendix 1) [6-8]. Out of the total number, 74.8 percent of them were available in the USA, 67.4 percent in the UK ($P = .05$ between the USA and UK), and 37 percent in the RS ($P < .05$ in comparison to both, the USA and UK, as well as the world).

Thus, the most of the 135 worldwide drugs for treating malignant disease were available in the USA and UK, while their availability was quite small in the RS.

According to the BNF [8], the pharmacological groups of drugs intended to be applied to people with malignant diseases were categorized into three main classes: cytotoxic drugs, drugs affecting the immune response, and sex hormones and hormone antagonists in malignant disease. The first class contains five subclasses (alkylating drugs, anthracyclines and other cytotoxic antibiotics, antimetabolites, vinca alkaloids and etoposide, Tables 1-3 the second one was classified to: antiproliferative immunosuppressants, corticosteroids and other immunosuppressants, anti-lymphocite monoclonal antibodies, and other immunomodulating drugs Table 4. Four subclasses also make the third class for treating malignant diseases: oestrogens, progestogens, androgens, and hormone antagonists Table 5.

The total number of 113 generic drugs represented all the anti-cancer drugs in the BNF [8]. They were present at the UK market as INN or brand-name drugs. In the RS it was found 71 anti-cancer drugs [6] Tables 1-5: the column Products, written in bold italic letters) out of 113 that were existed in the BNF (written in regular letters). That makes 62.8% of the generic drugs available in the UK ($P < .05$).

In spite of a lower number of drugs in the RS compared to the UK, all pharmacological classes were represented by some drugs. As could be expected, more of them goes back (pripadaju) to the older pharmacologic groups. Unlike expensive anti-cancer drugs, the drugs that were not so expensive were widely available in the RS (alkylating drugs, anthracyclines, antimetabolites, vinca alkaloids, etoposide, platinum compounds).

3.1 Pharmaceutical Products

In the BNF, the generic name (INN) of drugs was most often represented with one, very seldom with two products, no one with four Table 1-5. In the RS market the situation was quite opposite: there were much more products for one generic-name drug, even 3-6

products. As for examples it can be given doxorubicin (n=4 products) Table 1, gemcitabine (n=4) and etoposide (n=4) Table 2, carboplatin (n=6) and cisplatin (n=5) (Table 3), megestrol acetate (n=3), anastrozole (n=3) and letrozole (n=3) Table 5.

Altogether, 113 generic names of drugs in the UK were represented with 145 products, while 71 in the RS were represented with 123 products. It means that for one generic drug 1.28 products were available in the UK, while in the RS, they amounted to 1.73 products.

3.2 Prices of Drugs

Usually, anti-cancer drugs are quite expensive. However, prices of the newer classes of anti-cancer drugs are dramatically more expensive than those of the conventional ones [12]. The prices of anti-cancer drugs in the BNF were within a very wide range, from a very few to GBP 15000 for one drug package/pharmaceutical formulation, which depend on the drug class and the amount of pharmacological active substance. There were about 20 drugs that cost more than 1000 GBP per package/ pharmaceutical formulation.

The most expensive drug in the UK market was ipilimumab, which was not present in the RS Table 3. This human monoclonal antibody was approved in the USA in March 2011, in the UK in November 2012 for the second line treatment of melanoma that cannot be treated with surgery or that has been spread to other parts of the body. A single package of this drug in the UK costed up to GBP 15.000 [8].

The price of ipilimumab was followed by the price of lenalidomide, derivative of thalidomide (up to GBP 4368) which was approved in the USA in 2005 year, in 2009 in the UK, an was not available at the RS market Table 4. As a drug class, a family of protein kinase inhibitors were most expensive with regard to a single package Table 3. They cost from GBP 620 to 3138.8.

Although not in the same extent as in the BNF, very expensive drugs were also present at the RS market. Most of them belong to the protein kinase inhibitors (n=5, Table 3). These drugs were the only representatives in a group of drugs which cost more than GBP 1000 per package/pharmaceutical formulation.

In most cases there were no similarities in the retail prices of drugs between the UK and the RS, irrespective of whether they belong to the INN or brand-name drugs. Furthermore, some prices in the RS were lower in both the older and newer classes than in the UK as for example: estramustine phosphate, doxorubicin, epirubicin, idarubicin hydrochloride Table 1, fludarabine phosphate, gemcitabine, vincristine sulphate, vinorelbine Table 2, carboplatin, cisplatin, oxaliplatin, docetaxel, pacitaxel, irinotecan hydrochloride Table 3, exemestane, letrozole and bicalutamide Table 5. However, some drugs were more expensive in the RS than in the UK: pemetrexed, etoposide Table 2, hydroxyurea, nilotinib, sunitinib (Table 3), megosteron acetate, tamoxifen (20-mg tabs), goserelin (3.6-mg implant) Table 5.

The drug prices and the increasing incidence of malignant diseases all over the world with about 12 million new patients annually [13] must be confronted with the ability of the society to support both the direct and indirect costs of treating malignant diseases. In this regard the most noticeable differences were in the availability of new classes of drugs between the UK and the RS. Despite the fact that some of these drugs were present in the RS, the indication fields for them, however, were very narrow and limited, opposite to the developed countries (e.g. UK, USA). Furthermore, very often these drugs in the RS were not the drugs of the first line, while in the developed countries they have been introduced in the treatment much

earlier as the drugs of the first line. Rituximab, imatinib, and bevacizumab could be given as examples**.**

Rituximab is recommended for the first-line treatment of stage III-IV follicular lymphoma as well as the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma in the developed countries. Rituximab monotherapy as the maintenance therapy is an option for the treatment of patients with relapsed stage III or IV of follicular non-Hodgkin's lymphoma. However, in the RS, rituximab can be administrated in the treatment of the aggressive CD20 positive B-non-Hodgkin's lymphoma [6].

In the USA, imatinib mesylate, the KIT tyrosine kinase inhibitor, is approved to be applied after the surgical removal of KIT (CD117)-positive gastrointestinal stromal tumors (GISTs) to help prevention of tumor recurrence. It is also approved for the unrespectable KIT-positive GISTs [14]. In the RS, however, imatinib is approved only for unresectable tumors [6].

Bevacizumab [15], which has almost the same price in the RS and in the UK as a brand-name drug, is widely used in developed countries during the first two lines of treatments of colorectal cancer metastatic disease, as it has been proved to prolong survival. However, in the RS it has been approved only for a very narrow indication field such as the neoadjuvant treatment for potentially resectable liver metastases of colorectal origin, with the aim to achieve their resectability. In these cases, bevacizumab was allowed to be applied for not more than 10 cycles [6].

Contrary to bevacizumab, cetuximab is approved in the RS for the similar indication as in most other European countries. It could be applied for the treatment of metastatic colorectal cancer in spite to irinotecan treatment, but only in patients with tumors expressing the wild-type KRAS gene [6,16].

Because of the extremely limited funds for the health care in the RS, indications for anti-cancer drugs is narrower in comparison to developed country. That may be a part of the health policy to better control on health budget since the RS, in spite of the less desired economic situation, provides national health insurance to its population with the aim to treat as many patients as it is possible.

3.3 The International Nonproprietary Name Versus Brand-name Drugs

The prices are among the most prominent differences between generic and brand-name drugs. It is well known that companies which first obtain authorization to place a new medicinal product in the market have an exclusive right to sell it under the brand name. These drugs must be more expensive than the generics. Such prices stimulate the research in drug discovery.

This study showed that the brand-name drugs were equally available in both countries: one generic name in the UK was represented with 0.91 (n=103/113) brand-name drugs, in the RS with 1.0 (n=70/71) Tables 1-5. However, the INN drugs were twice as more represented in the RS than in the UK: 0.37 (n=42/113) in the UK, versus 0.75 (n=53/71) in the RS (Tables 1-5).

As it was expected, the brand-name drugs in the UK were usually more expensive than the INN drugs Tables 1-5. In the RS, however, price differences between the generic and brand-name could not be found almost at all, i.e. these prices were the same or very similar Tables 1-5.

Table 1. Anti-cancer drugs in the Republic of Serbia (RS) and the United Kingdom (UK). *CYTOTOXIC DRUGS: Alkylating drugs, Anthracyclines and other cytotoxic antibiotics*

Drug (generic name)	Products (UK/RS)	Pharmaceutical Form	Price (GBP) (UK/RS) (UK:retail, RS:wholesale)
Alkylating Drugs			
Bendamustine hydrochloride	Levact®/ NA	Injection, powder	25-mg vial = 69.45/ NA 100-mg vial = 275.81/ NA
Busulphan	Busilvex®/ NA	IVI, 6 mg/ml	10-ml vial = 201.25/ NA
	Myleran®/ Busulfan (List D)	Tablets, f/c, 2 mg	25-tab pack = 5.20/ List D
Carmustine	Gliadel®/ Carmustin (List D)	Implant (7.7 mg) Injection, 100 mg	585.34/ NA NA/ List D
Chlorambucil	Leukeran®/ Hlorambucil (List D)	Tablets, f/c, 2 mg	25-tab pack = 8.36/ List D
Cyclophosphamide	Cyclophosphamide (NP)/ Cyclophosphamide (List D), Endoxan®	Tablets, s/c, 50 mg Injection, powder	100 = 20.2/ List D 500-mg vial = 5.66/ 2.95 1-g vial = 10.66/ 5.53
Estramustine phosphate	Estracyt®/ Estracyt®	Capsules, 140 mg	100-cap pack = 171.28/ 83.27
Ifosfamide	Ifosfamide (NP)/ Holoxan®	Injection, powder	1-g vial = 43.53/ 16.3 2-g vial = 88.62/ NA
Lomustine	Lomustine (Medac)/ Lomustine (List D)	Capsules, 40 mg	20-cap pack = 455.62/ List
Melphalan	Alkeran®/ Melphalan (List D)	Tablets, 2 mg Injection, powder	25-tab pack = 13.75/ List D 50-mg vial = 33.13/ List D
Thiotepa	Thiotepa (Goldshield), Tepadina®/ Thiotepa (List D)	Injection, powder	15 mg-vial = 5.2, 123.0/ List D 100 mg-vial = 736.0/NA
Treosulfan	Treosulfan (Medac) / NA	Capsules, 250 mg Injection, powder	100-cap pack = 435.03/ NA Inj: 1 g = 39.44/ NA 5 g = 152.41/ NA
Anthracyclines and Other Cytotoxic Antibiotics			
Bleomycin	Bleomycin (NP)/ Bleocin-S	Injection, powder	15 000-unit vial = 15.56/ 15.48
Dactinomycin (Actinomycin D)	Dactinomycin (NP)/ Daktinomicin (List D)	Injection, powder-special order	No price/ List D
Daunorubicin	Daunorubicin (NP)/ Daunoblastina®	Injection, powder	10-mg vial = NA/ 5.32 20-mg vial = 55.0/ NA
	DaunoXome®/ NA	IVI	50-mg vial = 137.67/ NA
Doxorubicin hydrochloride	Doxorubicin (NP)/ Doxorubicin “Ebewe”, Doxorubicin-Teva, Adriablastina RD, Sindroxocin®	Injection, powder	10-mg vial = 18.72/ 2.66 50-mg vial = 96.86/ 13.31

		Injection, 2 mg/ml	5-ml vial = 20.6/ 2.65 25-ml vial = 103.0/ 13.31 100-ml vial = 275.0/ NA
	Caelyx® (pegylated) / NA	IVI, 2 mg/ml	10-ml vial = 360.23/ NA 25-ml vial = 712.49/ NA
	Myocet® (citrate complex) / NA	Injection, powder	50-mg vial = 456.13/ NA
Epirubicin hydrochloride	Epirubicin(NP), Pharmorubicin®/ Epirubicin "Ebewe", Episindan®, Farmorubicin RD®	Injection, 2 mg/ml	5-ml vial = 19.04, 19.31/ 3.93 25-ml vial = 92.12, 96.54/ 19.63 50-mg vial = 95.54, NA/ NA 100-mg vial = 306.2, 386.16/ NA
Idarubicin hydrochloride	Zavedos®/ Zavedos®	Capsules Injection, powder	1-cap (5 mg) pack = 41.47/ NA 1-cap (10 mg) pack = 69.12/ NA 5-mg vial = 87.36/ NA 10-mg vial = 174.72/ 93.5
Mitomycin	Mitomycin C Kyowa®/ Mitomicin (List D)	Injection, powder	2-mg vial = 5.89/ List D (5-mg via 10-mg vial = 19.37/ List D 20-mg vial = 36.94/ List D 40-mg vial = 73.88/ NA
Mitoxantrone (Mitozantrone)	Mitoxantrone (NP), Onkotrone®/ Mitoxantron "Ebewe"	IVI, 2 mg/ml	5-ml vial = NA/ 38.34 10-ml vial = 100.0, 121.85/ 73.53 12.5-ml vial = NA, 152.33/ NA 15-ml vial = NA, 203.04/ NA

Legend: NP = nonproprietary name; NA = not available

Table 2. Anti-cancer drugs in the Republic of Serbia (RS) and the United Kingdom (UK). CYTOTOXIC DRUGS: Antimetabolites, Vinca alkaloids and etoposide

Drug (generic name)	Products (UK/RS)	Pharmaceutical form	PRICE (GBP) (UK/RS) (UK:RETAIL, RS:WHOLESALE)
Anti metabolites			
Azacitidine	Vidaza®/ NA	Injection, powder	10-mg vial = 321.0/ NA
Capecitabine	Xeloda®/ Xeloda®	Tablets, f/c	60-tab (150 mg) pack = 40.02/37.29 120-tab (500 mg) pack = 265.55/ 230.38
Cladribine	Leustat®/ NA	IVI, 1 mg/ml	10-ml vial = 159.7/ NA
	Litak®/ Litak®	Injection (sc), 2 mg/ml	5-ml vial = 165.0/ 1119.54 (5 vial)
Clofarabine	Evoltra®/ NA	IVI, 1 mg/ml	20-ml vial = 1153.2/ NA
Cytarabine	Cytarabine (NP)/ Cytosar® (iv, im, sc, it), Alexan® "Ebewe" (iv, im, sc, it)	Injection (iv, sc, it) Injection (iv, sc)	20 mg/ml: 5-ml vial = 3.9/ 1.74 25-ml vial = 19.5/ NA 50 mg/ml: 10-ml vial = NA/ 8.67 20-ml vial =NA/ 15.1 100 mg/ml: 1-ml vial = 4.0/ NA 5-ml vial = 20.0/ NA 10-ml vial = 39.0/ NA 20-ml vial = 77.5/ NA 1 g-vial = NA/ 15.1
	DepoCyte®/ NA	Injection (it)	50-mg vial = 1223.75/ NA
Fludarabine phosphate	Fludarabine (NP), Fludara®/ Fludara®, Sindarabin®, Fludarabine-Teva	Injection, powder Tablets, f/c, 10 mg	50-mg vial = 140.4, 147.07/ 286.33 (5 vials), 57.3 15-tab pack = NA, 268.12/ NA 20-tab pack = NA, 350.7/ NA
Fluorouracil	Fluorouracil (NP)/ 5-Fluorouracil "Ebewe", Fluorouracil-Teva, Fluorouracil (List D)	Injection	25 mg/ml: 10-ml vial = 3.2/ NA 20-ml vial = 6.4/ NA 100-ml vial = 32.0/ NA 50 mg/ml: 5-ml vial= NA/ 1.05, 5.25 (5 vials) 10-ml vial = 6.4/ 1.7, 6.79 (5 vials) 20-ml vial = 12.8/ List D 50-ml vial = 32.0/ NA 100-ml vial = 64.0/ List D
Gemcitabine	Gemcitabine (NP), Gemzar®/ Gemzar®, Gemcitabin Sandoz®, Gemcitabin PharmaSwiss, Gitrabin®	Injection, powder	200-mg vial = 32, 32.55/ 10.7 1-g vial = 162, 162.76/ 50.66 1.5-g vial = 213.92, NA/ NA 2-g vial = 324.0, NA/ 101.88
Mercaptopurine	Puri-Nethol®/ Mercaptopurine (List D)	Tablets, 50 mg	25-tab pack = 22.54/ List D

Methotrexate	Methotrexate (NP)/ Methotrexat "Ebewe", Methotrexate, Methotrexate-Teva	Injection	2.5 mg/ml: 2-ml vial = 1.68/ NA 10 mg/ml: 1-ml vial = NA/ 2.71 5-ml vial = NA/ 2.92 25 mg/ml: 2-ml vial = 3.0/ 2.92 20-ml vial = 30.0/ 17.78 100 mg/ml: 5-ml vial = NA/ 17.78 10-ml vial = 78.33/ 29.53 50-ml vial = 380.07/ NA
Nelarabine	Atriance®/ NA	IVI, 5 mg/ml	50-ml vial = 222.0/ NA
Pemetrexed	Alimta®/ Alimta®	Injection, powder	100-mg vial = 160.0/ NA 500-mg vial = 800.0/ 1040.8
Raltitrexed	Tomudex®/ NA	Injection, powder	2-mg vial = 175.0/ NA
Tegafur with uracil	Uftoral®/ NA	Capsules, 100+224 mg	36-cap pack = 96.12/ NA 120-cap pack = 320.4/ NA
Tioguanine	Lanvis® / NA	Tablets, 40 mg	25-tab pack = 54.49/ NA
Vinca Alkaloids And Etoposide			
Etoposide	Etoposide (NP)/ Etoposid "Ebewe", Lastet, Etoposide-Teva, Sintopozid®	IVI, 20 mg/ml	5-ml vial = 12.15/ 5.09, 50.86 (10v) 10-ml vial = 29.0/ NA 25-ml vial = 60.75/ NA
	Etopophos®/ NA	Injection, powder	100-mg vial = 26.17/ NA
	Vepesid®/Lastet cap	Capsules	25 mg, 40 = NA/ 81.57 50 mg, 20 = 99.82/ 81.57 100 mg, 10-cap pack = 87.23/ 81.57
Vinblastine sulphate	Vinblastine (NP)/ Vinblastin	Injection, 1 mg/ml	5-ml vial = NA/ 7.22 (2 mg/ml) 10-ml vial = 13.09/ NA
	Velbe®/ NA	Injection, powder	10-mg amp = 14.15/ NA
Vincristine sulphate	Vincristine (NP), Oncovin®/ Vincristin, Vincristine, Sindovin®	Injection, 1 mg/ml	1-ml vial = 13.47, 14.18/ 3.04, 15.21 (5 vials) 2-ml vial = 26.66, 28.05/ NA 5-ml vial = 44.16, NA/ NA 10-ml vial = NA, NA / 3.04, 0, 0
Vindesine sulphate	Eldisine®/ NA	Injection, powder	5-mg vial = 78.3/ NA
Vinflunine	Javlor®/ NA	IVI, 25 mg/ml	2-ml vial = 212.5/ NA 10-ml vial = 1062.5/ NA
Vinorelbine	Vinorelbine (NP), Navelbine®/ Vinorelbin "Ebewe", Vinorelsin®	IVI, 10 mg/ml Capsules	1-ml vial = 29.0, 29.75/ 11.18 5-ml vial = 139, 139.98/ 50.34 20 mg: 1-cap pack= NA, 43.98/ NA 30 mg: 1-cap pack= NA, 65.98/ NA 80 mg: 1-cap pack:NA, 175.92/ NA

Legend: NP = nonproprietary name; NA = not available

Table 3. Anti-cancer drugs in the Republic of Serbia (RS) and the United Kingdom (UK). CYTOTOXIC DRUGS: Other antineoplastic drugs

Drug (generic name)	Products (UK/RS)	Pharmaceutical form	Price (GBP) (UK/RS) (UK:retail, RS:wholesale)
Other Antineoplastic Drugs			
Amsacrine	Amsidine®/ NA	IVI, 5 mg/ml	1.5+13.5ml(75-mg) amp=54.08/NA
Arsenic trioxide	Trisenox®/ NA	IVI, 1 mg/ml	10-ml amp = 250.9/ NA
Bevacizumab	Avastin®/ Avastin®	IVI, 25 mg/ml	4-ml vial = 242.66/ 234.71 16-ml vial = 924.4/ 940.0
Bexarotene	Targretin®/ NA	Caps, 75 mg	100-cap pack = 937.5/ NA
Bortezomib	Velcade®/ Velcade®	Injection, powder	3.5-mg vial = 762.38/ 925.75
Catumaxomab	Removab®/ NA	IPI. 100 µg/ml	10 µg prefilled syringe = 510.0/ NA 50 µg prefilled syringe=2550.0/ NA
Cetuximab	Erbutux®/ Erbutux®	IVI, 5 mg/ml	20-ml vial = 178.1/ 152.76 100-ml vial = 890.5/ NA
Crisantaspase	Erwinase®/L-asparaginase (List D)	Injection, powder	Vial: 10000-unit vial = 613.0/ List D
Dacarbazine and temozolomide — Dacarbazine	Dacarbazine (NP)/ Dacarbazin (List D)	Injection, powder	100-mg vial = 5.05/ List D 200-mg-vial = 7.16/ List D 500-mg vial = 16.5/ NA 600-mg vial = 22.5/ NA 1-g vial = 31.8/ NA
Dacarbazine and temozolomide — Temozolomide	Temozolomide (NP), Temodal®/ Temodal®	Capsules, 5-cap pack; Prices per pac	5-mg cap = 13.58, 16.29/ 15.5 20-mg cap = 54.3, 65.16/ 63.69 100-mg cap = 271.52, 325.8/ 318.5 140-mg cap = 380.18, 456.12/ NA 180-mg cap = 488.74, 586.44/ NA 250-mg cap = 678.8, 814.5/794.59
Eribulin	Halaven®/ NA	Injection, 440 µg/ml	2-ml vial = 313.0/ NA
Hydrocarbamide (Hydroxyurea)	Hydroxycarbamide (NP), Hydrea®/ Litalir®	Caps, 500 mg	100-cap pack = 10.47, 10.47/ 30.43
Ipilimumab	Yervoy®/ NA	IVI, 5 mg/ml	10-mg vial = 3750.0/ NA 40-mg vial = 15000.0/ NA
Mitotane	Lysodren®/ Mitotane (List D)	Tabl, 500 mg	100-tab pack = 590.97/ List D
Panitumumab	Vectibix®/ NA	IVI, 20 mg/ml	5-ml vial = 379.29/ NA 20-ml vial = 1517.16/ NA
Pentostatin	Nipent®/ NA	Injection, powder	10-mg vial = 863.78/ NA

Platinum compounds	Carboplatin	Carboplatin (NP)/ Carboplatin "Ebewe", Carboplatin, Carboplatin-Teva, Carboplastin, Karboplatin	Injection, 10 mg/ml	5-ml vial = 22.04/ 4.8 15-ml vial = 56.92/ 12.95 45-ml vial = 168.85/ 43.23 60-ml vial = 260.0/ 61.53
	Cisplatin	Cisplatin (NP)/ Cisplatin "Ebewe", Cisplatin, Cisplatin-Teva, Sinplatin®, Platosin®	Injection, 1 mg/ml Injection, powder	10-ml vial = 5.85/ 7.61 (5 vials), 2.46 (0.5 mg/ml) 50-ml vial = 24.5/ 7.61 100-ml vial = 50.22/ 7.61 (0.5 mg/ml) 50-mg vial = 17.0/ NA
	Oxaliplatin	Oxaliplatin (NP)/ Eloxatin®, Oxaliplatin "Ebewe", Sinoxal®	Injection, powder IVI, 5 mg/ml	50-mg vial = 150.0/ 49.08 100-mg vial = 299.5/ 98.16 10-ml vial = 156.75/ 49.08 20-ml vial = 330.0/ 98.16 40-ml vial = 622.38/ NA
Porfimer sodium and temoporfin	Porfimer sodium	Photofrin®/ NA	Injection, powder	15-mg vial = 154.0/ NA 75-mg vial = 770.0/ NA
	Temoporfin	Foscan®/ NA	Injection, 1 mg/ml	3-ml vial = 1800.0/ NA 6-ml vial = 3400.0/ NA
Procarbazine		Procarbazine (NP)/ Procarbazine (List D)	Caps, 50 mg	50-cap pack = 199.6/ List D
Protein kinase inhibitors	Dasatinib	Sprycel®/ NA	Tablets, f/c. 20, 50 mg = 60-tab pack, 80, 100, 140 mg = 30-tab pack Prices per pack	20-mg tab = 1252.48/ NA 50-mg tab = 2504.96/ NA 80-mg tab = 2504.96/ NA 100-mg tab = 2504.96/ NA 140-mg tab = 2504.96 / NA
	Erlotinib	Tarceva®/ Tarceva®	Tablets, f/c, 30-tab pack Prices per pack	25-mg tab = 378.33/ 351.17 100-mg tab = 1324.14/ 1213.57 150-mg tab = 1631.53/ 1463.28
	Everolimus	Afinitor®, Votubia®/ NA	Tablets, 30-tab pack Prices per pack	2.5-mg tab = NA, 1200.0/ NA 5-mg tab = 2250.0, 2250.0/ NA 10-mg tab = 2970.0, NA/ NA
	Gefitinib	Iressa®/ Iressa®	Tablets, f/c, 250 mg	30-tab pack = 2167.71/ 1655.91
	Imatinib	Glivec®/ Glivec®	Tablets, f/c, Capsules	100 mg : 60-tab pack = 862.19/ NA 120-caps pack = NA/ 1432.68 400 mg : 30-tab pack = 1724.39/ 1474.08
	Lapatinib	Tyverb®/ NA	Tablets, f/c, 250 mg	70-tab pack = 804.30/ NA

				84-tab pack = 965.16/ NA
	Nilotinib	Tasigna®/ Tasigna®	Capsules, 112-caps pack, Prices per pack	150-mg cap = 2432.85/ NA 200-mg cap = 2432.85/ 2839.22
	Pazopanib	Votrient®/ NA	Tablets, f/c, 30-tab pack, Prices per pack	200-mg tab = 560.5/ NA 400-mg tab = 1121.0/ NA
	Sorafenib	Nexavar®/ NA	Tablets, f/c, 200 mg	112-tab pack = 2980.47/ NA
	Sunitinib	Sutent®/ Sutent®	Capsules, 28-cap pack Prices per pack	12.5-mg cap = 784.7/ 888.54 25-mg cap = 1569.4/ 1768.55 50-mg cap = 3138.8/ 3534.26
	Temsirolimus	Torisel®/ NA	Infusion, 25 mg/ml	1.2-ml amp = 620.0/ NA
Taxanes	Cabazitaxel	Jevtana®/ NA	IVI, 40 mg/ml	1.5-ml vial = 3696.0/ NA
	Docetaxel	Docetaxel (NP), Taxotere®/ Taxotere®	Infusion	10 mg/ml 2-ml vial = 162.75, NA/ 42.56 8-ml vial = 534.75, NA/ 158.91 16-ml vial = 1069.5, NA/ NA 20 mg/ml 1-ml vial = 154.61, 162.75/ 42.56 4-ml vial = 508.01, 534.75/158.91 7-ml vial = 720.1, NA/ NA 8-ml vial = NA, 1069.5/ NA 40 mg/ ml 1.5-ml vial = NA, NA/ 98.05 6-ml vial = NA, NA/ 356.41
	Paclitaxel	Paclitaxel (NP), Taxol®/ Paclitaxel "Ebewe", Paclitaxel Pharmaswiss, Paclitaxel Teva, Sindaxel®	Infusion, 6 mg/ml	5-ml vial = 66.85, 116.05/ 25.29 16.7-ml vial = 200.35, 347.82/ 100.67 25-ml vial = 300.52, 521.73/118.1 50-ml vial = 601.03, 1043.46/302
		Abraxane®/ NA	IVI, powder	100-mg vial = 246.0/ NA
Topoisomerase I inhibitors	Irinotecan hydrochloride	Irinotecan (NP), Campto®/ Campto®, Irinotekan Sandoz®, Irinotensin®	Infusion, 20 mg/ml	2-ml vial = 49.03, 53.0/ 25.58 5-ml vial = 120.25, 130.0/ 58.29 15-ml vial = 370.5, 390.0/ 185.61 25-ml vial = 601.25, NA/ NA
	Topotecan	Topotecan (NP), Hycamtin®/ NA	Capsules, 10-cap pack Prices per pack IVI, powder	25- µg cap = NA, 75.0/ NA 1-mg cap = NA, 300.0/ NA 1-mg vial = 97, 97.65/ NA 4-mg vial = 290.0, 290.62/ NA
Trabectedin		Yondelis®/ NA	Injection, powder	250- µg vial = 363.0/ NA 1-mg vial = 1366.0/ NA
Trastuzumab		Herceptin®/ Herceptin®	IVI, powder	150-mg vial = 407.4/ NA 440-mg vial = NA/ 1328.65
Tretinoin		Vesanoid®/ Vesanoid®	Caps, 10 mg	100-cap pack = 160.63/ 130.22

Legend: NP = nonproprietary name; NA = not available

Table 4. Anti-cancer drugs in the Republic of Serbia (RS) and the United Kingdom (UK). Drugs affecting the immune response

Drug (generic name)		Products (UK/RS)	Pharmaceutical form	Price (GBP) (UK/RS) (UK:retail, RS:wholesale)
Anti-lymphocyte monoclonal antibodies				
Alemtuzumab		MabCampath®/ NA	IVI, 30 mg/ml	1-ml vial = 264.11/ NA
Ofatumumab		Arzerra®/ NA	IVI, 100 mg/5 ml	5-ml vial = 182.0/ NA 50-ml vial = 1820.0/ NA
Rituximab		MabThera®/ Mabthera®	IVI, 10 mg/ml	10-ml vial = 174.63/ 381.1 (2 vials) 50-ml vial = 873.15/ 941.0
Other immunomodulating drugs				
Interferon alfa	Interferon alfa 2b	IntronA/ IntronA	Injection, 10 mil units/ml Injection pen, 1.5-ml cartridge	1-ml vial = 42.35/ NA 2.5-ml vial = 105.95/ NA 15 million units/ml = 76.28/ 74.39 25 million units/ml = 127.14/ NA 50 million units/ml = 254.28/ NA
	Interferon alfa 2a	Roferon-A®/ Roferon-A®	Injection, 0.5 ml, prefilled syringe	3 million-unit = 14.2/ 12.0 4.5 million-unit = 21.29/ 17.16 6 million-unit = 28.37/ NA 9 million-unit = 42.57/ 35.6 18 million-unit (0.6 ml) = 85.15/ 72.13
	Peginterferon alfa 2a	Pegasys®/ Pegasys®	Injection	135-µg prefilled syringe = 107.76/ 99.28 180-µg prefilled syringe=124.4/NA 135-µg prefilled pen = 107.76/ NA 180-µg prefilled pen = 497.6/ NA
	Peginterferon alfa 2b	ViraferonPeg®/Pegintron®	Injection, prefilled pen	50-µg prefilled pen = 66.46/ 62.58 80-µg prefilled pen = 106.34/ 99.81 100-µg prefilled pen 132.92/126.46 120-µg prefilled pen = 159.51/ 147.88 150-µg prefilled pen=199.38/191.2
Aldesleukin		Proleukin®/ NA	Injection, powder	18-million unit vial = 112.0/ NA
Lenalidomide and Thalidomide				
Lenalidomide		Revlimid®/ NA	Capsules, 21-cap pack Prices per pack	5-mg cap = 3570.0/ NA 10-mg cap = 3780/ NA 15-mg cap = 3969.0/ NA 25-mg cap = 4368.0/ NA
Thalidomide		Thalidomide Celgene®/ Thalidomide (List D)	Capsules, 50 mg	28-cap pack = 298.48/ List D
Mifamurtide		Mepact®/ NA	IVI, powder	4-mg vial = 2375.0/ NA

Legend: NP = nonproprietary name; NA = not available

Table 5. Anti-cancer drugs in the Republic of Serbia (RS) and the United Kingdom (UK). Sex hormones and hormone antagonists in malignant diseases

Drug (generic name)	Products (UK/RS)	Pharmaceutical form	Price (GBP) (UK/RS) (UK:retail, RS:wholesale)
1. Oestrogenes			
Diethylstilbestrol	Diethylstilbestrol (NP)/ NA	Tablets, 28-tab pack	1-mg tab = 54.93/ NA 5-mg tab = 183.5/ NA Prices per pack
2. Progestagenes			
Medroxyprogesterone acetate	Provera®/ NA	Tablets	100 mg: 60-tab pack =29.98/ NA 100-tab pack =49.94/ NA 200 mg: 30-tab pack = 29.65/ NA 400 mg: 30-tab pack = 58.67/ NA
Megestrol acetate	Megace®/ Megace®, O'Tentika®, Megoxi®	Tablets, 160 mg Suspension, 240 ml (40 mg/ml)	30-tab pack = 19.52/ 31.26 100-tab pack = NA/ 103.78 Suspens = NA/ 63.64
3. Hormone antagonists			
3.1. Breast cancer			
Anastrozole	Anastrozole (NP), Arimidex® (f/c)/ Arimidex®, Trasolette®, Aremed®	Tablets, 1 mg	28-tab pack = 5.99, 68.56/ 20.06
Exemestane	Aromasin®/ Aromasin®	Tablets, s/c, 25 mg	30-tab pack = 88.9/ 24.83 90-tab pack = 266.4/ NA
Fulvestrant	Faslodex®/ NA	Injection, 50 mg/ml, prefilled syringe	1x5-ml (250-mg) = 348.27/ NA 2x5-ml (250-mg) = 522.41/ NA
Letrozole	Letrozole (NP), Femara® (f/c)/ Femozol®, Letrozole medico uno®, Femara®	Tablets, 2.5 mg	14-tab pack = 49.9, 49.9/ NA 28-tab pack = 84.86, 84.86/ NA , 18.54, NA 30-tab pack = NA, NA/ 19.86, NA, 23.84
Tamoxifen	Tamoxifen (NP)/ Nolvadex®,, Tamoxifen	Tablets, 30-tab pack Prices per pack Oral solution, 10mg/5ml	10-mg tab = 5.71/ 2.38 20-mg tab = 2.95/ 3.48 40-mg tab = 12.4/ NA 150 ml = 29.61/ NA
Toremifene	Fareston®/ NA	Tablets, 60 mg	30-tab pack = 29.08/ NA
3.2. Gonadorelin analogues and gonadotrophin-releasing hormone antagonists			
Gonadorelin analogues			
Buserelin	Suprefact®/ NA	Injection, 1 mg/ml Nasal spray, 100 µg/metered spray	2x5.5-ml vial = 23.69/ NA 4x10-g bottle spray pump = 101.87/ NA

Goserelin	Novgos®, Zoladex®/ Zoladex®	Implant, 3.6 mg	Syringe (applicator) = 58.5, 65.0/ 74.58
	Zoladex® LA/ Zoladex® LA	Implant, 10.8 mg	Syringe applicator = 235.0/ 219.9
Histrelin	Vantas®/ NA	Implant, 50 mg	1 pack = 990.0/ NA
Leuprorelin acetate	Prostap® SR DCS/ Lupron®	Injection, prefilled syr.	3.75-mg syringe = 75.24/ 74.79
	Prostap® 3 DCS/ Lupron®	Injection, prefilled syr.	11.25-mg vial = 225.72/ 220.51
Triptorelin	Decapeptyl® SR, Gonapeptyl Depot®/ Diphereline®	Injection, powder, prefilled syringe	3-mg vial = 69.0, NA/ NA 3.75-mg vial = NA, 81.69/ 78.14 11.25- mg vial = 207.0, NA/220.51 22.5-mg vial = 414.0, NA/ NA
Anti-androgens			
Abiraterone acetate	Zytiga®/ NA	Tablets, 250 mg	120-tab pack = 2930.0/ NA
Bicalutamide	Bicalutamide (NP), Casodex® (f/c)/ Casodex®, Bicadex®	Tablets, 28-tab pack Prices per pack	50-mg tab=4.39, 128.0/25.08, 20.9 150-mg tab = 9.73, 240.0/ NA
Cyproterone acetate	Cyproterone Acetate (NP), Cyprostat® (scored tab)/ Androcur®, Cyprocur®	Tablets	50 mg: 56-tab pack = 31.54, NA/ 17.77, 0 (50 tab),NA, 31.99(90 tab) 168-tab pack = NA, 87.0/ NA 100 mg:84-tab pack=76.6, 87.0/NA
Flutamide	Flutamide (NP)/ Flutastin®, Flucinom®	Tablets, 250 mg	30-tab pack = NA/ 6.76 84-tab pack = 37.65/ NA 90-tab pack = NA/ 20.28 100-tab pack = NA/ 22.54
Gonadotrophin-releasing hormone antagonists			
Degarelix	Firmagon®/ NA	Injection, powder	80-mg vial = 129.37/ NA 2x120-mg vials = 260.0/ NA
3.3. Somatostatin analogues			
Lanreotide	Somatuline® LA/ NA	Injection	30-mg vial = 323.0/ NA
	Somatuline Autogel®/ Somatuline Autogel®	Injection, prefilled syringe	60 mg = 551.0/ 532.0 90 mg = 736.0/ 574.2 120 mg = 937.0/ 807.7
Octreotide	Octreotide (NP), Sandostatin®/ Sandostatin®	Injection	50 µg /ml, 1-ml amp=3.7, 2.98/NA 100 µg /ml, 1-ml amp = 6.53, 5.6/ 26.82 (5 vials) 200 µg /ml, 5-ml vial = 69.66, 69.66/ NA 500 µg /ml, 1-ml amp = 33.87, 27.1/ NA
	Sandostatin Lar®/ Sandostatin Lar®	Injection, powder	10-mg vial = 427.13/ 396.82 20-mg vial = 705.5/ 684.0 30-mg vial = 903.13/ 888.8

Legend: NP = nonproprietary name; NA = not available

In comparison the same brand-name drugs, it was demonstrated that they seldom had the same price in the two countries. Furthermore, in some cases the same brand-name drugs had a lower price in the RS than in the UK (Estracyt, Zavedos, Taxotere, Campto, etc). The brand-name drugs in the RS very rarely were more expensive than in the UK: Litak, Alimta, Avastin, Velcade, Tasigna, Sutent. Even more, brand-name drugs in the RS were sometimes cheaper than the INN in the UK (ifosfamide, doxorubicin, epirubicin, vincristine, vinorelbine, oxaliplatin, paclitaxel, irinotecan, flutamide).

The price policy of drugs is very complex. The most important participants in determination the drug prices are the state government and pharmaceutical industry. Pharmaceutical industry must estimate which is the lowest price that is acceptable to them. Because of that, the same product has different prices in developed and in developing countries, but also within developed and developing group of countries. As the prices of medicines in the RS are under the national drug pricing policy, this area was not the investigated goal of the present study.

4. DISCUSSION

Most of the differences among countries found in this study for the compared determinants of anti-cancer drugs could be the direct consequence of the financial capability of each county. For example, it is estimated that about 18% (2.5 trillion US dollars) of national gross domestic product (GDP) in the USA was spent in 2009 for the total health care, which increased for 2.3% in comparison to 2007, when it was 15.7% [13]. In the UK it was directed to the health care 8.4% of GDP in 2007, in Australia 8.9%, in Canada 10.1% [17]. However, in the RS, 5.2% of GDP in 2010 was earmarked to the total health care [18].

Financial resources directed for the treatment of malignant diseases also differ between countries. In the UK, GBP 5.86 billion were spent for malignant diseases in 2009-2010, which represents 5.6% of the total health spending [13]. In the USA cancer care cost about 5% of the total health-care spending in 2010, while in 2004 it was 4.1% in the Netherlands, 7% in Sweden, even 9.3% in Japan [19]. This is a large amount of money, having in mind the GDP in these countries.

Obtained data in this study about the availability of anti-cancer drugs in the RS could be in correlation with the very bad economic situation in the country. The first and the most prominent place belongs to the GDP. It was very low: in 2010 it was only EUR 28006.1 million [18]. Furthermore, only EUR 1456.317 million of GDP was directed to the entire health care system. Thus, the GDP per capita in the RS was EUR 3.841 in 2010 [18], while in the UK it was EUR 26.000 in 2009 [12]. It means that the RS was able to cover the whole health care activities per inhabitant only with EUR 199.72 per year. However, this amount per capita in the USA was about USD 11.000, and about 550 US dollars per capita were spent annually for the treatment of malignant diseases [20]. In the best case of all the above mentioned, it could be possible to allocate less than EUR 20 per capita for the treatment of malignant disease in the RS. Accordingly, the assortment of anti-cancer drugs in the world, USA and UK could not be accessible in a whole in the RS. Having in mind that a 6-month treatment of patient with new drugs introduced in 2005-2009 costs EUR 9.000-20.500 [12], the UK and the USA societies could struggle more successfully against the expensive anti-cancer health care, including drug treatments, and also orientation to drugs recently approved.

To estimate what is better for a patient, and also for the whole society, the fundamental postulate in clinical pharmacology about the balance between the benefit-to-risk (harm) and cost-effectiveness analysis must be fulfilled in all the treatments. In addition, before any drug application, decision-makers have to consider the pharmaco economic facts and health budget in order to provide as much as possible of health care quality, especially in the countries with very limited financial opportunities, among which is the RS. It should be assessed whether doing more for patients always equates to more spending.

5. CONCLUSION

A very difficult challenge is placed before the developing countries, as for example before Serbia, regarding the treatment of malignant disease, due to a very rapid increment in the cost of cancer care, which is the result of greater incidence of malignant diseases, more people with malignant diseases treated, more expensive drugs introduced, serious medical problems as complications of the drug treatment, etc. [20]. These countries must beat a great battle to avoid deleterious scenario of an unreachable aim in treating malignant diseases because of insufficient funds. In this regard is the (utopian) appeal to the world: the goal of the world society as a whole needs to be focused to equal access, or at least to optimization access of the new, effective and safe anti-cancer drugs to all patients around the world.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Appendix 1. Anti-cancer drugs that were in 2011 year in the world, United States of America (USA), United Kingdom (UK) and Republic of Serbia (RS)

Drug (generic name)	World/countries				Drug (generic name)	World/countries			
	World	USA	UK	RS		World	USA	UK	RS
Aclarubicin	+	-	-	-	Mercaptopurine	+	+	+	+
Alemtuzumab	+	+	+	-	Methotrexate	+	+	+	+
Alitretionin	+	+	+	+	Mifamurtide sodium	+	-	+	-
Altretamine	+	+	-	-	Miltefosine	+	-	-	-
Aminoglutethimide	+	+	+	-	Miriplatin hydrate	+	-	-	-
5-Aminolevulinic acid	+	+	+	-	Mitobronitol	+	-	-	-
Amrubicin	+	-	-	-	Mitoguazone diH	+	-	-	-
Amsacrine	+	-	+	-	Mitomycin	+	+	+	+
Anastrozole	+	+	+	+	Mitotane	+	+	+	+
Asparaginase	+	+	+	+	Mitoxantrone H	+	+	+	+
Azacitidine	+	+	+	-	Nedaplatin	+	-	-	-
Bendamustine H	+	+	+	-	Nelarabine	+	+	+	-
Bevacizumab	+	+	+	+	Nilotinib	+	+	+	+
Bexarotene	+	+	+	-	Nilutamide	+	+	-	-
Bicalutamide	+	+	+	+	Nimotuzumab	+	-	-	-
Bleomycin sulfate	+	+	+	+	Nimustine H	+	-	-	-
Bortezomib	+	+	+	+	Ofatumumab	+	+	+	-
Busulfan	+	+	+	+	Oxaliplatin	+	+	+	+
Capecitabine	+	+	+	+	Paclitaxel	+	+	+	+
Carboplatin	+	+	+	+	Panitumumab	+	+	+	-
Carmofur	+	-	-	-	Pazopanib H	+	+	+	-
Carmustine	+	+	+	+	Pemetrexed disodium	+	+	+	+
Catumaxomab	+	-	-	-	Pentostatin	+	+	+	-
Cetuximab	+	+	+	+	Peplomycin sulfate	+	-	-	-
Chlorambucil	+	+	+	+	Pipobroman	+	-	-	-
Chlormethine H	+	+	+	-	Pirarubicin	+	-	-	-
Cisplatin	+	+	+	+	Porfimer sodium	+	+	+	-
Cladribine	+	+	+	+	Pralatrexate	+	+	-	-
Clofarabine	+	+	+	-	Procarbazine H	+	+	+	+
Cyclophosphamide	+	+	+	+	Raltitrexed	+	-	+	-
Cytarabine	+	+	+	+	Ranimustine	+	-	-	-
Dacarbazine	+	+	+	+	Razoxane	+	-	-	-
Dactinomycin	+	+	+	+	Rituximab	+	+	+	+
Dasatinib	+	+	+	-	Romidepsin	+	+	-	-
Daunorubicin	+	+	+	+	Sipuleucel-T	+	+	-	-
Decitabine	+	+	-	-	Sizofiran	+	-	-	-
Denileukin diftitox	+	+	-	-	Sorafenib	+	+	+	-
Docetaxel	+	+	+	+	Streptozocin	+	+	-	-
Doxifluridine	+	-	-	-	Sunitinib malate	+	+	+	+
Doxorubicin	+	+	+	+	Tamibarotene	+	-	-	-
Epirubicin H	+	+	+	+	Tamoxifen citrate	+	+	+	+
Eptaplatin	+	-	-	-	Tegafur	+	-	+	-
Erlotinib H	+	+	+	+	Temoporfin	+	-	+	-

Estramustine sodium P	+	+	+	-	Temozolomide	+	+	+	+
Etoposide	+	+	+	+	Temsirolimus	+	+	+	-
Exemestane	+	+	+	-	Teniposide	+	+	-	-
Floxuridine	+	+	-	-	Testolactone	+	+	-	-
Fludarabine P	+	+	+	+	Thiotepa	+	+	+	+
Fluorouracil	+	+	+	+	Tioguanine	+	+	+	-
Flutamide	+	+	+	+	Topotecan H	+	+	+	-
Fotemustine	+	-	-	-	Toremifene citrate	+	+	+	-
Fulvestrant	+	+	+	-	Tositumomab	+	+	-	-
Gefitinib	+	+	+	+	Trabectedin	+	-	-	-
Gemcitabine H	+	+	+	+	Trastuzumab	+	+	+	+
Gemtuzumab ozogamicin	+	+	-	-	Treosulfan	+	-	-	-
Hydroxycarbamide	+	+	+	+	Trofosfamide	+	-	-	-
Ibritumomab tiuxetan	+	+	+	-	Tasonermin-TNF	+	-	-	-
Idarubicin H	+	+	+	+	Ubenimex	+	-	-	-
Ifosfamide	+	+	+	+	Valrubicin	+	+	-	-
Imatinib mesilate	+	+	+	+	Verteporfin	+	+	-	-
Interleukin-2: aldesleukin	+	+	+	-	Vinblastine sulfate	+	+	+	+
Irinotecan H	+	+	+	+	Vincristine sulfate	+	+	+	+
Ixabepilone	+	+	-	-	Vindesine sulfate	+	-	+	-
Lapatinib tosilate	+	+	+	-	Vinflunine	+	-	+	-
Lenalidomide	+	+	+	-	Vinorelbine tartarate	+	+	+	+
Letrozole	+	+	+	+	Vorinostat	+	+	-	-
Lomustine	+	+	+	+	Zinostatin	+	-	-	-
Melphalan	+	+	+	+	*Total*	n=135	n=101	n=91	n=50

Legend: h = hydrochloride; p = phosphate

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=548&id=14&aid=4922