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GnRH agonists and antagonists in prostate cancer

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This manuscript describes the System of Objectified Judgement Analysis (SOJA) method applied to gonadotropin-releasing hormone (GnRH) agonists and antagonists in prostate cancer. The following selection criteria were used: efficacy, safety, tolerability, dosage frequency, user-friendly formulation, drug interactions, precaution and documentation. The GnRH agonists goserelin and leuprorelin show the highest scores, mainly based on more extensive documentation compared with the agonists buserelin and triptorelin. The antagonists abarelix and degarelix show low scores, based on a higher incidence of adverse events, a higher dosage frequency, more drug interactions and a more limited documentation compared with the agonists. The availability of a generic formulation of leuprorelin may lead to a reduction in cost.

Keywords: Drug selection, GnRH (gonadotropin-releasing hormone) agonists, GnRH antagonists, goserelin, leuprorelin, prostate cancer, SOJA (System of Objectified Judgement Analysis) method

Introduction Prostate cancer

Prostate carcinoma is, after lung carcinoma, the most frequent form of cancer in men [1]. About 8,000 new patients are diagnosed with prostate cancer in The Netherlands each year [2]. The diagnosis of localized prostate cancer has increased considerably, probably because of the measurement of prostate specific antigen (PSA), which is useful in the detection of early stage prostate cancer [1]. A detailed description of the treatment of all stages of prostate cancer falls outside the scope of this manuscript. The reader is referred to the Dutch national guideline for a full overview of the treatment of prostate cancer [1].

Androgens stimulate the growth of both normal and cancerous prostate cells. Androgen deprivation therapy (ADT) is the primary treatment for patients with advanced prostate cancer [2]. Gonadotropin-releasing hormone (GnRH), also known as luteinising hormone release hormone (LHRH) is secreted by the hypothalamus and stimulates the hypophysis to secrete LH, follicle stimulating hormone (FSH) and adrenocorticotropic hormone (ACTH). LH activates the testes to produce testosterone. Chronic administration of GnRH agonists (analogues) blocks the secretion of LH, FSH and ACTH by the hypophysis. This results in a reduction of circulating testosterone levels. GnRH agonists increase survival as effectively as bilateral orchiectomy or treatment with oestrogens [2].

Androgen deprivation therapy (ADT) is a palliative and not a curative treatment of advanced or metastatic prostate cancer. It can normalize serum levels of PSA and can produce objective tumour responses. This antitumour activity can improve quality of life in patients with metastatic prostate cancer by reducing bone pain as well as the rates of complications, such as pathologic fracture, spinal cord compression, and ureteral obstruction. The duration of response to ADT for patients with metastatic disease is highly variable, and most prostate cancer patients eventually experience disease progression despite treatment. Patients who have progressed while on ADT are said to have castration-resistant disease [2].

Applications of GnRH agonists and GnRH antagonists

Patients with high-risk or locally advanced prostate cancer should be treated with external beam radiotherapy plus hormone treatment for at least two years.

Neoadjuvant GnRH agonists are recommended for four to six months in patients receiving radical radiotherapy for high-risk disease and should be considered in patients with intermediate-risk disease. Adjuvant hormonal therapy for two to three years is recommended for men receiving neo-adjuvant hormonal therapy and radical radiotherapy who are at high risk of prostate cancer mortality [1]. The drugs are indicated in the treatment of advanced or metastatic prostate cancer. GnRH agonists are the drugs of choice in metastatic prostate cancer, although a recent guideline from the European Society of Medical Oncology (ESMO) stated that antagonists could be an alternative [1]. Combined androgen depletion (GnRH agonists + orchiectomy) does not offer advantages over chemical or surgical castration only [1].

Guidelines for the treatment of prostate cancer do not specify a medicine of choice within the drug classes. There are no published tools available that could aid therapy choice. In this article the SOJA method was applied to both GnRH agonists and antagonists in order to make a transparent and rational selection of the most suitable medicines.

Methods

The SOJA method is a model for rational drug selection for formulary purposes [3]. See [2] for a detailed description of the methodology. The outcome of this study should be seen as the basis for discussions within formulary committees and not as the absolute truth. The present score is specific for the European situation.

The selection criteria and the relative weights that are assigned by the authors are shown in Table 1. For drugs included in this analysis, see Table 2.

Results

Efficacy

Improved overall survival should be the aim of all cancer treatment but this requires very large scale and long-term studies

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Table 1: Selection criteria and weighting for rational drug selection

Selection criteria	Weighting
1. Clinical efficacy	300
2. Safety	200
3. Tolerability	100
4. Dosage frequency	80
5. User-friendly formulation	100
6. Drug interactions	60
7. Precautions	60
8. Documentation	100

Table 2: Drugs included in the analysis

GnRH agonists	GnRH antagonists
Buserelin (Suprefact)	Abarelix (Plenaxis)
Goserelin (Zoladex)	Degarelix (Firmagon)
Leuprorelin (Lucrin, Eligard, generics)	
Triptorelin (Pamorelin)	

to establish. Also, both relapse-free survival and disease-free survival are used alternative endpoints in the judgement of clinical efficacy. Relapse-free survival is probably a more relevant endpoint than disease-free survival, because death unrelated to prostate cancer or its complications is included in the latter endpoint.

Outcomes that have been used in trials to establish the role of hormonal therapy in men with advanced prostate cancer include overall survival, measurable tumour response, changes in serum PSA, skeletal-related events, and quality of life (QoL). Complicating the interpretation of results, many studies were conducted prior to the routine use of serum PSA testing in screening and monitoring of disease and therefore these studies do not reflect typical contemporary patient populations or current practice patterns [4].

The prolonged natural history of advanced prostate cancer, its occurrence in older men who often have substantial comorbidity, and the heterogeneity of disease between patients complicate the use of overall survival as an endpoint in assessing response to treatment. The standard classifications of complete response, partial response, stable disease, and progressive disease are inadequate to evaluate response in most men with metastatic prostate cancer. Measurable disease is present in a small fraction of patients. Bone metastases are the most common site of disease, and bone involvement is difficult to measure objectively. Bone scan interpretation is variable, and there is a long healing time when lesions do respond to treatment [4].

PSA levels as a measure of efficacy

The appropriate use of serum PSA as a response endpoint for hormone therapy has not been well studied. The rate of PSA decline following initial hormone therapy relative to the rate of

rise prior to initiation of hormone therapy is highly predictive of the time to prostate cancer-specific death [4]. The median survival of those with low PSA levels (< 0.2 ng/mL) was much longer than those with PSA levels of above 4 ng/mL [4].

Inclusion and exclusion criteria

In most cases, we have only used double-blind randomized studies to judge clinical efficacy of drugs included in SOJA analyses. The SOJA model is an instrument that enables users of the programme to determine, on the basis of agreed criteria, an order of merit for the various medicines available in a specific category [3]. This was not done in this SOJA score, because very few double-blind studies have been performed. For this reason, open, randomized phase III studies were included in the analysis. Non-randomized studies and studies comparing GnRH agonists with the addition of a drug such as flutamide or placebo were not included in the analysis, as these studies investigated the effects of the drug added to the GnRH agonist. Studies including a minimum of 25 patients per treatment arm were included in the analysis. Studies with short acting GnRH agonist formulations or nasal formulations were excluded. Similarly, studies in which hormonal treatment was not distinguished from orchiectomy in the same treatment arm were excluded, as well as studies that did not specify the GnRH agonist by name [5].

Direct comparative studies

Few direct comparative studies between GnRH (ant)agonists were identified. One retrospective study was excluded [6] as well as two other studies with a very small number of patients [7, 8] and one non-comparative study [9].

Abarelix versus leuprorelin

One study compared abarelix to leuprorelin. As could be expected testosterone surge was not seen in the abarelix group and did occur in the leuprorelin group [10].

Degarelix versus goserelin

Two studies compared degarelix and goserelin. Testosterone levels decreased more rapidly in the degarelix arm than in the goserelin arm, at eight weeks the levels were similar [11]. The effects of prostate volume and PSA levels were similar at 12 weeks [12]. At the same time point, more patients reported a > 3 point decrease in the International Prostate Symptom Score on degarelix than on goserelin: 36% vs 27% [12].

Degarelix versus leuprorelin

One study compared leuprorelin with degarelix 240 mg (n = 201). The testosterone response rates were comparable at one year. PSA levels declined more quickly in the degarelix group. The final reductions at 364 days were similar in the treatment groups [13-15].

Goserelin versus leuprorelin

A double-blind study compared goserelin 3.6 mg every 28 days (n = 540) and leuprorlin (n = 273) in patients with stage D2 (metastatic) prostate cancer. Both drugs were given in combination with either bicalutamide or (50 mg once daily) or flutamide 250 mg tid. The median follow-up was 160 weeks. The effects on time to progression and survival were similar [16].

Leuprorelin versus triptorelin

Two studies compared leuprorelin and triptorelin in patients with advanced prostate cancer. The effects on testosterone were identical. LH and PSA levels fell to a similar extent in both medicines [17, 18].

Studies with individual drugs

Buserelin

In one study buserelin depot was compared to polyestradiol phosphate (PEP). A more favourable effect of buserelin on disease progression was observed after three years of treatment [19]. This study is difficult to interpret because the comparator is not approved in The Netherlands.

Goserelin

Localized prostate cancer

Many studies were performed with goserelin. The medicine was studied as add-on to radiotherapy [20-44], showing lower PSA failure [28, 32, 34], increased five years disease-free survival [21, 31, 33, 36, 40] and 10 years [32] and lower degrees of local progression [23, 26, 33], better progression-free survival [26] and lower disease specific mortality at 10 years [23, 28, 33]. There was no effect on overall survival in the majority of the studies. Only one study showed an effect on overall survival at five and 10 years [37, 38].

Advanced prostate cancer

Six studies compared the monthly 3.6 mg and the 10.8 mg dose given every three months of goserelin in patients with advanced prostate cancer. The effects on testosterone levels were similar in the studies [45-50].

Other studies compared goserelin (3.6 mg monthly) to various medicines, such as polyestradiol phosphate (PEP) [51], diethylstilbestrol [52-54], bicalutamide [55-57] and orchiectomy [58-61]. Another study compared intermittent and continuous ADT [62].

Goserelin resulted in a longer time to progression [51], objective response rate [52, 53, 58] or no differences in clinically relevant endpoints [54-57, 59-62].

Metastatic prostate cancer

Several studies compared ADT with goserelin with or without flutamide with surgical orchiectomy in patients with metastatic prostate cancer [63-69], resulting in similar effects on objective response rates, time to disease progression and overall survival.

The EORTC 30853 study compared orchiectomy [n = 161] with a combination of goserelin (3.6 mg monthly) plus flutamide (250 mg tid orally, n = 163) in patients with metastatic prostate cancer. Significantly more favourable effects on objective progression and death from cancer were seen in the ADT group [70-74]. The time from objective progression to death was however longer in the orchiectomy group [72]. At longer follow-up (7.2 years) the advantages of ADT were maintained [75].

Other studies compared combinations of goserelin, flutamide and finasteride [76], goserelin *versus* extramustine [77], goserelin *versus* cyproterone acetate [78]. No differences were found in

the first two studies, a longer time to progression was found for goserelin compared to cyproterone acetate [78].

Leuprorelin

Localized prostate cancer

Several studies were performed with leuprorelin: three versus eight months of neoadjuvant therapy with leuprorelin [79], as add-on to surgery [80]. The medicine was also studied as add-on to radiotherapy [20, 81, 82].

PSA was reduced compared to surgery alone. Positive surgical margins and lymph node involvement were seen more often in the group with surgery alone [80]. A higher overall survival was seen compared to radiotherapy alone [81]. Another study showed no positive effects on quality of life [82].

Advanced prostate cancer

One study investigated the effects of leuprorelin or oral bicalutamide on bone mineral density (BMD). The results were more favourable for bicalutamide [83].

Studies comparing one and three months formulations showed no relevant differences concerning effects on testosterone levels and PSA [84-87]. This was also the case for a comparison of three and six months formulations in a mixed population [88].

Leuprorelin prior to radical prostatectomy was compared to no pretreatment by a US study group. This study showed no differences in clinical relapse-free or PSA relapse-free survival rates between the groups [89, 90].

Triptorelin

Localized prostate cancer

One study compared preoperative triptorelin with no hormonal treatment in patients with localized prostate cancer. Triptorelin did not show favourable effects on postoperative PSA or skeletal events [91].

Advanced prostate cancer

One study compared triptorelin (+flutamide) with PEP. The primary endpoint was overall survival. No differences in mortality were observed at shorter or longer follow-up [92-94]. The 28 days and 3 months formulations showed similar effects on testosterone, LH and PSA levels [95]. Use of triptorelin prior to prostatectomy resulted in a lower rate than the control group, but there was no effect on progression-free survival [96-97].

Metastatic prostate cancer

Triptorelin was as effective as orchiectomy regarding effects on metastases and pain scores [98].

Although the levels of evidence were quite variable, no clinically meaningful differences were identified in clinical efficacy among buserelin, goserelin, leuprorelin and triptorelin in localized, advanced or metastatic prostate cancer. The clinical efficacy of goserelin and leuprorelin are much better documented than the other drugs.

It is not yet clear whether or not intermediate therapy with GnRH agonists is as safe and effective as continuous therapy [5].

All medicines are awarded 80%.

ORIGINAL RESEARCH

Safety

The incidence of severe adverse reactions was low for all compounds. Very few direct comparative studies between GnRH agonists and antagonists were identified. Agonists in general may induce depression, which can be severe. The incidence of severe adverse events was low to moderately high in most studies. The duration and size of most studies was insufficient to make firm statements concerning relative safety in the long term. There are no indications for major differences between the drugs concerning safety, with the exception of abarelix, which shows anaphylactic reactions at a higher rate than is the case with the other drugs.

Abarelix is awarded 60%, whereas the other medicines are awarded 70%.

Tolerability

Gonadotropin-releasing hormone (GnRH) agonists were associated with frequent, but harmless side effects. The side effects in direct comparative studies that are most relevant are summarized in Table 3.

The most common side effects result from the mechanism of action of the drugs, leading to impotence, decreased sexual drive and hot flushes. When GnRH agonists are given as monotherapy, testosterone surge may occur in the early phases of treatment.

Dosage frequency

A low dosage frequency is convenient to the patient and may increase compliance with therapy. The highest score (100%) was awarded to the lowest dose frequency (every six months), the lowest score (20%) was awarded to the highest dose frequency (every week). Scores for different dosage frequencies are given in Table 4. Leuprorelin was awarded 90%, because the generic formulation was included in the analysis. Six months formulations of goserelin and leuprorelin are not available in The Netherlands, but these are approved in other European

countries. The dosage frequency of the agonists is more favourable than the antagonists.

User-friendly dosage forms

A user-friendly dosage form which is easy to store and handle is convenient to the patient and the caregiver. User-friendly scores ranged from 30% for drugs stored at room temperature to 15% for drugs stored in a refrigerator, and 0% for drugs stored below 0°C. Drugs that required no reconstitution had a score of 30%, drugs that needed complicated reconstitution had a score of 10%. Ease of administration ranged from 40% for easy, to 10% for complex. Score for different drugs are shown in Table 5.

The hybrid generic implant formulation of leuprorelin was used for calculation of the score. Eligard is not ready for use and needs to be reconstituted and kept in the refrigerator.

All agonists are given subcutaneously in a depot formulation. No independent studies comparing the ease of use of the implants are available. The ease of administration is better for the antagonists, as no implant has to be injected.

Drug interactions

No specific studies were performed. There are almost no known interactions with any of the GnRH agonists. Buserelin and goserelin may lower glucose tolerance, which could lead to decreased efficacy of antidiabetic medication.

Special precautions

Data were collected from the summaries of product characteristics (SPCs) for each drug. The warnings and precautions of the GnRH agonists are summarized in Table 6.

More special precautions are applicable to abarelix and degarelix. These drugs are awarded 60%. Although there are differences in the SPCs of the GnRH agonists, it is unclear whether this reflects real differences between the drugs. These medicines are given a score of 70%.

Table 3: Incidence of adverse events in clinical trials

	Decreased libido	Erectile dysfunction	Asthenia	Arthralgia	UTI	Fatigue	Hot flushes	Injection site reactions	Total	Reference(s)
Leu Aba						8% 14%				10
Gos Deg							17% 10%	0% 22%	35% 35%	11
Gos Deg	6% 7%	9% 8%	9% 7%			9% 6%	63% 60%	0% 33%		12
Leu Deg				9% 4%	9% 3%	5% 6%	26% 21%	< 1% 40%	78% 81%	13
Gos Leu			23% 19%				52% 55%			16
Gos	67%	76%	20–25%	8–12%			54–76%			45, 47, 53, 55, 56, 59
Leu	81%					14–77%	96%		78%	83, 88
Tri							66–76%			95, 98

Table 4: Drug dosage frequencies for GnRH agonists

Drug	Trade name	Dosage	Score
Buserelin	Suprefact	9.45 mg per 3 months 6.3 mg per 2 months	90%
Goserelin	Zoladex	10.8 mg per 3 months 3.6 mg per month	90%
Leuprorelin	Lucrin, Eligard, generics (Sandoz)	45 mg per 6 months (Eligard) 22.5 mg per 3 months (Eligard) 7.5 mg per month (Eligard) 30 mg per 6 months (Lucrin) 11.25 mg per 3 months (Lucrin) 3.75 mg per month (Lucrin) 5 mg per 3 months (generics) 3.6 mg per month (generics)	90%
Triptorelin	Pamorelin	22.5 mg per 6 months 11.25 mg per 3 months 3.75 mg per month	100%
Abarelix	Plenaxis	100 mg on days 1, 15 and 29, IM, followed by 100 mg every 4 weeks	60%
Degarelix	Firmagon	240 mg once SC, followed by 80 mg per month	60%

GnRH: gonadotropin-releasing hormone; IM: intramuscular; SC: subcutaneous.

Table 5: User-friendly dosage for GnRH agonists under room temperature storage

Drug	Preparation	Ease of injection	Score
Buserelin	Ready for use	Easy	100%
Goserelin	Ready for use	Easy	100%
Leuprorelin	Ready for use (generics)	Easy	100%
Triptorelin	Needs to be reconstituted, easy to perform	Easy	90%
Abarelix	Needs to be reconstituted, complex to perform	More complicated	65%
Degarelix	Needs to be reconstituted, easy to perform	Easy	90%

GnRH: gonadotropin-releasing hormone.

Documentation

The score for this criterion is divided into four sub-criteria: (1) number of randomized comparative studies; (2) number of patients in these studies; (3) number of years marketed; and (4) number of patient days worldwide.

The first two of these sub-criteria are indicative of the overall clinical documentation of the drugs in randomized controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies leave no doubt about the clinical efficacy and safety of this drug in the studied population. The latter two criteria are indicative of the overall clinical experience with the drug. These sub-criteria may introduce a bias to the advantage of older drugs, but this is done

intentionally. The safety of a newly introduced drug cannot be guaranteed from the results of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions (e.g. patients with diminished renal function) were excluded. Both the number of patients that have been treated on a worldwide basis and the period that a certain drug has been available are of importance, as it may take time until adverse reactions occur. For a summary of these data, see Table 7.

The overall SOJA score is presented in Table 8.

Discussion

There is currently no major need to make formulary choices within the GnRH agonists and antagonists in most countries. The drugs are usually not included in the hospital formulary because they are primarily used outside the hospital. In The Netherlands, many expensive drugs will be transferred to the hospital budget in January 2015. This will lead to discussions concerning formulary selection, because the cost of these drugs will be the responsibility of the hospital. Therefore, there is a need for tools to aid formulary choices. We have not included the criterion acquisition cost, to

allow for a pre-selection only on quality aspects. Only the drugs with the highest scores will be considered as options for the treatment of patients with prostate cancer. After completion of the study, it turned out that the medicines in the present analysis would not be transferred to the hospital budget in 2015.

The weighting of the selection criteria reflects the opinion of the authors. Of course, such opinions are always open for debate. Therefore, all existing SOJA productions are available on the Internet (www.tablet.sojaonline.nl), allowing each user of the method to assign his/her own relative weight to each criterion, thereby calculating a personal score [101]. None of the SOJA productions is financially supported by pharmaceutical companies.

Goserelin and leuprorelin show the highest scores. The main advantage compared with buserelin and triptorelin is the better documentation for the treatment of prostate cancer. Because the differences in score between goserelin and leuprorelin (and possibly triptorelin) are limited, these drugs are acceptable as first-line therapy. Clearly the judgement of the authors concerning the properties of the medicines has an impact on the final outcomes. There are however few indications that there are clinically relevant differences between the agonists regarding clinical efficacy, safety and tolerability.

It should be noted that the studies with leuprorelin were performed with various formulations, whereas this was not the case for the other medicines. A specification of the applied formulation was only provided in a few studies: Lupron [17, 83], Enantone [18] and Sandoz generic formulation [87]. The 16 other studies did not specify the formulation, although the vast majority of studies used a dose of 7.5 mg per 28 days or 22.5 mg

Table 6: Warnings and precautions for GnRH agonists

	Buserelin	Goserelin	Leuprorelin	Triptorelin
Start anti-androgen prior to treatment	+	+	+	+
Hypertension	Check BP			
Glucose tolerance	Decrease possible	Decrease possible		
Osteoporosis	Increased risk	Increased risk		Increased risk
Depression in anamnesis	Should be treated	Should be treated	Should be treated	
Doping tests		Positive reactions		
Urinary tract obstruction in anamnesis			Not recommended	
Lab tests			Acid phosphatase may increase temporarily	
Gonadotropin producing adenoma				May become manifest
Oral anticoagulation				Local haematoma

GnRH: gonadotropin-releasing hormone.

per three months [10, 13, 16, 20, 79, 81, 86, 99, 102]. The 3.75 mg or 11.25 strengths were used in two studies [80, 89].

Acquisition cost plays a key role in the final selection of the drug of choice. The recent introduction of a generic leuprorelin implant formulation, which does not need reconstitution and can be stored outside of a refrigerator [87], and which is at least as effective as previously used leuprorelin formulations and was well tolerated in a relatively large group of patients (n = 818) [103] may be a good starting point for a renewed discussion on drug selection for the treatment of prostate cancer. Major cost savings might be applicable, because the acquisition cost of the various drugs has always been quite high. It seems likely that the need for a careful economic evaluation of drugs in oncology will increase throughout Europe.

Table 7: Clinical documentation and experience for GnRH agonists

Drug	Studies	Patients	Years	Patient days (million)	References	Score
Buserelin	1	75	> 10	> 100	19	53%
Goserelin	> 20	> 1,000	> 10	> 100	11, 12, 16, 20, 21, 26, 31, 33, 35, 36, 39, 41, 43, 45-51, 53-56, 58-63, 65-70, 76-78	100%
Leuprorelin	20	> 1,000	> 10	> 100	10, 13, 16-18, 20, 79-89, 99, 100	100%
Triptorelin	9	> 1,000	> 10	> 100	17, 18, 91, 92, 95, 96, 98	86%
Abarelix	1	180	3	1	10	14%
Degarelix	3	680	4	1	11-13	31%

GnRH:gonadotropin-releasing hormone.

Table 9 provides an overview of prices of the various agents in countries throughout Europe. The generic formulation is less expensive than the other medicines in most countries, with the interesting exception of The Netherlands. Prices are also quite different between countries, prices in Belgium are considerably lower than in other countries. Prices may be lower after negotiations between hospitals and companies.

The GnRH antagonists, degarelix and abarelix, show considerably lower scores than the GnRH

Table 8: GnRH agonist SOJA scores

	Efficacy	Safety	Tolerability	Frequency	User-friendly	Interactions	Precautions	Documentation	Score
Weight	300	200	100	80	100	60	60	100	1,000
Buserelin	240	140	60	72	100	60	42	53	767
Goserelin	240	140	60	72	100	60	42	100	814
Leuprorelin	240	140	60	72	100	60	42	100	814
Triptorelin	240	140	60	80	90	60	42	86	798
Abarelix	240	120	60	48	65	42	36	14	625
Degarelix	240	140	50	48	90	42	36	31	677

GnRH: gonadotropin-releasing hormone; SOJA: System of Objectified Judgement Analysis.

Table 9: Annual cost of a 3-month course of selected GnRH agonists across Europe

Country	Enantone/Lucrin	Zoladex	Eligard	Sandoz
Germany	Euros 1,724.52	Euros 2,224.46	Euros 1,843.40	Euros 1,537.20
Italy	Euros 1,840.56	Euros 2,573.90	Euros 1,472.48	Euros 1,300.49
Sweden	Euros 1,665.12	Euros 1,491.81	Euros 1,433.28	Euros 1,172.16
Switzerland	CHF 1,875.96	CHF 1,679.32	CHF 2,316.00	CHF 1,295.08
Belgium	Euros 605.44	Euros 542.92	Euros 1,478.92	Euros 544.00
Austria	Euros 1,436.00	Euros 1,511.60	Euros 1,292.40	Euros 746.72
Hungary	HUF 408,932.00	HUF 422,840.00	HUF 995,988.00	HUF 299,224.00
Poland	PLN 3,316.60	PLN 2,865.28	PLN 2,883.04	PLN 2,416.56
Netherlands	Euros 1,063.76	Euros 1,398.80	Euros 1,159.60	Euros 1,304.80

GnRH: gonadotropin-releasing hormone.

agonists. Based on current data, these drugs should not be considered as first-line therapy for the treatment of prostate cancer. Their acquisition cost is also higher than those of (the already expensive) GnRH agonists. The 2013 guideline for the treatment of prostate carcinoma of the European Association of Urology assigned a limited place to GnRH antagonists: ‘Overall, this new family of agents seems appealing, but their advantages over GnRH agonists are far from proven. The use of GnRH antagonists is limited by a monthly formulation. Suppression of the initial flare-up with monotherapy is only clinically relevant in a few, symptomatic, metastatic patients’ [104].

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