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ORIGINAL RESEARCH

Aggressive anticancer treatment in the last 2 weeks of life

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Background: There is a concern that terminally ill cancer patients may be aggressively treated due to the rapidly growing possibilities of anticancer treatment. The aim of this study was to evaluate the use of anticancer treatment at the end of life (EoL).

Materials and methods: This retrospective study included adult patients with advanced solid cancers who were treated at the Institute of Oncology Ljubljana and died of cancer between January 2015 and December 2019. A multiple logistic regression model was used to assess an association between the aggressiveness of anticancer treatment (i.e. systemic therapy, radiotherapy and surgery) in the last 2 weeks of life and year of death, age at death, sex, prognosis of cancer and enrolment into the specialist palliative care (SPC).

Results: We included 1736 patients in our analysis. Overall, 13.7% of patients were enrolled into the SPC and 14.4% received anticancer treatment in the last 2 weeks of life. The odds of receiving anticancer treatment significantly increased over time [odds ratio (OR) 1.15, 95% confidence interval (CI) 1.04-1.27]. There was an increased use of novel systemic therapy (e.g. small-molecule targeted therapy and immunotherapy) at the EoL. Older patients had significantly lower odds to receive anticancer treatment in the last 2 weeks of life as compared to younger patients (OR 0.96, 95% CI 0.95-0.98). As compared to patients receiving only a standard oncology care, those also enrolled into the SPC had significantly lower odds for anticancer treatment in the last 2 weeks of life (OR 0.22, 95% CI 0.12-0.43).

Conclusions: Terminally ill cancer patients have increased odds for receiving anticancer treatment, especially novel systemic therapies, in the last 2 weeks of life. Younger patients and those not enrolled into the SPC are at particular risk for anticancer treatment at the EoL.

Key words: aggressive, anticancer treatment, systemic therapy, specialist palliative care, end of life

INTRODUCTION

Anticancer treatment can be recommended to patients with advanced cancer with an aim to improve quality of life (QoL) irrespective of its impact on survival.[1,2] However, it is well known that anticancer treatment, such as palliative chemotherapy (ChT), can have a detrimental effect on QoL at the end of life (EoL).[3] The two most commonly defining features for EoL are life-limiting disease with irreversible decline and expected survival in terms of months or less.[4] The clinicians' prediction of survival in patients with advanced cancer is often inaccurate and too optimistic.[5] Although several prognostic tools were developed and validated to reduce the inaccuracy of clinicians' prediction of survival, there is currently no consensus on the most appropriate tool to be used in everyday clinical practice.[6] Inaccurate assessment of survival may lead to aggressive anticancer treatment in patients with advanced cancer.

Recently, the armamentarium of anticancer drugs used in patients with advanced cancer has expanded enormously. Therefore, there is a growing concern of aggressive anticancer treatment and other health care at the EoL.[7,8] Such aggressive treatment may be inconsistent with patients' EoL preferences and thus makes caregivers' bereavement difficult; it is also of a low socioeconomic value for the health system itself.[9,10] Previously, several research groups found that administration of palliative ChT to terminally ill patients has become more common over time.[11-13] Moreover, there are several known factors related to patients (e.g. younger age, male sex), cancer (e.g. specific tumour types such as breast cancer, general consideration of increased chemosensitivity) and the health system (e.g. enrolment into the palliative care, being cared for in a teaching hospital) which are associated with an increased administration

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of ChT at the EoL.[11,14] The indicators of Earle et al., which reflect overuse of anticancer treatment near death, unplanned medical encounters and hospice care are the most widely accepted for evaluation of the aggressiveness of EoL anticancer treatment and care.[15] There is a valid concern that increased use of palliative ChT and other novel systemic therapies (STs), such as small-molecule targeted agents and immune checkpoint inhibitors, might set off a domino effect with increasing use of other treatment modalities such as palliative radiotherapy (RT) and surgery (SRG) in terminally ill cancer patients.

The aim of our study was to evaluate an association between anticancer treatment in the last 2 weeks of life and year of death, age at death, sex, prognosis of cancer and enrolment into the specialist palliative care (SPC).

MATERIALS AND METHODS

Data sources and patient cohort

This retrospective cohort study analysed the aggressiveness of anticancer treatment at the EoL in adult patients with advanced solid cancers who were treated at the Institute of Oncology Ljubljana (IOL) and died of cancer between January 2015 and December 2019. IOL is the central and main teaching tertiary cancer centre in Slovenia. The demographic characteristics and diagnoses of patients with cancer who lived in the broader Ljubljana area and died between 2015 and 2019 due to cancer were identified at the Slovenian Cancer Registry. At the IOL, the electronic health records (EHRs) of the identified patients were accessed and checked for the eligibility criteria. The analytic cohort included individuals who met the following criteria: (i) age $\geq$ 18 years at the time of death, (ii) residency in the broader area of Ljubljana, including eight municipalities with ~340 000 residents, (iii) death between 1 January 2015 and 31 December 2019 due to the cancer and (iv) locally advanced or metastatic breast, gastrointestinal, genitourinary, gynaecological, lung or other cancer (i.e. head/neck cancer, germline cell carcinoma and sarcoma) at the time of death.

This study was approved by the National Medical Ethics Committee of the Republic of Slovenia on 7 January 2021 (0120-484/2020/4).

Outcome measures and statistical analysis

According to the indicators of Earle et al., an anticancer therapy is considered aggressive when $\geq$10% of patients receive ChT in the last 2 weeks of life.[15] In this study, the aggressiveness of anticancer therapy was assessed as a proportion of patients who received at least one modality of anticancer therapy, including ST (ChT, small-molecule targeted therapy, immunotherapy and other biological therapies, hormonal therapy excluded), RT and/or SRG in the last 2 weeks of life at the IOL.

All collected data from the EHRs were double checked and inconsistencies resolved. Analysis began with descriptive summaries of demographic and clinical variables. The multiple logistic regression model was used to assess an association between the aggressiveness of anticancer treatment (i.e. ST, RT and SRG) in the last 2 weeks of life and year of death, age at death, sex, prognosis of cancer and enrolment into the SPC. Prognosis of included solid cancers was defined on the basis of the 5-year net survival data for these cancer types in Slovenia during 2012-2016.[16] Three categories of the prognosis were defined: (i) good with a 5-year net survival of 72.1%-96.9% (melanoma, thymus, thyroid, breast, uterine, cervical, prostate, testicle and penile cancer), (ii) intermediate with a 5-year net survival of 43.3%-65.8% (head/neck, adrenal gland, kidney, bladder, ovary, colorectal cancer, bone and soft-tissue sarcoma) and (iii) poor with a 5-year net survival of 6.8%-35.55% (pharynx, oesophagus, stomach, lung cancer, mesothelioma, pancreas, biliary tract, liver, cancer of unknown primary and glioblastoma).

We conducted statistical analyses using IBM® SPSS® version 29.0. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were provided. *P* values of $<$0.05 were deemed statistically significant. No adjustments for multiple comparisons were made.

RESULTS

Eligible patient cohort

The initial search identified 4029 potentially eligible patients for the analysis. After review of the EHRs, 2293 patients were excluded due to the following reasons: (i) 429 patients were diagnosed with other types of cancers, including haematological malignancies and lymphoma, (ii) 1484 patients did not have locally advanced or metastatic cancer at the time of death, (iii) 133 patients did not receive complete treatment/management at the IOL, (iv) 192 patients had missing data in their EHRs, (v) 23 patients died of reasons not related to cancer and (vi) 32 patients rejected treatment of their cancer (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.102937).

Patients' characteristics

We included 1736 patients into our analysis; of these 868 (50.0%) were women. Their median age at the time of death was 70.0 years, interquartile range (62.0-78.0 years). The youngest and the oldest patient in our cohort died at the age of 18 and 98 years, respectively. A distribution of the number of deaths by year during the observed period is presented in Figure 1. Overall, 542 (31.2%), 320 (18.4%), 288 (16.6%), 274 (15.8%), 108 (6.2%) and 204 (11.8%) patients died from lung, gastrointestinal, genitourinary, breast, gynaecological cancer and other cancers, respectively (Figure 1). Overall, prognosis was good, intermediate and poor in 572 (32.9%), 424 (24.4%) and 740 (42.6%) included patients, respectively (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.102937). None of the patient participated in a clinical trial. Overall, 237/1736 (13.7%) patients were enrolled into the SPC. Of these,

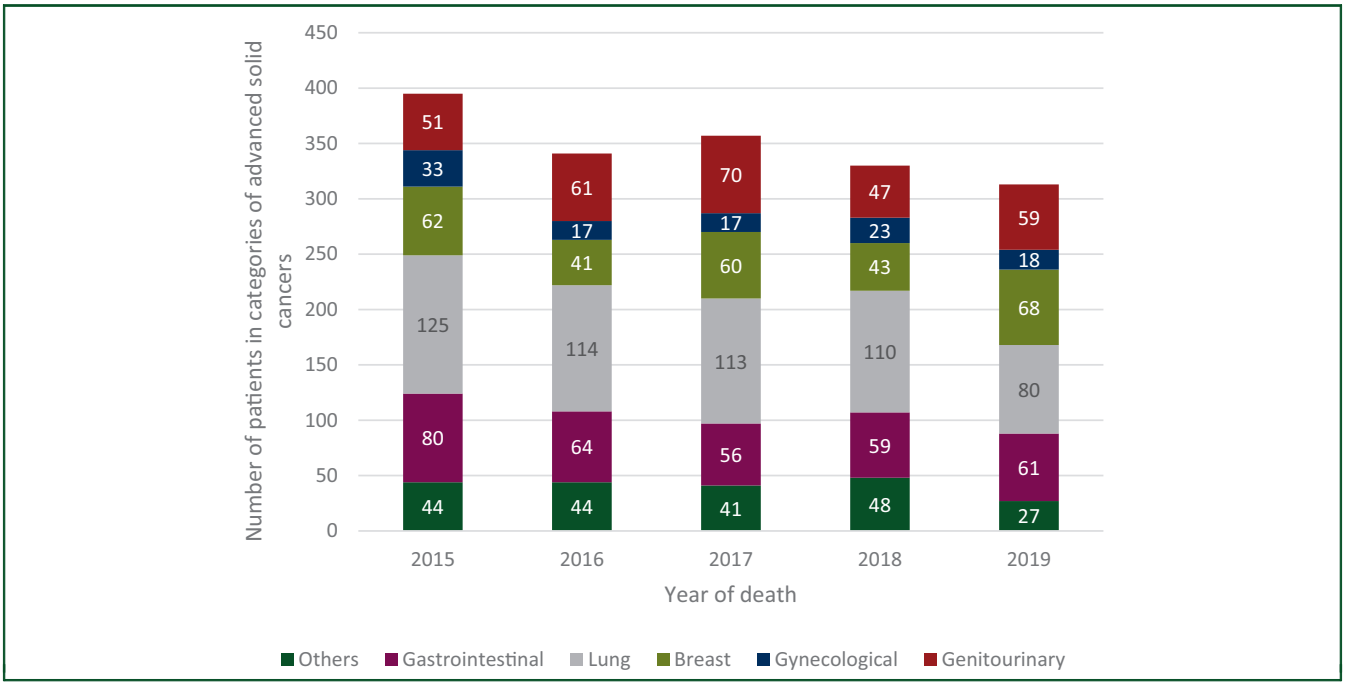

Figure 1. **Frequency distribution of patients by year of death and category of advanced solid cancers.**

44.3%, 32.5% and 23.2% had good, intermediate and poor prognosis, respectively.

Anticancer treatment in the last 2 weeks of life

Overall, 14.4% (250/1736) of patients received at least one modality of anticancer treatment (i.e. ST, RT or SRG) in the last 2 weeks of life. The proportion of patients who received anticancer treatment was 12.7% (50/395) in 2015 and increased to 17.3% (54/313) in 2019 (Figure 2). Overall, 250 patients received 252 courses of different modalities of anticancer treatment as two patients received both ST and RT in the last 2 weeks of life (Figure 3). Of these, 125 (49.6%) were ST, 118 (46.8%) RT and 9 (0.5%) SRG. Proportions of patients who received RT were 6.3% (25/395) and 6.7% (21/313) in years 2015 and 2019, respectively. No patient in 2015 and only one (0.3%) patient in 2019 underwent SRG (Figure 3).

Overall, 125 patients received ST in the last 2 weeks of life. Six patients received two different types of ST (Figure 4). The proportion of patients who received ChT did not change substantially over time; it was 5.1% (20/395) in 2015 and 5.1% (16/313) in 2019. In contrast, the proportion of patients who received novel STs increased from 1.5% (6/395) in 2015 to 5.4% (17/313) in 2019 ($P = 0.006$) (Figure 4).

Predictors of anticancer treatment in the last 2 weeks of life

The odds of receiving anticancer therapy in the last 2 weeks of life increased by 15% each the following year (OR 1.15, 95% CI 1.04-1.27). Older patients had significantly lower odds to receive anticancer treatment in the last 2 weeks of life as compared to younger patients (OR 0.96, 95% CI 0.95-0.98). As compared to patients receiving only a standard oncology care those also enrolled into the SPC had significantly lower odds for anticancer treatment in the last 2 weeks of life (OR 0.22, 95% CI 0.12-0.43). Sex and prognosis of cancer were not significantly associated with receipt of anticancer treatment in the last 2 weeks of life (Table 1).

DISCUSSION

The problem of receiving aggressive anticancer treatment and other care at the EoL has been recognized and is well defined in the scientific literature.[7,8] However, due to the rapidly evolving new anticancer therapies, a concern of aggressive anticancer treatment in terminally ill and dying patients in oncology remains.[17] Results of our study show that the use of anticancer treatment in the last 2 weeks of life has significantly increased from 2015 to 2019. While the use of ChT, RT and SRG did not change substantially over time, there was a trend of increasing use of novel, very costly ST (i.e. small-molecule targeted agents, immune checkpoint inhibitors and other biological agents). Younger patients and those not enrolled into the SPC had a higher probability of receiving aggressive anticancer treatment at the EoL as compared to older patients and patients receiving only a standard oncology care, respectively.

In general, ChT is still a mainstay of ST in patients with advanced cancer. In our study, a proportion of patients who received ChT did not substantially change over the studied period of time (Figure 4). According to the results of published studies, administration of ChT in the last 2 weeks of life varies between 5% and 13%.[11,12,14,18-24] The proportion of our patients who received ChT is reassuringly lower than that previously reported in the literature and lower than a margin of 10%, which is an indicator of aggressive

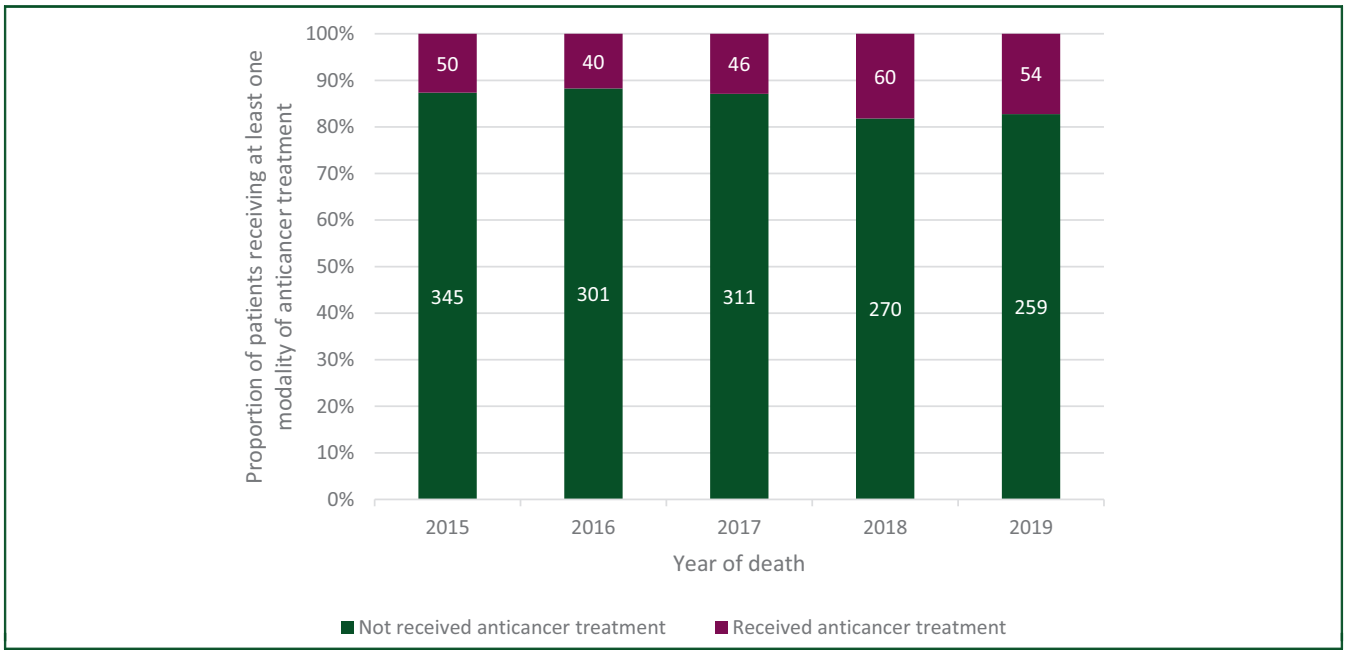

Figure 2. Frequency distribution of patients who received and did not receive at least one modality of anticancer therapy (i.e. systemic therapy, radiotherapy and/or surgery) in the last 2 weeks of life.

treatment with ChT.[15] However, our results need to be interpreted in the broader context of a rapidly changing landscape of different types of ST and not only ChT. In our study we observed a trend of increasing use of novel ST (i.e. small-molecule targeted therapy, immune checkpoint inhibitors and other biological agents); while only 1.5% of patients received novel ST in the year 2015, this proportion increased to 5.4% in the year 2019 (Figure 4). A recent similar but larger study from the United States showed that, overall, ST use at the EoL did not change from 2015 to 2019; however, ChT was used less and immunotherapy more often.[25] Recent studies showed increasing use of immune checkpoint inhibitors in patients with metastatic urothelial cancer, non-small-cell lung cancer and melanoma at the EoL, despite no evidence that this practice is beneficial for patients.[26,27] Similarly, it has been previously reported that

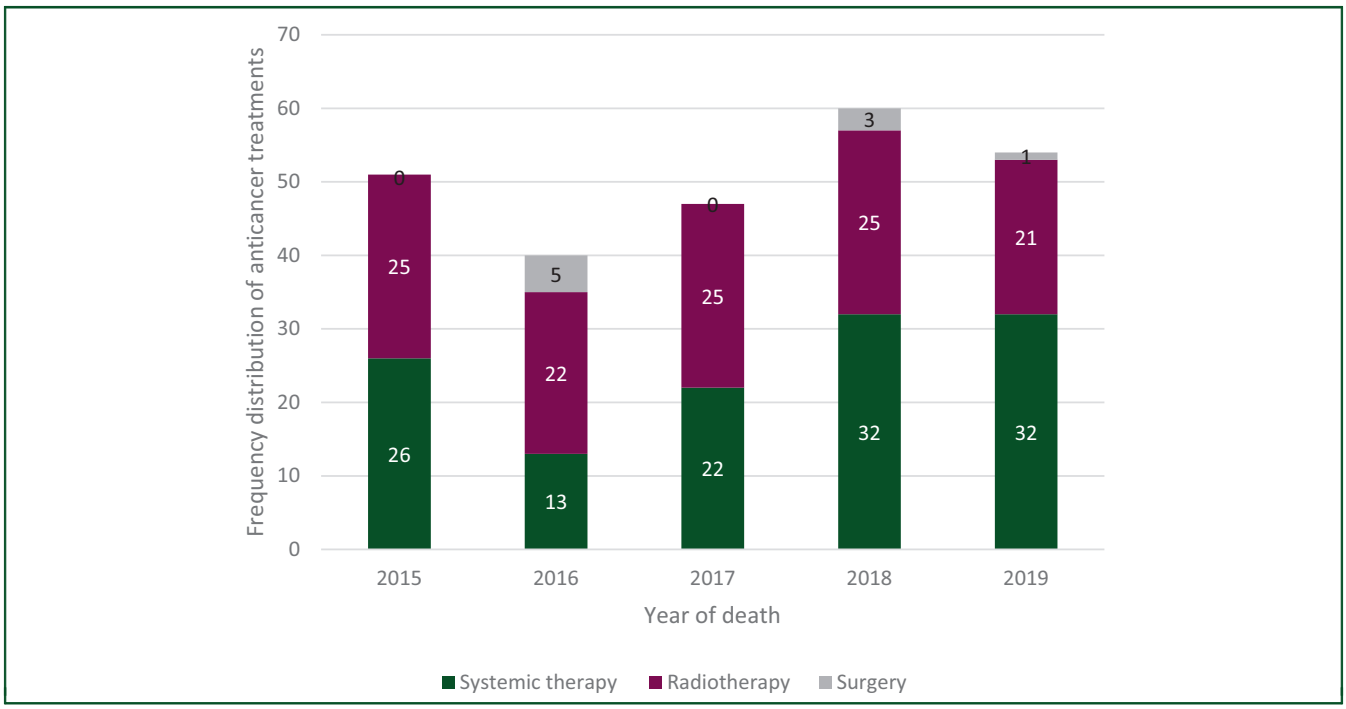

Figure 3. Frequency distribution of different anticancer treatments including systemic therapy, radiotherapy and surgery in the last 2 weeks of life.
One patient in 2015 and one patient in 2017 received both systemic therapy and radiotherapy.

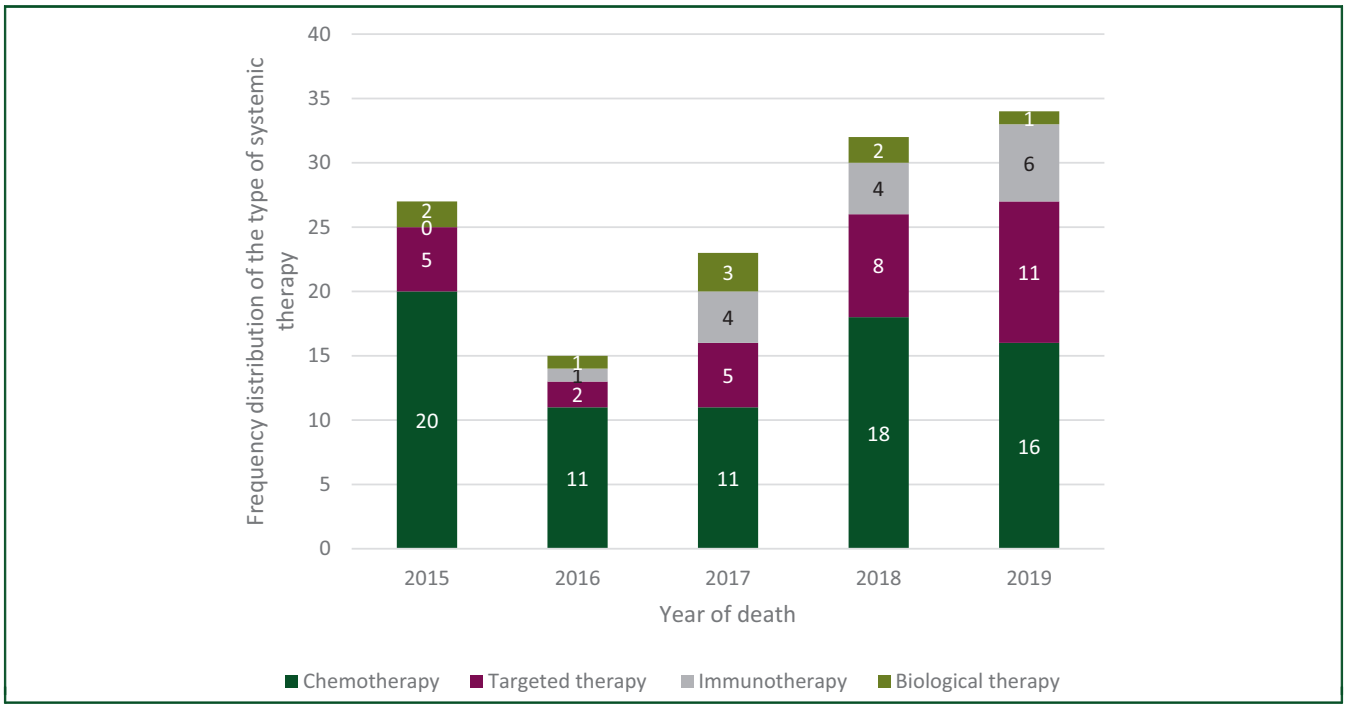

Figure 4. Frequency distribution of the type of systemic therapy in the last 2 weeks of life.
Six patients received two types of systemic therapy: one patient in 2015 (biological therapy + small-molecule targeted therapy), two patients in 2016 (chemotherapy + small-molecule targeted therapy and chemotherapy + immunotherapy), one patient in 2017 (chemotherapy + biological therapy) and two patients in 2019 (chemotherapy + small-molecule targeted therapy and small-molecule targeted therapy + biological therapy).

novel ST such as targeted agents became widely used in the last few months of life of patients with advanced cancer.[28,29] The discovery of novel ST with accompanying specific toxicity profiles and the possibility of oral treatment blurred the boundary between active and palliative interventions as oncologists, patients and their families may perceive per-oral targeted agents less aggressive treatment as compared to ChT.[30] However, it is well known that costly novel ST can cause substantial toxicity, including toxic deaths in patients with advanced cancer.[31] Moreover, in practice patients sometimes receive these agents continuously despite progressive disease or are re-challenged with them after a period of treatment.[32] Results of published studies show that targeted agents are prescribed twice as common as non-targeted agents at the EoL; additionally, the use of targeted agents was reported even in palliative care units in these studies.[28,29] However, evidence shows that metronomic therapy which is based on repeated administration of relatively low-cost and safe low doses of antineoplastic drugs might be a reasonable option of treatment in some patients with very advanced cancer.[33-36] In summary, increasing use of novel STs, including small-molecule targeted agents and immunotherapy near the EoL, is becoming problematic. Such practice can be detrimental for patients and may waste financial and human resources in the health care systems. We propose that the use of novel STs becomes an additional quality-of-care indicator at the EoL.

Table 1. Multiple logistic regression analysis exploring the association between different predictors and the use of aggressive anticancer treatment in the last 2 weeks of life

Predictor	OR	95% CI	*P* value
Sex			
Male (REF)			
Female	1.12	0.85-1.49	0.43
Age at death (per year)	**0.96**	**0.95-0.98**	**<0.001**
Year of death (per each the following year)	**1.15**	**1.04-1.27**	**0.01**
Prognosis of cancer			
Poor (REF)			
Intermediate	1.04	0.70-1.53	0.86
Good	1.28	0.92-1.78	0.14
Enrolment into the SPC			
No (REF)			
Yes	**0.22**	**0.12-0.43**	**<0.001**

Bold values indicate statistically significant results.
CI, confidence interval; OR, odds ratio; REF, reference category; SPC, specialist palliative care.

In our study, the proportion of patients who received RT or underwent SRG was 6.8% and 0.5% in the last 2 weeks of life, respectively. In contrast to ST, use of RT and SRG did not change substantially over time (Figure 3). RT is commonly used to palliate symptoms in patients with advanced cancer and to prevent impending severe morbidity. According to the American Society for Radiation Oncology consensus statement, palliative RT is safe and effective.[37] However, despite its important role in the management of symptoms in patients with advanced cancer, recommendations to guide its use at the EoL are lacking. Such recommendations would be useful because RT may cause short-time side-effects and sometimes requires weeks to show its palliative effect and therefore may be futile or even detrimental when administered in the last 2 weeks of life.[38,39] In the large Surveillance,

Epidemiology, and End Results (SEER)—Medicare study, 7.6% of patients received RT in the last month of life.[40] Despite impending death, a substantial proportion of patients receives prolonged irradiation schedules which are obviously not beneficial for patients at the EoL.[40,41] Decisions about palliative surgical procedures might be even more challenging in this setting. At the EoL care literature, an overtreatment is defined as a medical intervention that is extremely unlikely to help a patient, while it is misaligned with patient's wishes or both.[42] In fact, surgical procedures carried out for symptomatic relief, such as for example malignant bowel obstruction in a patient facing life-threatening cancer, are in accordance with the priorities of palliative care.[43-45] However, advance care planning and discussions about care goals could prevent aggressive surgical treatment at the EoL, especially in the last 2 weeks of life.[46]

In our study, use of aggressive anticancer treatment at the EoL was significantly associated with younger age (Table 1). This finding is in line with a large body of evidence showing that older patients receive ChT less often than younger patients.[11,14,23,47] However, we did not find any significant association between prognosis of cancer and gender with anticancer treatment in the last 2 weeks of life. Previous studies reported that patients with advanced breast cancer, lung cancer and gynaecological cancers were more likely to undergo ChT at the EoL than patients with other types of solid cancer.[12,48,49] In contrast to our findings, there is some evidence that women receive fewer treatment and medical interventions at the EoL as compared to men.[50,51] An explanation could be in treatment preferences, family support and terminal illness at older age.

We also showed that patients enrolled into the SPC had significantly lower odds to receive anticancer treatment at the EoL as compared to patients receiving only a standard oncology care (OR 0.22, 95% CI 0.12-0.43; Table 1). Of note, standard oncology care in Slovenia usually also involves a palliative care (i.e. non-SPC) which is provided by the teams of treating oncologists and general practitioners. However, the quality of current non-SPC in our country is very likely not comparable to the well-developed palliative care in the Western world. Evidence shows that prescription of ChT at the EoL is strongly associated with access to palliative care. In hospitals where patients have access to the SPC a prescription of ChT is declining.[52] Earlier cessation of anticancer treatment and concurrent inclusion of palliative care can contribute to a higher QoL and longer survival as compared to standard oncology care.[53] The EoL discussion is also associated with fewer life-sustaining procedures and lower rates of admission to the intensive care unit.[54] There is also evidence that medical expenses are very high in patients with advanced cancer in the last month of life.[55] In summary, available evidence and results of our study suggest that enrolment of patients with advanced cancer into palliative care decreases the risk for aggressive anticancer treatment at the EoL. Access to high-quality palliative care has important implications for patients' lives and lower medical expenses.

Cessation of treatment in terminally ill cancer patients is a complex topic interfering with personal, social and psychological dimensions.[56] There may be several reasons why treating oncologists may not discontinue treatment at the EoL. Firstly, active treatment may give a patient and his caregivers a sense of control over the disease and active fighting.[14] Secondly, recommending a new course of treatment may be an easier option for the oncologist than emotionally difficult discussions of cessation of treatment and transition to palliative care. Decisions about treatment are complex and usually depend on the relationship between the oncologist and patient and patient's and caregivers' expectations and priorities as well as social environment and perspectives.[14] Thirdly, predictions of the length of survival by oncologists are often overly optimistic.[5,57] However, more accurate prognostication is feasible and can be achieved by combining clinical experience and evidence from the literature which is based on well-defined prognostic factors.[58] For example, poor performance status (PS) and indices of limited activity and functional autonomy are major predictors of the approaching death. Additionally, symptoms such as dysphagia, xerostomia, weight loss, anorexia, cachexia, dyspnoea, delirium and cognitive impairment as well as some laboratory parameters (e.g. elevated bilirubin and/or C-reactive protein, lymphocytopenia, leucocytosis) often characterize the terminal phase of disease.[58] Various prognostic tools, which are based on the aforementioned prognostic factors, symptoms and laboratory parameters can predict survival more accurately and may be especially helpful for inexperienced clinicians.[6] For example, palliative performance scale (PPS) and prognosis in palliative care study (PiPS) models were specifically designed to estimate a 14-day survival in patients with advanced cancer.[59,60] Fourthly, use of aggressive treatment at the EoL is associated with poor access to palliative care. Ceasing aggressive cancer treatments earlier by introducing palliative care can increase survival time and QoL in patients with advanced cancer.[53] Furthermore, hospice care is beneficial at the EoL as it offers the utmost important symptom control and the time to accept the finality of the diagnosis without distractions of active intervention.[56,61] The suboptimal access to palliative care in Slovenia and other Eastern European countries may be associated with more aggressive anticancer treatment at the EoL.[62] Finally, financial incentives may have a substantial impact on treatment decisions by oncologists. For example, in the United States and Australia, oncologists receive financial reimbursements for the administration of ChT but little or no reimbursement for emotionally and time-consuming EoL discussions with patients and caregivers.[14] However, in Slovenia all cancer patients have access to cancer care within the public health system and medical oncologists do not receive any financial reimbursement for the administration of ST at any stage of cancer care.

For the first time we have shown that in Slovenia a substantial proportion of cancer patients receive aggressive anticancer treatment in the last 2 weeks of life. Our study included patients from a single academic cancer centre where ~60% of all Slovenian cancer patients are treated. However, there are several limitations to our study. Firstly, our study was retrospective and therefore results are highly

dependent on the accuracy of data entered into the EHRs by the treating oncologists. Secondly, additional explanatory variables could be included into the multivariable analysis. However, data on these potential variables in the patients' EHRs are not applicable to our environment (e.g. ethnicity and place of living) or might not be accurate or complete (e.g. PS, symptoms of impending death, comorbidities and social status). Also, due to the lack of relevant information we were not able to calculate PPS or PiPS and seek an association between symptoms of impending death and anticancer treatment at the EoL in our study. For the same reason we were also not able to assess a toxicity of anticancer therapy in this retrospective study. Thirdly, our study results should be interpreted cautiously as dates of death of included patients were not known when anticancer treatment was prescribed/administered. In contrast, results of a prospective study where we would be able to assess anticancer treatment only in patients with clear indicators of terminal phase of cancer, including deteriorating PS, might lead to different conclusions. Moreover, a study of patients' (e.g. palliation of symptoms and patients' values) and caregivers' perspectives at the approaching death could give us an additional insight about the anticancer treatment at the EoL. Future prospective studies should also pay more attention to the cost-effectiveness of anticancer treatment in terminally ill patients with cancer, taking into the account also indirect costs related to the toxicity of systemic anticancer therapy. Fourthly, a small number of patients who received novel ST were included in our study. This limitation could be alleviated by a larger sample size achieved by the inclusion of other cancer centres and/or by a longer studied time period. Finally, as IOL is an academic institution, results of our study may not be generalizable to non-academic cancer centres in Slovenia and in other European countries. However, our findings might be an important signal of the risk of aggressive anticancer treatment at the EoL in the rapidly evolving field of medical oncology, especially in countries with sub-optimally developed palliative care where novel STs are available.

Conclusions

Aggressive anticancer treatment at the EoL is a well-recognized problem. Results of our study show that anticancer treatment in the last 2 weeks of life became more aggressive mainly due to the increasing use of novel ST. General awareness of this problem and further efforts to mitigate it, including development of palliative care, are required.

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DISCLOSURE

The authors have declared no conflicts of interest.

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