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High-Intensity Care in the End-of-Life Phase of Castration-Resistant Prostate Cancer Patients: Results from the Dutch CAPRI-Registry

Hans M. Westgeest, MD,[1,*] Malou C.P. Kuppen, MD,[2,*,i] Fons A.J.M. van den Eertwegh, MD, PhD,[3] Inge M. van Oort, MD, PhD,[4] Juleon L.L.M. Coenen, MD, PhD,[5] Jeroen R.J.A. van Moorselaar, MD, PhD,[6] Katja K.H. Aben, PhD,[7,8] Andre M. Bergman, MD, PhD,[9] Daan ten Bokkel Huinink, MD,[10] Joan van den Bosch, MD,[11] Mathijs P. Hendriks, MD,[12,ii] Menuhin I. Lampe, MD,[13] Jules Lavalaye, MD, PhD,[14] Niven Mehra, MD, PhD,[15] Tineke J. Smilde, MD, PhD,[16] Rik D.M. Somford, MD, PhD,[17,iii] Lidwine Tick, MD, PhD,[18] Nir I. Weijl, MD, PhD,[19] Yes A.J. van de Wouw, MD, PhD,[20] Winald R. Gerritsen, MD, PhD,[15] and Carin A. Uyl-de Groot, PhD[2]

Abstract

Background: Intensive end-of-life care (i.e., the overuse of treatments and hospital resources in the last months of life), is undesirable since it has a minimal clinical benefit with a substantial financial burden. The aim was to investigate the care in the last three months of life (end-of-life [EOL]) in castration-resistant prostate cancer (CRPC).

Methods: Castration-resistant prostate cancer registry (CAPRI) is an investigator-initiated, observational multicenter cohort study in 20 hospitals retrospectively including patients diagnosed with CRPC between 2010 and 2016. High-intensity care was defined as the initiation of life-prolonging drugs (LPDs) in the last month, continuation of LPD in last 14 days, >1 admission, admission duration ≥14 days, and/or intensive care admission in last three months of life. Descriptive and binary logistic regression analyses were performed.

Results: High-intensity care was experienced by 41% of 2429 patients in the EOL period. Multivariable analysis showed that age (odds ratio [OR] 0.98, 95% confidence interval [CI] 0.97–0.99), performance status (OR 0.57, 95% CI 0.33–0.97), time from CRPC to EOL (OR 0.98, 95% CI 0.97–0.98), referral to a medical oncologist (OR 1.99, 95% CI 1.55–2.55), prior LPD treatment (>1 line OR 1.72, 95% CI 1.31–2.28), and opioid use (OR 1.45, 95% CI 1.08–1.95) were significantly associated with high-intensity care.

[1]Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands.
[2]Institute for Medical Technology Assessment, Erasmus School of Health Policy and Management, Rotterdam, the Netherlands.
[3]Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.
Departments of [4]Urology, [7]Health Evidence, and [15]Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands.
[5]Department of Oncology, Isala, Zwolle, the Netherlands.
[6]Department of Urology, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands.
[8]Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands.
[9]Division of Medical Oncology, the Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands.
[10]Department of Internal Medicine, Diakonessenhuis, Utrecht, the Netherlands.
[11]Department of Internal Medicine, Albert Schweitzer Ziekenhuis, Dordrecht, the Netherlands.
[12]Department of Internal Medicine, Northwest Clinics, Alkmaar, the Netherlands.
[13]Department of Urology, Medical Center Leeuwarden, Leeuwarden, the Netherlands.
[14]Department of Nuclear Medicine, St Antonius Hospital, Nieuwegein, the Netherlands.
[16]Department of Internal Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands.
[17]Department of Urology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands.
[18]Department of Internal Medicine, Maxima Medical Center, Eindhoven, the Netherlands.
[19]Department of Internal Medicine, MCH-Bronovo Hospital, 's-Gravenhage, the Netherlands.
[20]Department of Internal Medicine, VieCuri Medical Center, Venlo, the Netherlands.
*These authors contributed equally to this work.
[i]ORCID ID (https://orcid.org/0000-0001-8908-1684).
[ii]ORCID ID (https://orcid.org/0000-0001-6687-5393).
[iii]ORCID ID (https://orcid.org/0000-0002-5277-6586).
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Conclusions: High-intensity care in EOL is not easily justifiable due to high economic cost and little effect on life span, but further research is awaited to give insight in the effect on patients' and their caregivers' quality of life.

Keywords: castration-resistant prostate cancer; end-of-life care; high-intensity care; hospital admission; life-prolonging drugs

Introduction

Several life-prolonging drugs (LPDs) have been registered for the treatment of metastatic castration-resistant prostate cancer (mCRPC): taxane chemotherapy (TAX, i.e., docetaxel, cabazitaxel), androgen receptor-targeting therapies (ART, i.e., abiraterone acetate, enzalutamide), and an alpha-emitting isotope (radium-223 dichloride).

The disease trajectory of incurable cancer as mCRPC shows a slow decline over months or years, followed by a rapid decline over the last few months resulting in death.[1] In a contemporary real-world cohort, we previously reported a median overall survival (OS) of 26 months.[2] Several prognostic models and individual factors have been studied to aid in the identification of the beginning of the end of life (EOL).[3–5] However, the overestimation of survival by clinicians shows that identification of EOL remains challenging.[6–8] This optimism about survival can lead to suboptimal delivery of palliative care. This does not only come at high economic costs, but is also not in line with the patient's preferences.[7]

The focus of EOL care should shift from active LPD treatment to symptom management and meeting the subjective needs of patients.[9] In EOL, patients are less willing to accept treatment complications and want a dignified EOL, as comfortable as possible.[10–13] Intensive use of hospital care in EOL does not meet patient's needs, since the contribution to survival is minimal and the effect on quality of life is not evident.[14–16]

Potential indicators for high-intensity care near the EOL have been identified and include the intensive use of chemotherapy, low rates of hospice use, and interventions resulting in emergency room (ER) visits, hospitalization, or intensive care unit (ICU) admissions.[14,15] Although high-intensity care in EOL can have possible substantial financial and clinical harms, population-based, disease-specific data are lacking. We aim to investigate the use of high-intensity care, more specifically the use of treatments and hospitalization in EOL in CRPC. We will focus on changes in care during the disease trajectory and differences between treated and untreated patients.

Methods

Study design and setting

CAPRI (castration-resistant prostate cancer registry) is an investigator-initiated, observational multicenter cohort study in 20 Dutch hospitals, which were selected on the basis of geographical spread and the type of hospital (i.e., four academic hospitals, 11 large teaching hospitals, and five general hospitals). The study design has been described before.[2] The study was approved by a medical Ethics Committee and in accordance to Dutch law, no informed consent was necessary for this observational registry. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

All CRPC patients diagnosed between 2010 and 2016 in the 20 hospitals were included retrospectively. CRPC was either defined by the criteria set by the European Association of Urology[17] or by the treating physician (e.g., starting treatment, including agents as bicalutamide based on prostate-specific antigen [PSA] progression). Predefined and readily available data from medical records were collected retrospectively by trained data managers. CRPC patients with docetaxel for metastatic hormone-sensitive prostate cancer ($n = 14$) were excluded.

In the current analysis, we only included patients with a registered date of death in their medical files. We assumed all deaths were related to CRPC since the reason of death was not registered.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they were registered during a hospital visit or admission one month prior or after the start of the last three months of life. All data have been regularly updated for all patients until December 31, 2017.

Outcome

Outcomes were treatment utilization and hospital admissions in the last three months of life. First, outcomes were evaluated during the course of CRPC: from CRPC diagnosis to the last six months of life (CRPC-6mo), from the last six to the last three months of life (6–3mo), and in last three months of life (3mo-death). Second, we investigated outcomes in subgroups based on LPD treatment (i.e., docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, or radium-223) in the last three months of life: patients without LPD in the last three months of life (''no LPD treatment''), patients with LPD started before the last three months of life but continued in the last three months of life (''LPD continuation''), and patients initiating new LPD in the last three months of life (''LPD initiation'').

The second outcome parameter was high-intensity care, which was defined as the occurrence of at least one of these items: initiation of LPD in the last month of life (1), continuation of LPD within the last 14 days of life (2), more than one hospital admission in the last three months of life

(3), admission duration of ≥14 days in the last three months of life (4), and ICU admission in the last three months of life (5). Hospice use and ER visits were not evaluable from our database and were excluded as indicators in this analysis.

Statistical analyses

The sample size was not based on power calculations. Descriptive statistics were performed using Cochranes Q test or Friedman test. One-way analysis of variance (ANOVA), Kruskal–Wallis, or chi-square test was used to test for differences between LPD subgroups. *Post hoc* analyses using pairwise comparison with Bonferroni correction were performed in case of significant differences. Univariable and multivariable binary logistic regression incorporating known prognostic factors were performed on original data and pooled data after multiple imputation using Markov Chain methods. A *p*-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM®, Armonk, NY) was used for all analyses.

Results

In total 2432 of 3616 (68%) CRPC patients included in the CAPRI died during follow-up; three patients (<1%) were excluded due to missing date of death. The median follow-up duration was 19.4 months (range 0.4–92 months) from CRPC diagnosis.

Treatment characteristics

In CRPC-6mo 52% ($n=1256$) was treated with an LPD compared with 44% ($n=1074$) in the last 6–3mo, and 39% ($n=951$) in the last three months of life ($p<0.01$). Most patients started LPD before the last three months of life and continued treatment in this period (729 of 951 patients). The number of patients initiating new LPD declined between CRPC-6mo and the last 6–3mo (52% vs. 21%, $p=0.05$) and remained stable between the last 6–3mo and last three months of life (21% vs. 15%, $p=0.45$) (Table 1). In the last three months of life TAX was prescribed in 6%, ART in 9%, and radium-223 rarely (1%).

Patient and disease characteristics

Median age at the start of last three months of life was 77 years. Performance score declined from CRPC diagnosis to the last three months of life (valid percentages Eastern Cooperative Oncology Group [ECOG] >1 of 14% and 47%, respectively) with increasing bone and visceral metastases (valid percentages of 88% vs. 93% and 21% vs. 30%, respectively). Laboratory values also deteriorated with higher PSA, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and lower Hb at the start of last three months of life (Supplementary Table S1).

Patients initiating a new LPD in the last three months of life had a better clinical condition than patients without LPD treatment: they were younger (median 74 vs. 80 years, $p<0.01$), had better ECOG performance score (PS) (valid

Table 1. Treatment Characteristics during the Course of Castration-Resistant Prostate Cancer

	CRPC-6mo	*6–3mo*	*EOL phase*	*Adjusted* p-*value*[a]
Total systemic treatment utilization, *n* (%)				<0.001
No	315 (13)	736 (30)	992 (41)	
Yes	1821 (75)	1590 (66)	1437 (59)	
Missing	293 (12)	103 (4)	0 (0)	
Type of utilized therapy, *n* (%)				<0.001
Non-LPD	565 (23)	516 (21)	486 (20)	
LPD	1256 (52)	1074 (44)	951 (39)	
Docetaxel	969 (40)	319 (13)	230 (10)	<0.001
Cabazitaxel	224 (9)	171 (7)	133 (6)	<0.001
Abiraterone	603 (25)	426 (18)	384 (16)	<0.001
Enzalutamide	395 (16)	275 (11)	253 (10)	<0.001
Radium-223	104 (4)	83 (3)	69 (3)	0.001
New therapy initiated, *n* (%)				<0.001
No	315 (13)	1637 (67)	1953 (80)	
Yes	1821 (75)	689 (28)	476 (20)	
Missing	293 (12)	103 (4)	0 (0)	
Type of new initiated therapy, *n* (%)				0.001
Non-LPD	565 (23)	187 (8)	103 (4)	
LPD	1256 (52)	502 (21)	373 (15)	
Docetaxel	969 (40)	134 (6)	86 (4)	<0.001
Cabazitaxel	224 (9)	90 (4)	51 (2)	<0.001
Abiraterone	603 (25)	152 (6)	132 (5)	<0.001
Enzalutamide	395 (16)	104 (4)	91 (4)	<0.001
Radium-223	104 (4)	37 (2)	21 (1)	<0.001

[a]Adjusted for multiple testing using Bonferroni correction.

6–3mo, last six to the last three months of life; CRPC, castration-resistant prostate cancer; CRPC-6mo, CRPC diagnosis to the last six months of life; EOL, end-of-life phase (i.e., last three months of life); LPD, life-prolonging drugs (i.e., docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, or radium-223).

percentages for ECOG PS 0–1 in 61% vs. 46%, $p < 0.01$), and less comorbidities (Charlson score 6 in 58% vs. 47%, $p < 0.01$). However, known prognostic factors were less favorable: more opioid use (valid percentages of 72% vs. 60%, $p = 0.01$), higher PSA (median 160 vs. 96 ng/mL, $p < 0.01$), higher ALP (median 216 vs. 170 U/L, $p < 0.01$), and higher LDH (median 328 vs. 299 U/L, $p = 0.04$) at the start of the last three months of life (Table 2).

Hospital admissions

The number of admissions per three months was higher in the last three months of life: ≥2 admissions in 24% in the last three months of life compared to 11% in last 6–3mo and 5% CRPC-6mo, ($p < 0.01$) with a median admission duration of respectively 9 and 7 versus 1.5 days ($p < 0.01$). In last three months of life, admissions were more likely due to complications of the disease CRPC ($n = 582$, 24%) and blood transfusions ($n = 183$, 8%) than in CRPC-6mo and last 6–3mo (Table 3).

More patients initiating LPD in the last three months of life ($n = 281$, 75%) were admitted to the hospital than patients without LPD treatment ($n = 655$, 49%) and with LPD continuation ($n = 429$, 59%) ($p < 0.01$). Admission duration was significantly longer in patients initiating LPD compared with patients continuing LPD (median 11 vs. 9 days, $p = 0.02$). Although infrequent in absolute numbers, significantly more patients ($n = 11$, 3%) initiating new LPD in the last three months of life were admitted to the ICU (Table 4).

High-intensity care

High-intensity care was experienced by 992 patients (41%): >1 hospital admission ($n = 592$, 24%), admission duration of ≥14 days ($n = 423$, 17%), continuation of LPD in the last 14 days ($n = 397$, 16%), initiation of LPD in last month ($n = 81$, 3%), or ICU admission ($n = 39$, 2%).

Multivariable analysis of pooled data after multiple imputation showed that high-intensity care was less likely in older patients (OR 0.980, 95% confidence interval [CI] 0.968–0.993, $p < 0.01$), patients with ECOG ≥2 (OR 0.569, 95% CI 0.334–0.968, $p = 0.04$), and longer time from CRPC diagnosis to EOL (OR 0.977, 95% CI 0.970–0.984, $p < 0.01$). Opioid use (OR 1.453, 95% CI 1.083–1.951, $p = 0.02$), one or two prior LPD treatments (OR 1.527, 95% CI 1.192–1.957, $p < 0.01$ and OR 1.723, 95% CI 1.305–2.275, $p < 0.01$, respectively), and referral to medical oncologist (OR 1.988, 95% CI 1.551–2.547, $p < 0.01$) were associated with higher odds of high-intensity care (Table 5).

Discussion

This analysis of real-world data on EOL care in Dutch CRPC patients showed that 41% of all patients experienced high-intensity care in EOL. To our knowledge, this is the first study on EOL care in a large, unselected prostate cancer population within the timeframe in which new LPDs became available. Moreover, since we collected prognostic factors over time, we were able to evaluate which factors were associated with high-intensity care.

We observed a shift in treatment choices from TAX in early CRPC phases to ART in the last three months of life. In comparison to other studies, the use of TAX was low (16% vs. 30%),[16,18,19] which was explained by the fact that our study was performed in the era with the availability of newer LPDs as ART. Clinicians seem more reluctant to treat patients with TAX and may prefer ART because of less impact (oral vs. intravenous administration) and a milder adverse event profile, especially later in the disease trajectory when ECOG PS declines.

The reasons to initiate LPD were not documented. In EOL, LPDs add little to a patient's survival making the use of LPDs seem unreasonable. However, since clinicians often overestimate a patient's survival, it is possible that they do not adequately identify the start of EOL.[6–8] This is supported by the fact that patients initiating new LPD were younger with better performance score. Moreover, treatment could also have been considered a necessity since these patients had more aggressive disease characteristics (i.e., higher PSA, ALP, and LDH). In addition to a survival benefit, LPDs could be started for the prevention of complications and/or symptoms with preservation of quality of life, which seems reasonable since pain and/or opioid use were common in patients starting an LPD in EOL. However, the advantages on quality of life in EOL are not widely studied, so the initiation of a new LPD in patients with aggressive disease should be carefully considered based on the little effect on survival.[3–5]

We showed that patients with more aggressive disease characteristics and good performance score were more likely to experience high-intensity care in EOL. As stated before, clinicians were more likely to initiate an LPD in patients with aggressive disease states and an adequate level of fitness. It has been reported that patient preference in treatment initiation also plays an important role, since patients often strive for survival when time from diagnosis is short, they are young and feel fit.[13] Aggressive disease characteristics can also lead to a higher risk for admission related to complications or the underlying disease. Patients who continued or initiated LPD in the last three months of life were more frequently admitted to the hospital than patients who did not use LPDs, mostly due to disease-related complications (40%). However, treatment-related admissions were also prevalent (37%) in patients initiating LPD.

Forty-one percent experienced high-intensity care in our CRPC cohort. While Dutch clinicians may be more reserved in starting new LPDs, they were likely to admit a patient to the hospital for supportive care even in EOL. This is supported by an admission rate of 35% in the last week of life in a Dutch general oncologic population.[20] The threshold for hospitalization in the Netherlands may be low, since the population has mandatory insurance, including hospital care. It is also notable that some patients with mCRPC, including those with refractory cancer-related pain, may need and benefit from hospital admission near EOL for symptom control. Although the effect of high-intensity care on patients' quality of life is unknown, an adequate organization of palliative care either in or outside the hospital (e.g., by general practitioners, GPs) improves quality of life of both patients and caregivers and may lead to reduce costs by reducing the amount of time spend in hospitals.[21] During our study period, a transmural palliative care team was not available in all treatment centers and specific arrangements differed between centers, which could affect hospital admission rate.[22] A palliative care team should play a key role

Table 2. Baseline Characteristics at Start of End of Life Based on Life-Prolonging Drugs Treatment

	No LPD treatment (n = *1327*)	*LPD continuation* (n = *729*)	*LPD initiation* (n = *373*)	*Adjusted* p-*value*[a]
Age, years				<0.001
Median (range)	80 (51–99)	74 (46–96)	74 (50–93)	
≥75 years, *n* (%)	956 (72)	346 (48)	180 (48)	
ECOG PS, *n* (%)				0.007
0	30 (2)	31 (4)	21 (6)	
1	161 (12)	175 (24)	139 (37)	
>1	219 (17)	172 (24)	103 (28)	
Unknown	917 (69)	351 (48)	110 (30)	
Charlson score, *n* (%)				<0.001
6	629 (47)	453 (62)	217 (58)	
7–8	508 (38)	218 (30)	120 (32)	
9–10	122 (9)	50 (7)	29 (8)	
>10	67 (5)	8 (1)	7 (2)	
Unknown	1 (<1)	0 (0)	0 (0)	
Bone metastases, *n* (%)				<0.001
Yes	868 (65)	644 (88)	305 (82)	
No	90 (7)	21 (3)	17 (5)	
Unknown	369 (28)	64 (9)	51 (14)	
Visceral metastases, *n* (%)				0.181
Yes	103 (8)	115 (16)	58 (16)	
No	284 (21)	259 (36)	113 (30)	
Unknown	940 (71)	355 (49)	202 (54)	
Opioid use, *n* (%)				0.007
Yes	207 (16)	199 (27)	140 (38)	
No	138 (10)	90 (12)	54 (15)	
Unknown	982 (74)	440 (60)	179 (48)	
PSA, ng/mL				<0.001
Median (IQR)	96 (25–307)	200 (65–607)	160 (61–365)	
Unknown, n (%)	1058 (80)	423 (58)	35 (9)	
Hemoglobin, mmol/L				0.049
Median (IQR)	6.8 (5.9–7.6)	6.6 (5.9–7.4)	6.9 (6.1–7.5)	
Unknown, *n* (%)	717 (54)	239 (33)	59 (16)	
Alkaline phosphatase, U/L				0.001
Median (IQR)	170 (100–371)	213 (113–457)	216 (125–381)	
Unknown, *n* (%)	762 (57)	181 (25)	62 (17)	
Lactate dehydrogenase, U/L				0.021
Median (IQR)	299 (224–450)	342 (230–530)	328 (248–536)	
Unknown, *n* (%)	933 (70)	322 (44)	108 (29)	
Referred to medical oncologist, *n* (%)				<0.001
Yes	784 (59)	671 (92)	352 (94)	
No	523 (39)	54 (7)	21 (6)	
Unknown	20 (2)	4 (1)	0 (0)	
Prior LPD treatment lines, *n* (%)				<0.001
0	899 (68)	238 (33)	124 (33)	
1	193 (15)	214 (29)	125 (34)	
2	134 (10)	183 (25)	71 (19)	
≥3	101 (8)	94 (13)	53 (14)	
Prior treatment, *n* (%)				
Docetaxel	296 (22)	439 (60)	217 (58)	<0.001
Cabazitaxel	75 (6)	84 (12)	49 (13)	<0.001
Abiraterone acetate	212 (16)	203 (28)	98 (26)	<0.001
Enzalutamide	161 (12)	107 (15)	47 (13)	0.252
Radium-223	17 (5)	36 (5)	17 (5)	0.109

Characteristics measured in period of one month prior or after the start of last three months of life.
[a]Adjusted for multiple testing using Bonferroni correction.
ECOG PS, Eastern Cooperative Oncology Group performance score; IQR, interquartile range; PSA, prostate-specific antigen.

Table 3. Hospital Admissions during the Course of Castration-Resistant Prostate Cancer

	CRPC-6mo	*6–3mo*	*EOL phase*	*Adjusted* p-*value*[a]
Hospital admission, *n* (%)				<0.001
0	891 (37)	1331 (55)	935 (39)	
1	989 (41)	468 (19)	773 (32)	
≥2	121 (5)	276 (11)	592 (24)	
Missing	428 (9)	354 (15)	129 (5)	
Admission duration[b]				<0.001
Valid median	1.5	7	9	
IQR	1–3	3–13	4–16	
Missing, *n* (%)	3 (<1)	5 (<1)	22 (1)	
<14 days, *n* (%)	1056 (43)	567 (23)	920 (38)	<0.001
≥14 days, *n* (%)	41 (2)	172 (7)	423 (17)	
Admission reason, *n* (%)				
Diagnostic evaluation	232 (10)	104 (4)	177 (7)	0.178
Therapeutic	299 (12)	155 (6)	234 (10)	0.001
Complication of therapy	251 (10)	94 (4)	112 (5)	<0.001
Complication of CRPC	317 (13)	242 (10)	582 (24)	0.049
Blood transfusion	70 (3)	86 (4)	183 (8)	<0.001
Other	237 (10)	103 (4)	223 (9)	<0.001
ICU admission, *n* (%)				0.006
Yes	32 (1)	13 (1)	39 (2)	
No	1969 (81)	2062 (85)	2261 (93)	
Missing	428 (18)	354 (15)	129 (5)	

[a]Adjusted for multiple testing using Bonferroni correction.
[b]Number of admissions and admission duration calculated per three months.
ICU, intensive care unit.

Table 4. Hospital Admission in End of Life Based on Life-Prolonging Drugs Treatment

	No LPD treatment (n = *1327*)	*LPD continuation* (n = *729*)	*LPD initiation* (n = *373*)	*Adjusted* p-*value*[a]
Hospital admission, *n* (%)				<0.001
0	569 (43)	277 (38)	89 (24)	
1	400 (30)	241 (33)	132 (35)	
≥2	255 (19)	188 (26)	149 (40)	
Missing	103 (8)	23 (3)	3 (1)	
Admission duration, valid median	9	9	11	0.021
IQR	4–16	4–15	5–18	
Missing, *n* (%)	10 (2)	6 (1)	6 (2)	0.040
<14 days, *n* (%)	451 (34)	298 (41)	171 (46)	
≥14 days, *n* (%)	194 (15)	125 (17)	104 (28)	
Admission reason, *n* (%)				
Diagnostic evaluation	77 (6)	59 (8)	41 (11)	0.418
Therapeutic	108 (8)	80 (11)	46 (12)	0.607
Complication of therapy	19 (1)	42 (6)	51 (14)	<0.001
Complication of CRPC	220 (17)	212 (29)	150 (40)	<0.001
Blood transfusion	61 (5)	83 (11)	39 (11)	<0.001
Other	112 (8)	65 (9)	46 (12)	0.698
ICU admission, *n* (%)				0.013
Yes	12 (1)	16 (2)	11 (3)	
No	1212 (91)	690 (95)	359 (96)	
Missing	103 (8)	23 (3)	3 (1)	
Total number of high-intensity care indicators, *n* (%)				<0.001
0	1005 (76)	352 (48)	80 (21)	
1	190 (14)	246 (34)	120 (32)	
>1	132 (10)	131 (18)	173 (46)	

[a]Adjusted for multiple testing using Bonferroni correction.

Table 5. Univariable and Multivariable Logistic Regression Predicting any High-Intensity Care in End of Life

		Univariable analysis of original data			*Multivariable analysis of pooled data after imputation*		
	n	*OR*	*95% CI*	p	*OR*	*95% CI*	p
Age (years), cont.	2429	0.958	0.949–0.967	<0.001	0.980	0.968–0.993	0.002
ECOG PS							
0	82	REF	—	—	REF	—	—
1	475	0.870	0.542–1.394	0.562	0.832	0.487–1.422	0.487
≥2	494	0.687	0.429–1.100	0.118	0.569	0.334–0.968	0.038
State, visceral							
No	656	REF	—	—	REF	—	—
Yes	276	1.119	0.844–1.484	0.433	0.960	0.669–1.379	0.819
Hemoglobin (mmol/L), cont.	1414	0.907	0.827–0.994	0.037	0.901	0.797–1.019	0.093
LDH (U/L), cont.	1066	1.000	1.000–1.000	0.209	1.000	0.999–1.000	0.106
ALP (U/L), cont.	1424	1.000	0.999–1.000	0.043	1.000	0.999–1.000	0.121
PSA (U/L), cont.	913	1.000	1.000–1.000	0.902	1.000	1.000–1.000	0.320
Opioid use							
No	282	REF	—	—	REF	—	—
Yes	546	1.540	1.153–2.058	0.004	1.453	1.083–1.951	0.015
Time from CRPC diagnosis to EOL phase (months), cont.	2429	0.988	0.983–0.993	<0.001	0.977	0.970–0.984	<0.001
LPD started before EOL phase							
0	1023	REF	—	—	REF	—	—
1	556	1.942	1.570–2.401	<0.001	1.527	1.192–1.957	0.001
≥2	850	1.936	1.604–2.337	<0.001	1.723	1.305–2.275	<0.001
Referral to medical oncologist							
No	598	REF	—	—	REF	—	—
Yes	1807	2.612	2.123–3.214	<0.001	1.988	1.551–2.547	<0.001
Year of death							
2010–2011	226	REF	—	—	REF	—	—
2012–2013	684	0.962	0.708–1.306	0.802	1.048	0.751–1.462	0.782
2014–2015	837	1.132	0.840–1.525	0.416	1.178	0.839–1.654	0.343
2016–2017	682	0.909	0.668–1.235	0.541	1.080	0.743–1.571	0.686

ALP, alkaline phosphatase; CI, confidence interval; cont., continuous variable; LDH, lactate dehydrogenase; OR, odds ratio; REF, reference category.

in the collaboration between various specialists and can proactively manage symptoms such as pain, which might otherwise acquire hospital admissions.

In the Netherlands, CRPC is generally treated by multidisciplinary teams, including both urologists and medical oncologists, but the arrangements within multidisciplinary teams differ between hospitals. Referral from urologist to medical oncologist increased the odds of high-intensity care in EOL. Although this can possibly be explained by an overall more aggressive treatment approach, it is more likely that the decision to initiate LPD was made by multidisciplinary teams based on patients' general health and disease characteristics and that these patients were referred to medical oncologists to start LPD, while patients opting for best supportive care remained treated by urologists.

This study reflects Dutch clinical practice, but may not be easily generalizable due to potential international differences (e.g., different organization of EOL care, treatment culture, and reimbursement systems). Our results concern a population with CRPC and cannot be generalized to other cancer types.[23]

Moreover, the indicators for high-intensity care in our analysis is commonly used.[24] We were not able to include hospice use and ER visits, which are well-known indicators for high-intensity care, since they were not captured in our registry. We chose a period of last three months of life as a cutoff for EOL. This period was appropriate for CRPC according to the experts in our steering committee, but might differ in other cancer types.

A limitation is that we only captured in-hospital data. First, we excluded patients if the death date was not known in the participating hospitals, which were probably patients without in-hospital care in EOL. Therefore, the use of high-intensity care in the total population could be overestimated. Second, high-intensity care included only specific hospital resources and data on the role of the GP and palliative care teams were unavailable. The fact that we were not able to include all relevant data as ER visits and hospice stays is a major limitation. The overuse of hospital resources in patients who are likely to die soon seems not easily justifiable from both a patient's perspective (i.e., there is little to no effect on patient's life span) and from a societal perspective (i.e., the economic burden of the use of LPDs and hospital resources is high). However, the effect of this high-intensity care on other aspects of a patient's wellbeing as quality of life is not yet known. Adequate guidance can improve quality of life, satisfaction, and prevent high-intensity care in EOL with unnecessary hospital admissions,[25–28] but we could not evaluate the role of the GP and palliative care teams.

Another limitation is the missing data particularly in baseline characteristics. Missing data are inherent to the retrospective observational nature of this study. Multiple imputation offers a valid solution for missing data in multivariable analysis. The exact reason of death was also not registered. We assumed all deaths were related to CRPC, which seems a safe assumption because of the progressive nature of this disease and general relative short median OS, but this may be an overestimation.

Conclusion

High-intensity care in EOL in CRPC occurred in 41%. While Dutch clinicians seemed reserved to start LPD in the last three months of life, hospital admissions were frequent especially in patients starting a new LPD. Higher age and poor performance score were associated with lower chances of high-intensity care. High-intensity care is not easily justifiable from both patient and economic perspective, but further research is warranted to give insight into the effect on quality of life.

Authors' Contributions

All the authors have made significant contribution to this article, have seen and approved the final article, and have agreed to this submission.

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Author Disclosure Statement

M.C.P.K. has received travel/accommodation expenses from Ipsen; H.M.W. has received travel/accommodation expenses from Ipsen and honoraria from Roche. F.A.J.M.v.d.E. has received study grants from Sanofi and Roche; travel expenses from MSD Oncology, Roche, Pfizer and Sanofi; honoraria from Bristol-Myers Squibb; and is a member of the advisory board of Bristol-Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, and Merck. I.M.v.O. has received study grants from Astellas, Janssen, and Bayer, and has a consulting/advisory role for Astellas, Janssen, Bayer, Roche, and Mdx health. J.L.L.M.C. is a member of the advisory board of Sanofi. J.R.J.A.v.M. has received honoraria/consultation fees of Astellas, AstraZeneca, Bayer, Janssen, and Sanofi-Genzyme. K.K.H.A. has no conflict of interest. A.M.B. has received study grants from Sanofi, Astellas, and Bayer; travel/accommodation expenses from Sanofi, Astellas, and Bayer; speaker fees of Sanofi, Astellas, Bayer, and Janssen; and has an consulting/advisory role for Sanofi, Astellas, and Bayer. D.t.B.H. has no conflict of interest. J.v.d.B. has no conflict of interest. M.P.H. has no conflict of interest. M.I.L. has no conflict of interest. J.L. has no conflict of interest. N.M. has received study grants from Astellas, Janssen, Pfizer, Roche, and Sanofi Genzyme; has a consulting/advisory role for Roche, MSD, BMS, Bayer, Astellas, and Janssen; and has received travel/accommodation expenses from Astellas and MSD. T.J.S. has no conflict of interest. R.D.M.S. has received study grants from Astellas and honoraria from Astellas and Janssen. L.T. has no conflict of interest. N.I.W. has no conflict of interest. Y.A.J.v.d.W. has no conflict of interest. W.R.G. has received speaker's fees from Bayer and MSD; study grants from Bayer, Astellas, and Janssen-Cilag; and is a member of the advisory board of Bristol-Myers Squibb, Astellas, Bayer, Sanofi, and Amgen. C.A. U.-d.G. has received study grants from Boehringer Ingelheim, Astellas, Celgene, Sanofi, Janssen-Cilag, Bayer, Amgen, Genzyme, Merck, Glycostem Therapeutics, Astra Zeneca, and Roche.

Supplementary Material

Supplementary Table S1

References

1. Murray SA, Kendall M, Boyd K, Sheikh A: Illness trajectories and palliative care. BMJ 2005;330:1007–1011.
2. Westgeest HM, Uyl-de Groot CA, van Moorselaar RJA, et al.: Differences in trial and real-world populations in the Dutch castration-resistant prostate cancer registry. Eur Urol Focus 2018;4:694–701.
3. Guinney J, Wang T, Laajala TD, et al.: Prediction of overall survival for patients with metastatic castration-resistant prostate cancer: Development of a prognostic model through a crowdsourced challenge with open clinical trial data. Lancet Oncol 2017;18:132–142.
4. Halabi S, Lin C-Y, Small EJ, et al.: Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. JNCI J Natl Cancer Inst 2013;105:1729–1737.
5. Halabi S, Lin C-Y, Kelly WK, et al.: Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2014;32:671–677.
6. World Palliative Care Alliance; WHO. Global atlas of palliative care at the end of life [Internet]. Geneva: World Health Organization, 2014: https://www.who.int/nmh/Global_Atlas_of_Palliative_Care.pdf (Last accessed October 2, 2019).
7. Glare P, Virik K, Jones M, et al.: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 2003;327:195–198.
8. Cheon S, Agarwal A, Popovic M, et al.: The accuracy of clinicians' predictions of survival in advanced cancer: A review. Ann Palliat Med 2016;5:22–29.
9. Dy SM, Shugarman LR, Lorenz KA, et al.: A systematic review of satisfaction with care at the end of life. J Am Geriatr Soc 2008;56:124–129.
10. Smith R: A good death. An important aim for health services and for us all. BMJ 2000;320:129–130.
11. Steinhauser KE, Christakis NA, Clipp EC, et al.: Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 2000;284:2476.
12. Heyland DK, Dodek P, Rocker G, et al.: What matters most in end-of-life care: Perceptions of seriously ill patients and their family members. CMAJ 2006;174:627–633.
13. Voogt E, van der Heide A, Rietjens JAC, et al.: Attitudes of patients with incurable cancer toward medical treatment in the last phase of life. J Clin Oncol 2005;23:2012–2019.
14. Earle CC, Neville BA, Landrum MB, et al.: Evaluating claims-based indicators of the intensity of end-of-life cancer care. Int J Qual Heal Care J Int Soc Qual Heal Care 2005;17:505–509.

15. Earle CC, Landrum MB, Souza JM, et al.: Aggressiveness of cancer care near the end of life: Is it a quality-of-care issue? J Clin Oncol 2008;26:3860–3866.
16. Pataky RE, Cheung WY, De Oliveira C, et al.: Population-based trends in systemic therapy use and cost for cancer patients in the last year of life. Curr Oncol 2016;23(Suppl. 1):S32–S41.
17. Cornford P, Bellmunt J, Bolla M, et al.: EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017;71:630–642.
18. Zaghloul HA, Murillo JR: Treatment given near the end of life in castration-resistant prostate cancer. Am J Hosp Palliat Med 2012;29:536–540.
19. Earle CC, Neville BA, Landrum MB, et al.: Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol 200422:315–321.
20. Meeussen K, Van den Block L, Echteld MA, et al.: End-of-life care and circumstances of death in patients dying as a result of cancer in Belgium and the Netherlands: A retrospective comparative study. J Clin Oncol 2011;29:4327–4334.
21. Hearn J, Higginson IJ: Do specialist palliative care teams improve outcomes for cancer patients? A systematic literature review. Palliat Med 1998;12:317–332.
22. Brinkman-Stoppelenburg A, Boddaert M, Douma J, van der Heide A: Palliative care in Dutch hospitals: A rapid increase in the number of expert teams, a limited number of referrals. BMC Health Serv Res 2016;16:518.
23. Henson LA, Gomes B, Koffman J, et al.: Factors associated with aggressive end of life cancer care. Support Care Cancer 2016;24:1079–1089.
24. Earle CC, Park ER, Lai B, et al.: Identifying potential indicators of quality of end-of-life cancer care from administrative data. J Clin Oncol 2003;12:1133–1138.
25. Temel JS, Greer JA, Muzikansky A, et al.: Early palliative care for patients with metastatic non–small-cell lung cancer. N Engl J Med 2010;363:733–742.
26. Bakitas MA, Tosteson TD, Li Z, et al.: Early versus delayed initiation of concurrent palliative oncology care: Patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 2015;33:1438–1445.
27. Zimmermann C, Swami N, Krzyzanowska M, et al.: Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. Lancet 2014;383:1721–1730.
28. Greer JA, Pirl WF, Jackson VA, et al.: Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non–small-cell lung cancer. J Clin Oncol 2012;30:394–400.

Address correspondence to:
Malou C.P. Kuppen, MD
Institute for Medical Technology Assessment
Erasmus School of Health Policy and Management
PO Box 1738
Rotterdam 3000 DR
the Netherlands

E-mail: kuppen@eshpm.eur.nl