

Adverse events in deceased hospitalised cancer patients as a measure of quality and safety in end-of-life cancer care

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Abstract

Background: Anticancer treatment exposes patients to negative consequences such as increased toxicity and decreased quality of life, and there are clear guidelines recommending limiting use of aggressive anticancer treatments for patients near end of life. The aim of this study is to investigate the association between anticancer treatment given during the last 30 days of life and adverse events contributing to death and see if adverse events can be used as a measure of quality and safety in end-of-life cancer care

Methods: Retrospective cohort study of deceased hospitalised cancer patients using the Global Trigger Tool to identify adverse events. We used Poisson regression and binary logistic regression to compare adverse events and association with use of anticancer treatment given during the last 30 days of life.

Results: 30 % of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of life, mainly systemic anticancer treatment. These patients had 62 % more adverse events compared to patients not being treated last 30 days, 39 vs. 24 adverse events per 1 000 patient days ($p < 0.001$, OR 1.62 (1.23 – 2.15)). They also had twice the odds of an adverse event contributing to death compared to patients without such treatment, 33 vs. 18 % ($p = 0.03$, OR 2.10 (1.09 – 4.01)).

Conclusions: Anticancer treatment given during the last 30 days of life is associated with a significantly increased rate of adverse events and related mortality. Identifying these adverse events is clearly warranted to improve clinical practice and avoid overtreatment in end-of life cancer care.

Background

Effectiveness and safety are essential elements of value-based cancer care that need to be considered when making decisions about treatment during the entire continuum of the disease [1–3]. Striking the right balance between the two is a major clinical challenge, especially when the disease progresses towards the end of life. At this stage discontinuing anticancer treatment is one of five recommendations to reduce unnecessary treatment and increase the value of healthcare at for patients with advanced cancer [4, 5].

Survival is of critical concern for cancer patients, but near the end of life the quality of care and how patients spend their remaining time is just as important [6, 7]. Nevertheless, up to one out of five cancer patients receives anticancer treatment during the last 30 days of life without clear benefit of prolonging survival. The treatment also exposes them to the risk of severe negative consequences such as increased toxicity and decreased quality of life [8–10]. A meta-analysis of the efficacy and safety of anticancer treatment compared to palliative care found no difference in overall survival and significantly more severe adverse events among patients receiving anticancer treatment during the last 30 days of life [11]. This emphasises the need not to focus just on survival, but also the need to assess symptoms, toxicities and complications of anticancer treatment by systematically measuring adverse events [12].

Today, quality measures for end-of-life cancer care generally examine utilisation of healthcare services and use of systemic anticancer treatment, radiotherapy and specialist palliative care during the last month of life [13–15]. Although severe adverse events in cancer care are considered an important

outcome measure with high clinical value, current measurements do not include adverse events as an indication of quality and safety in end-of-life cancer care [16].

Thus, the objectives of our study is to investigate the association between anticancer treatment given during the last 30 days of life and adverse events contributing to death and see if adverse events can be used as a measure of quality and safety in end-of-life cancer care.

Methods

Study design

The study is a retrospective cohort study of deceased hospitalised cancer patients. We performed a standardised retrospective record review using the Global Trigger Tool (GTT) to identify adverse events contributing to death related to anticancer treatment given during the last 30 days of life.

Setting

The study was conducted at a public health trust in Northern Norway, providing healthcare to a population of 136 000 inhabitants. Nordland Hospital Trust has three somatic hospitals; one central teaching hospital and two smaller district general hospitals. Cancer patients are treated and hospitalised in all three hospitals, but only the central teaching hospital has a separate oncology and haematology department. It provides ambulatory chemotherapy, palliative radiotherapy and has a specialised unit for palliative care. None of the hospitals has a separate oncological inpatient unit. Accordingly, specialists in fields other than oncology retain the everyday medical responsibility for the cancer patients when they are admitted to hospital.

Study population

The cohort includes all cancer patients with solid tumours and haematological malignancies, 18 years or older who died in one of the three hospitals. Since there were no previous studies indicating incidence rates of adverse events contributing to death in this selected population we did a consecutive sampling of all cancer patients who dies in the three hospitals between January 1st 2012 and December 31st 2013. Of the 737 deceased hospitalised patients, 16 children under the age of 18 years were excluded. 247 (34 %) patients had cancer as primary or secondary diagnosis on discharge classified by the ICD-10 system. These cancer patients were divided into one group that had received any kind of anticancer treatment and a second group that had not received any anticancer treatment during the last 30 days of life. From the electronic patient records we obtained baseline demographics such as age, gender, length of stay, hospital, department, primary and secondary diagnosis on discharge. We also reviewed the patient records for the type of cancer, presence of metastases, setting (diagnostic, curative or palliative), the last

date of administration of parenteral or oral anticancer treatment (chemotherapy, targeted agents and immune therapy), the use of radiotherapy and cancer directed surgery, as well as the date for involvement of specialised palliative care.

Retrospective review

During six months in 2015, a team of two oncology nurses and one oncologist did a structured review of the patient records. The review was conducted according to the Norwegian version of the Institute of Healthcare Improvement GTT manual [17, 18]. The method is a two-stage process where the nurses independently review all records using triggers to identify adverse events. To the 48 general triggers, we added 21 specific oncology triggers developed by the 1000 Lives Plus Campaign in Wales, UK [19]. The two nurses independently identified the presence, category and severity of the AEs, before they discussed their findings with the oncologist and together reached consensus. To validate the results, two other physicians independently re-reviewed the records of adverse events contributing to death and confirmed/rejected the adverse event, severity and type of harm.

Definition and classification of adverse events

We defined an adverse event as: "Unintended physical injury resulting from or contributed to by medical care that requires additional monitoring, treatment or hospitalization, or that results in death" [18]. The severity of AEs was categorised according to the NCC MERP index [20]. Adverse events were recorded into six main categories: healthcare acquired infections, surgical complications, bleeding/thrombosis, medication harm, pressure ulcer and others. For medication-related adverse events, the generic name was documented.

Statistical analysis

We summarised the data using descriptive statistics and compared the groups using the Mann-Whitney U test for non-parametric continuous variables, and the Chi square, Fisher's exact or Linear-by-Linear test for categorical variables. There were no missing data. Incidence rates of adverse events, severities and categories of adverse events were compared using Poisson regression for generalised linear models. Binary logistic regression was used to analyse if adverse events were significantly associated with use of anticancer treatment during the last 30 days of life. We adjusted for known factors affecting the rate of adverse events, such as length of stay, age, hospital and gender. A p-value of <0.05 was considered significant. We used the statistical package IBM SPSS Statistics V.25.0 to analyse the data.

Results

Patient characteristics

Most patients had advanced cancer and were in a palliative care setting. Sixty percent of the patients received some kind of anticancer treatment, mainly systemic anticancer treatment. Patients receiving treatment during the last 30 days of life had a longer length of stay and were more often admitted to the central hospital. Patients with lung cancer, lymphoma and haematological malignancies were more likely to receive treatment during the last 30 days of life. Table 1 compare characteristics between patients receiving anticancer treatment during the last 30 days of life with patients not receiving such treatment.

Table 1 Characteristics

Variable	No anticancer treatment last 30 days <i>n</i> = 174		Anticancer treatment given last 30 days <i>n</i> =73		<i>P</i> value ^a
	<i>n</i>	%	<i>n</i>	%	
Age (years) - median (min - max)	72	(18 - 93)	74	(40 - 91)	NS
Length of stay (days) - median (min - max)	8	(0 - 84)	12	(0 - 68)	0.03
Gender					NS
Female	68	39 %	28	38 %	
Male	106	61 %	45	62 %	
Hospital					<0.01
District Hospital Lofoten	27	16 %	6	8 %	
District Hospital Vesterålen	47	27 %	11	15 %	
Central Hospital Bodø	100	57 %	56	77 %	
Department					NS
Internal medicine	76	44 %	44	60 %	
Surgery	91	52 %	25	34 %	
Others	7	4 %	4	6 %	
Primary malignancy					0.02
Upper gastrointestinal	34	20 %	5	7 %	
Colorectal	27	15 %	4	5 %	
Lung	38	22 %	21	29 %	
Breast	7	4 %	4	5 %	
Gynecological	5	3 %	2	3 %	
Urological	8	5 %	6	8 %	
Male genitalia	11	6 %	4	5 %	
Hematological and lymphoma	17	10 %	22	30 %	
Unknown origin	15	8 %	2	3 %	
Other ^b	12	7 %	3	4 %	
Setting					<0.001
Palliative	135	78 %	67	92 %	
Curable	2	1 %	3	4 %	

Diagnostic	37	21 %	3	4 %
Anticancer treatment				<0.001
Systemic treatment	64	37 %	52	71 %
Radiotherapy	5	3 %	14	19 %
Surgery	5	3 %	7	10 %
No treatment	100	57 %	0	0 %
Specialist palliative care				NS
>30 days before death	33	19 %	11	15 %
<30 days before death	32	18 %	14	19 %
Not involved	109	63 %	48	66 %

a) The *p* value measures the difference between the two groups and was set to 0.05. NS not significant.

b) The group consist of patients with cancer from head-neck, sarcoma, malignant melanoma, eye and CNS.

Treatment during the last 30 days of life

Anticancer treatment of any kind was given to 30 percent of patients during the last 30 days of life. Treatment given during the last 30 days was mainly systemic anticancer treatment (21 %). In addition, 8.5 percent of the patients received radiotherapy during the last 30 days of life, where of more than half during the last 10 days of life. Specialised palliative care was provided equally to both groups, 34 vs. 37 percent (Table 1).

Adverse events

Patients receiving anticancer treatment during the last 30 days of life had 62 percent more adverse events than patients not treated during the last 30 days of life, 39 vs. 24 adverse events per 1 000 patient days ($p < 0.001$, RR 1.62, CI 95% 1.23 – 2.15). Patients receiving treatment during the last 30 days of life experienced both more temporary adverse events (severity E and F) and more severe adverse events contributing to death (severity I), (Figure1). Patients in both groups receiving specialist palliative care had significantly fewer adverse events than patients not referred to palliative care, 23 vs. 32 adverse events per 1 000 patient days (RR 0.73, $p = 0.04$ CI 95% 0.54 – 0.98).

Types of adverse event

The most common types of adverse events were healthcare-acquired infections and medication related adverse events (Figure 2). There was no difference in the rate of healthcare-acquired infections between the groups. Patients receiving treatment during the last 30 days of life had significantly higher rates of medication related adverse events, 21 vs. 9 adverse events per 1 000 patient days ($p < 0.001$, RR 2.35, CI 95 % 1.55 – 3.58). Twenty-four percent of patients receiving systemic anticancer treatment had an adverse event related to the treatment. Bleeding or thrombosis also occurred more often in patients receiving treatment during the last 30 days, 5 vs. 2 adverse events per 1 000 patient days ($p = 0.003$, RR 2.62, CI 95 % 1.09 – 6.34).

Adverse events contributing to death

An adverse event contributed to death in 22 percent of all deceased hospitalised cancer patients. Patients receiving anticancer treatment during the last 30 days of life experienced nearly double the rate of adverse events contributing to death compared to patients not being treated during the last month of life, 33 vs. 18 percent ($p = 0.03$, adjusted OR 2.10, CI 95 % 1.09 – 4.01). Adverse events contributing to death were mainly medication harms and healthcare acquired infections. Systemic anticancer treatment contributed to death in 11 percent of patients receiving systemic anticancer treatment, all given during the last 30 days of life. For patients not receiving treatment during the last 30 days of life, healthcare acquired infections contributed to death for 58 percent of the patients. An adverse event contributed to death more commonly in patients with lymphoma and haematological malignancies. Radiotherapy did not contribute to the death of any patient.

Discussion

There are clear guidelines recommending limiting use of aggressive anticancer treatments for cancer patients near end of life [4, 12]. Still we found that one third of deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of their lives. Patients receiving anticancer treatment during the last 30 days of life also had an increased rate of adverse events compared to cancer patients not given treatment in this period. Most of the adverse events were temporary harms requiring medical intervention, often initiating or prolonging hospitalisation (severity E and F). Even less severe adverse events can cause an extra burden of harm and reduce the quality of life during the limited remaining time, when many patients prefer to be at home with their families [6, 21].

We found that one in five deceased hospitalised cancer patients had an adverse event contributing to death. This included all types of adverse events whether caused by systemic anticancer treatment, other medications or healthcare acquired infections. In a previous study we found that hospitalised cancer patients had an increased risk of adverse events in general compared to other hospitalised patients, and that they more often experienced adverse events related to medications [22].

Our findings are higher than those of registry studies showing that 4 – 27 percent of cancer patients die as a complications of anticancer treatment, but these studies do not specifically investigate occurrence of adverse events [14, 15, 23]. We also found that patients receiving anticancer treatment during the last 30 days had twice the odds of having an adverse event contributing to death compared to patients without such treatment. Considering that an adverse event can often be one of many factors contributing to death, it could be that receiving treatment in the last 30 days of life adds yet another layer of treatment related adverse events with an increased risk of hastening death.

Nearly one third of our deceased hospitalised cancer patients received some kind of anticancer treatment during the last 30 days of life, mainly systemic anticancer treatment. Similarly to other studies we found that patients receiving treatment during the last 30 days of life had a longer length of stay, were treated at larger hospitals and more often had lung cancer, lymphoma or haematological malignancies [24–28]. In other studies, the use of anticancer treatment during the last 30 days of life varied from 6 - 43 %, depending on country and patients included [29–31]. Our results are consistent with similar studies including all types of malignancies [15, 32], but the rates are higher than in registry studies of solid tumours indicating that Norway has among the lowest (6-10 %) use of systemic anticancer treatment during the last 30 days of life in Europe [23, 29]. Thus comparison of the results can be problematic due to differences in study design and included population [13].

Similar to other studies we find that medication harms and healthcare acquired infections were the most common adverse events [22, 33], but their occurrences differed between the groups. While healthcare acquired infections contributed to death of cancer patients in both groups, anticancer treatment related adverse events, contributing to death only occurred in patients who received such treatment during the last 30 days of life. Consequently, when measuring anticancer treatment related adverse events contributing to death we can be more pragmatic and limit the inclusion to deceased hospitalised patients treated during the last 30 days of life.

It is rarely straightforward to argue that anticancer treatment is the direct cause of death. Most likely, reduced functional status, malnutrition and immunosuppression amplify adverse events related to anticancer treatment and increase the negative impact on the patients` remaining lifetime [34]. Our study is not designed to investigate if these treatment-related adverse events affects survival, but nevertheless our results indicate that systemic anticancer treatment given during last 30 days of life can hasten the death of patients.

The proportion of patients treated with radiotherapy during the last 30 days of life in our study, was similar to the results of other studies [23, 35]. While radiotherapy in contrast to systemic anticancer treatment did not contribute to any deaths in our study, it still must be considered of little benefit when given during the last 30 days of life. The benefit of radiotherapy near end of life is questionable with only one out of four patients reporting symptom relief [36]. Patients receiving radiotherapy are also more often hospitalised and die in hospitals [23, 35]. Nearly half of our patients received radiotherapy during the last ten days of life, which must be considered futile and a misuse of the patients` time and focus.

Radiotherapy can provide needed palliation to patients with advanced cancer, but fractionation regimes should reflect life expectancy and sometimes it is better to provide palliative relief in other ways.

Early referral to palliative care is associated with improved quality of life, fewer acute hospital admissions and less aggressive cancer treatment near the end of life [37–39]. Even though palliative care should be an integrated part of oncology, patients are often first referred to palliative care when anticancer treatment ends [40]. However, only about a third of the patients in the two groups were referred to specialised palliative care and patients in both groups had fewer adverse events. Presumably, palliative care in itself is associated with fewer adverse events, but it not possible to determine if the reduction in adverse events is due to specialised palliative care or due to discontinuing of anticancer treatment.

Strength of our study is the completeness of the data. We have included all cancer patients who died during a two-year period at our hospitals. Norway has one of the highest rates of hospital deaths for cancer patients and cancer patients receiving treatment during the last 30 days of their lives are often hospitalised and die in hospital [29, 32]. We therefore argue that our study population is representative of cancer patients cared for by a general hospital trust. But, given the considerable variations in oncology practice within and across countries, the generalizability of our finding can be debated [29]. The main limitation of our study is that it is from only one hospital trust in Norway.

Known limitations of retrospective record reviewing such as information bias and subjective judgments may also apply to our study. Conscious of these limitations we have used a standardised review method (GTT method) with high sensitivity and specificity compared to other methods detecting adverse events [41]. To address limitations with the method of poor to moderate reliability, the review was conducted by a consistent and experienced oncology team [42–44]. In addition, we assessed the validity of our findings by having two physicians independently re-review and verify adverse events contributing to death. We found good correlation between the reviewers, where the severity changed only once and type of adverse event changed twice. However, when studying the intensity and safety of end-of-life care a retrospective design has the advantage since we only know the exact period before death retrospectively. A retrospective design allows for easy identification of cohorts of relevant patients and avoidance of inclusion bias [45].

Conclusion

Anticancer treatment given during the last 30 days of life is associated with a significantly increased rate of adverse events with twice the odds of having an adverse event contributing to death. Identifying these adverse events is clearly warranted to improve clinical practice and avoid overtreatment in end-of life cancer care. Doing so with a standardised review method on a limited number of deceased hospitalised cancer patients proved to be efficient. Measuring adverse events in such an approach can provide a pragmatic real time measure of quality and safety in end-of-life cancer care.

List Of Abbreviations

GTT Global Trigger Tool

NCC MERP National Coordinating Council on Medical Error Reporting and Prevention

Declarations

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics, Ministry of Education and Research in Norway has reviewed the study and categorised it as retrospective health record research, which does not require approval by the committee. Reference number 2013/1823.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ECH and BV designed the study. ECH led the review and collection of data. ECH, supervised by BV analysed the data. ECH, BV, CvP and CN together interpreted the data. ECH led the writing of the paper, while all the other authors contributed to revising the manuscript. All authors contributed substantially to the writing of the paper, and all reviewed and approved the final draft.

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Figures

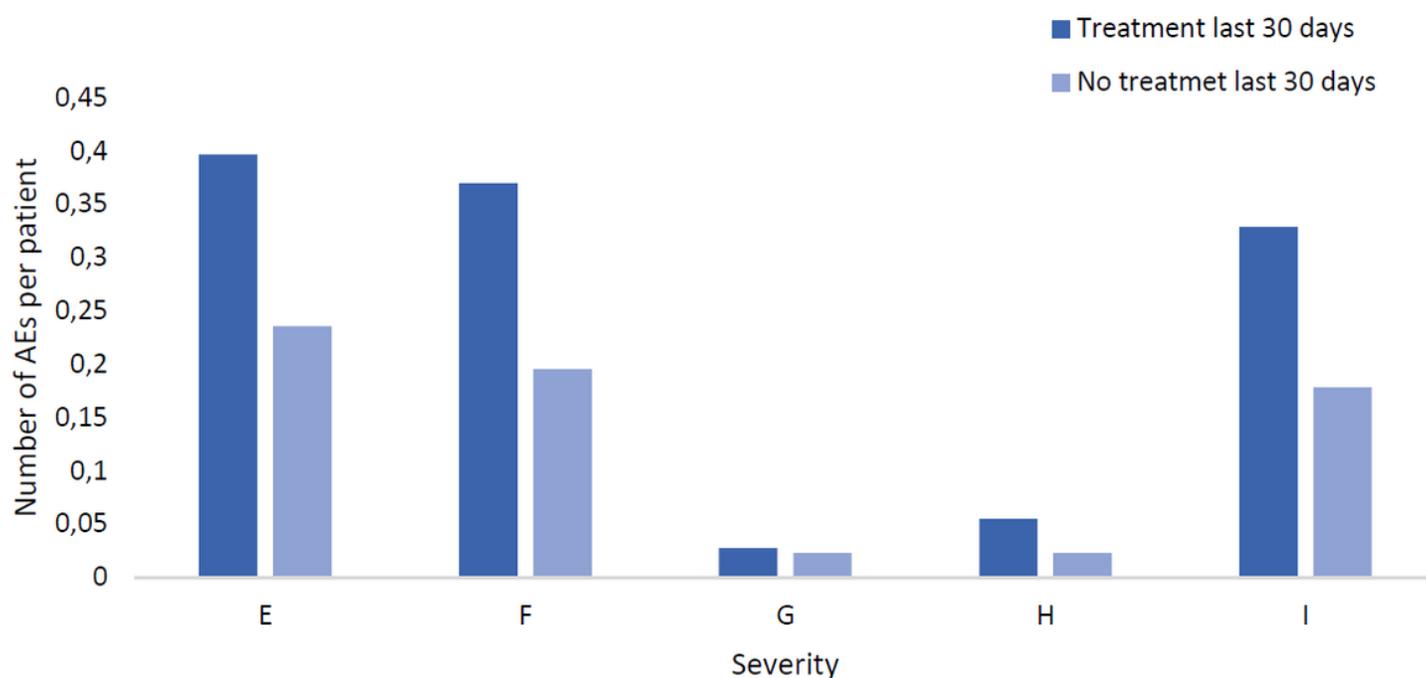


Figure 1

Severity of adverse events per patient categorised according to the NCC MERP Index. Comparing severity of adverse events between patient receiving or not receiving anticancer treatment during the last 30 days of life. Category E: temporary harm that required intervention Category F: temporary harm that required initial or prolonged hospitalisation Category G: permanent patient harm Category H: intervention required necessary to sustain life Category I: harm contributes to patient death

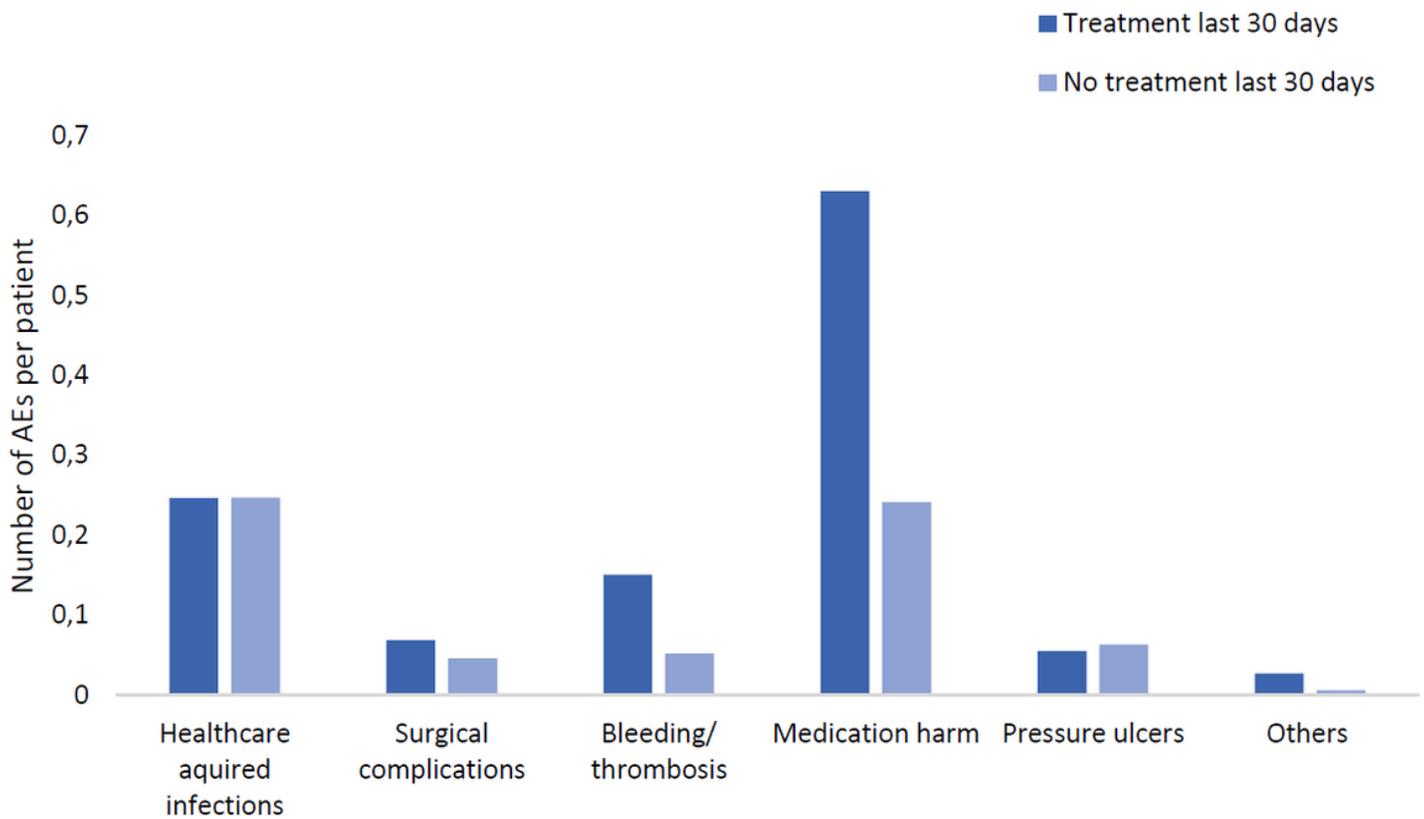


Figure 2

Type of adverse events per patient Comparing types of adverse events between patient receiving or not receiving anticancer treatment during the last 30 days of life.

Supplementary Files

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