

Rapid ascertainment of uptake of a new indication for abiraterone by use of three nationwide health care registries in Sweden

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Introduction

Several drugs have recently been shown to prolong life and improve quality of life in men with metastatic hormone sensitive (mHSPC) and castration resistant prostate cancer (CRPC) [1]. Specifically, two randomized clinical trials have shown an increased survival for men with mHSPC who in addition to treatment with Gonadotropin Releasing Hormone agonist (GnRH) received abiraterone combined with prednisone or prednisolone as primary treatment [2,3]. An extension of the indication for abiraterone to treat *de novo* mHSPC in adult men in combination with androgen deprivation therapy (ADT) plus prednisone or prednisolone was approved by the European Medicines Agency (EMA) in November 2017 with the restriction that the patient should have high-risk mHSPC, i.e. at least two out of three of the following factors: Gleason score 8–10, three or more bone metastases, or visceral metastases. Reimbursement for this extended indication was approved by The Dental and Pharmaceutical Benefits Agency in Sweden in June 2018 with the additional restriction that the patient should not be suitable for docetaxel [4]. Docetaxel is a chemotherapeutic drug with a lower cost than abiraterone that is recommended by the National Guidelines for use in men with *de novo* mHSPC, and there is no evidence that abiraterone is superior to docetaxel [4,5]. As abiraterone had already been approved by the EMA for treatment of CRPC in November 2012, and subsidized use on this new indication was approved on the June 2015 in Sweden, the uptake of the new indication cannot be monitored by data in the Prescribed Drug Registry as the only source of information since this registry does not include date of cancer diagnosis or the indication for treatment.

The aim of this study was to rapidly assess uptake in Sweden of the new indication for upfront use of abiraterone plus prednisolone in combination with GnRH in men with *de*

novo high-risk mHSPC by use of a clinical cancer register and two other nation-wide health care registries and to assess adherence to the restrictions of the indication.





Material and methods

The National Prostate Cancer Register (NPCR) of Sweden

The National Prostate Cancer Register (NPCR) of Sweden captures 98% of all incident prostate cancer (PCa) cases in Sweden compared to The Cancer Registry to which reporting is mandated by law [6,7]. In NPCR detailed information on cancer characteristics, work-up, and primary treatment is registered, but no information from the subsequent disease trajectory is recorded, e.g. progression or secondary treatment [6]. Data in NPCR were used to identify men with *de novo* mHSPC defined by bone metastases and/or visceral metastases on imaging at diagnosis. A dichotomous variable on the number of metastatic foci on bone imaging coded as one to three foci or four or more foci was added to NPCR in September 2018. High risk mHSPC was defined when at least two out of three of the following factors were fulfilled: Gleason score 8–10, four or more bone metastases, or visceral metastases. No impact on oncologic outcomes has been demonstrated when three or four bone metastases have been used as cut off criteria for high risk PCa [8].

The Patient Registry

The Patient Registry holds data on hospital discharge diagnoses for all patients in Sweden since 1987 with a virtually complete capture and is updated monthly. The Charlson Comorbidity Index (CCI) was calculated on the basis of ICD codes for the discharge diagnoses within ten years preceding the date of PCa diagnosis [6,9].

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The Prescribed Drug Registry

Since July 2005, all filled prescriptions in Sweden are registered in The Prescribed Drug Registry and data are available for analysis one month after a prescription has been filled [6,10]. All filled prescriptions for abiraterone (ATC code L02BX03) have been reported to this registry. We also retrieved filled prescriptions for opioids (ATC code N02A) within six months after date of PCa diagnosis in order to identify men who used a strong analgesic.

“The Statistics pathway” at The National Board of Health and Welfare

In order to provide a rapid ascertainment of drug use, The National Board of Health and Welfare (NBHW) provides a service in which data on subjects from a clinical register can be linked with data from other registers, e.g. The Prescribed Drug Registry and The Patient Registry, and only aggregated data are then returned to the researcher. Approval by the Research Ethics Board was obtained for a publication based such linkages.

Study population and procedure

On October 15, 2020, men with *de novo* mHSPC were identified in NPCR from the second quarter in 2018 to the third quarter in 2020 and a file with person identity number, cancer characteristics and region was submitted from NPCR to NBHW. At NBHW linkages to the Prescribed Drug Registry by use of the person identity number were performed to obtain data on filled prescriptions for abiraterone and opioids within six months after date of diagnosis and to the Patient Registry for ICD-10 codes to calculate CCI. Only data aggregated in a predefined table was then returned to the researchers.

Results

There were 2041 men registered in NPCR with *de novo* mHSPC, i.e. with bone metastases and/or visceral metastases on imaging, between June 1, 2018 and September 30, 2020 of whom 250 (12%) had filled a prescription for abiraterone within six months after the date of diagnosis (Table 1). For men diagnosed in the third quarter of 2020, only the fillings in that quarter were available. The proportion of men in NPCR who filled a prescription for abiraterone increased from 10/226 (4%) in the third quarter of 2018 to 58/223 (26%) in the first quarter of 2020, a quarter in which registration in NPCR is almost complete. Of note, in the second and third quarters of 2020, 17% of men with *de novo* mHSPC filled a prescription for abiraterone, despite the COVID-19 pandemic that affected Swedish health care.

There was a higher proportion of men with four or more bone metastases among men who had filled a prescription ('users'), than among men who had not filled a prescription ('non-users'), users 140/250 (56%) vs non-users 706/1791 (39%). There were 41/250 (16%) men with visceral metastasis among users vs 364/1791 (20%) among non-users. Gleason was ≥ 8 in 209/250 (84%) users vs 1210/1791 (68%) non-

users. There was a higher proportion of men with high risk mHSPC among users, 136/250 (54%) vs non-users, 676/1791 (38%). Median age at diagnosis was 73 years among users and 75 years among non-users. The proportion of men who had filled an opioid prescription was 38% for users and 35% for non-users, and CCI was 0 in 70% of users vs 60% of non-users.

The proportion of men with *de novo* mHSPC who had filled a prescription for abiraterone in each of the 21 Swedish regions ranged from 0 to 39%.

We compared the proportion of men who filled a prescription for abiraterone in men who were registered in NPCR soon after their diagnosis vs those who were registered late and found virtually no difference (data not shown).

In 2018, the proportion of men with *de novo* mHSPC who had been reported to NPCR by use of the diagnostic and the work-up form, which both are necessary in order to identify men with bone or visceral metastases on imaging, were 50% at three months after date of diagnosis, 80% after six months, and 95% after nine months (Figure 1).

Discussion

In this nationwide, population-based study in Sweden we found a slow but increasing uptake of the new indication of abiraterone, i.e. for treatment of newly diagnosed high-risk mHSPC in combination with GnRH plus prednisone or prednisolone. After reimbursement for this indication was approved by The Dental and Pharmaceutical Benefits Agency in Sweden in June 2018, overall 12% of all men diagnosed with *de novo* mHSPC had received abiraterone within six months after date of diagnosis. Uptake of the new indication for abiraterone varied from 0–39% in the 21 Swedish regions. Adherence to the restriction that only men with high-risk mHSPC and men not suitable for chemotherapy should receive abiraterone seemed low since only 54% of men who had filled a prescription for abiraterone had high risk mHSPC and 70% of these men had no comorbidities.

Strengths and limitations

The main strength of this cross-sectional study is that it is based on linkages of three nationwide, population-based registers with rapid and almost complete capture of data. NPCR provided data on the diagnosis of prostate cancer and occurrence and extent of metastases, which defined *de novo* high-risk mHSPC. Fillings in the Prescribed Drug Registry was used to define drug exposure and the Patient Registry provided data on comorbidity, used to assess if the drug was used in line with the indication approved for marketing authorization. These latter two registers are updated on a monthly basis.

Our study has some limitations. Neither NPCR nor the Patient Registry hold data on Eastern Cooperative Oncology Group/WHO Health organization Performance status (ECOG), a widely used index for assessment level of function in cancer patients. Instead we used the CCI based on hospital

Table 1. Number and proportion of men with *de novo* metastatic hormone sensitive prostate cancer (mHSPC) in the National Prostate Cancer Register of Sweden who filled a prescription for abiraterone within six months after date of diagnosis.

	Abiraterone		Total
	n	(%)	
Total number of men	250	(12)	2041
Date of diagnosis			
2018-Q2	0	(0)	86
2018-Q3	10	(4)	226
2018-Q4	24	(9)	282
2019-Q1	26	(11)	247
2019-Q2	34	(13)	256
2019-Q3	22	(8)	259
2019-Q4	41	(16)	257
2020-Q1	58	(26)	223
2020-Q2	21	(17)	124
2020-Q3	14	(17)	81
Number of metastases on bone imaging			
1–3 metastases	38	(7)	511
4 or more metastases	140	(17)	846
Missing	72	(11)	684
Visceral metastases			
Yes	41	(10)	405
No	206	(13)	1587
Missing	3	(6)	49
Gleason score			
< 8	26	(6)	358
≥ 8	209	(6)	1419
Missing	15	(6)	264
Risk group			
High risk ^a	136	(17)	812
Age at diagnosis, years			
Median (Q1, Q3)	73 (68, 77)		75 (69, 81)
<60	12	(12)	101
60–69	67	(15)	458
70–79	133	(15)	887
80+	38	(6)	595
Opioids during the first six months after diagnosis ^b			
Yes	94	(13)	725
No	156	(12)	1316
Charlson Comorbidity Index ^c			
0	176	(14)	1233
1	29	(9)	311
2	20	(10)	207
3+	25	(9)	290
Region			
Stockholm*	51	(19)	271
Uppsala*	1–4 ^d	(1–5)	76
Södermanland	12	(12)	97
Östergötland*	6	(6)	95
Jönköping	6	(8)	79
Kronoberg	19	(39)	49
Kalmar	1–4 ^d	(2–8)	52
Gotland	0	(0)	1–4
Blekinge	8	(16)	49
Skåne*	29	(12)	248
Halland	8	(12)	66
Västra Götaland*	36	(10)	351
Värmland	6	(8)	71
Örebro*	6	(8)	73
Västmanland	1–4 ^d	(2–7)	59
Dalarna	9	(11)	83
Gävleborg	5	(7)	75
Västernorrland	12	(17)	70
Jämtland	7	(18)	39
Västerbotten*	20	(23)	86
Norrbotten	1–4 ^d	(2–8)	48

^aTwo or more criteria out of: i) Gleason score ≥ 8; ii) Four or more bone metastases; iii) visceral metastasis.

^bFilled prescription for opioid in the Prescribed Drug Registry within six months after date of diagnosis.

^cCharlson Comorbidity Index based on discharge diagnoses in the Patient Registry.

^dApproximate number given in order to protect confidentiality due to small number of cases (four or below) who received abiraterone in a region.

*Indicates region with university hospital.

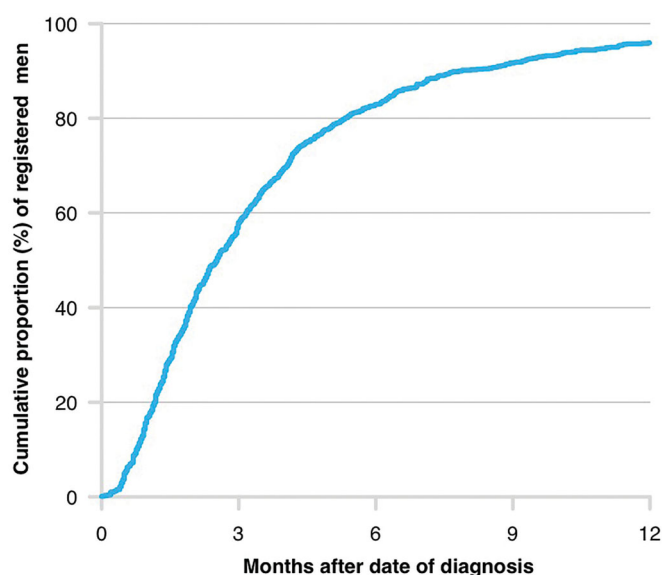


Figure 1. Cumulative proportion of men with *de novo* metastatic prostate cancer registered in the National Prostate Cancer Register (NPCR) of Sweden according to time after diagnosis in 2018.

Legend: Registration was based on information in the diagnostic and in the work-up form, which both are necessary in order to identify men with bone metastases and/or visceral metastases on imaging.

discharge diagnoses [6,9]. CCI has previously been shown to predict overall survival quite well in men in NPCR [11]. The extent of metastases could be assessed for around two thirds of the men by data on number of bone and visceral metastases. Notably, a recent study has shown that men with low-risk mHSPC also benefit from abiraterone [8]. The Prescribed Drug Registry does not capture data on drugs administered in-hospital, so this registry cannot be used to analyze docetaxel administration. Finally, there is some delay in reporting to NPCR and capture reaches 80% at six months and 95% around nine months after date of diagnosis. Thus, data for the second and third quarters in 2020 should be interpreted with caution since capture in NPCR was not complete and during that time period there was also an effect by the COVID-19 pandemic on cancer care.

National, regional, and local decisions with an impact on uptake of new drugs and new indications

Expenditure on cancer drugs in the EU has increased in both absolute and relative terms [12]. Against that backdrop it is not surprising that there are several checkpoints before the pricing and reimbursement status of a novel expensive cancer drug is decided. After approval of subsidized use by The Dental and Pharmaceutical Benefits Agency, the uptake of a new treatment in clinical practice is also influenced by other factors. First, national guidelines have to recommend the use of the subsidized drug, and likely more important, there has to be adherence to these recommendations [4]. Moreover, financing of the use of a new drug has to be decided on and there are different procedures for this step in different health care regions and regions.

Despite the efforts of the New Treatment council, a national working group that aims for fair, equal, and rational

use of medical drugs by making recommendations on drug use to the county councils, there were large regional differences in uptake of abiraterone for use in men with *de novo* mHSPC. In other settings, uptake of new cancer drugs has been much quicker. For example, a US study of new treatments for multiple myeloma in 2010–2016 reported that uptake of new combinations of drugs occurred almost in parallel with their regulatory approval [13].

Prescribed Drug Registries are also in existence in e.g. Denmark and Canada and somewhat similar rapid assessments of drug use have been performed. For example, a Danish study investigated the uptake of a new anticoagulant drug for treatment of atrial fibrillation [14]. Notably, in that study there were no data on the indication for the drug in approximately one third of the study subjects as there were no data from a clinical register but only data from the National Prescription Registry, the National Patient Registry, and the Danish Civil Registration System.

Conclusion

In conclusion, uptake of the new indication for abiraterone in men with *de novo* mHSPC was 12% within 27 months after approval of the subsidized use and there seemed to be a low adherence to the restriction to high-risk mHSPC and men not suitable for docetaxel. After approval for subsidized use by the Swedish Dental and Pharmaceutical Benefits Agency, the uptake of a new treatment in clinical practice is also influenced by other national, regional and local factors, and this seems to have resulted in a slow uptake and large regional differences.

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Disclosure statement

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Disclaimer

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