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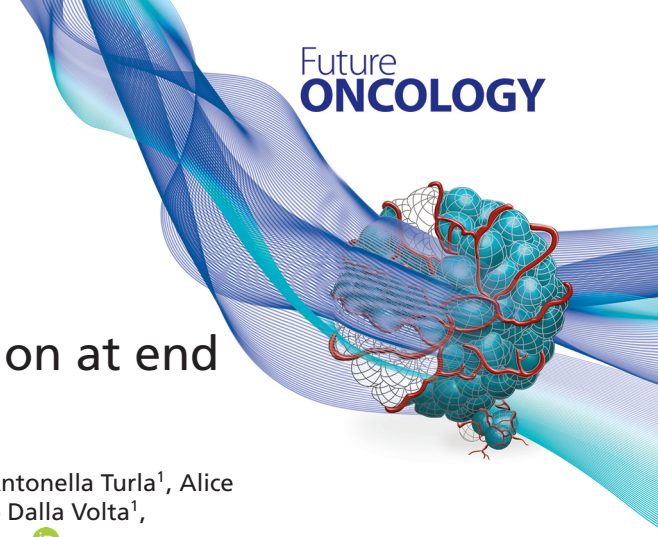

Oncological treatment administration at end of life: a retrospective study

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Background: This work evaluated the proportion of patients who continue therapy until their last month of life or initiate a new therapy in the last 3 months of life (end of life [EOL]). **Methods:** Data for 486 patients were retrospectively collected. **Results:** In EOL, 205 (42.3%) received systemic therapy. Better performance status (last month OR: 0.39; 95% CI: 0.25–0.60; $p < 0.001$; last 3 months OR: 0.47; 95% CI: 0.34–0.65; $p < 0.001$) and lack of activation of palliative care (last month OR: 0.26; 95% CI: 0.13–0.54; $p < 0.001$; last 3 months OR: 0.18; 95% CI: 0.10–0.32; $p < 0.001$) were associated with higher probability of EOL therapy. **Conclusion:** A non-negligible proportion of patients in real-life settings continue to receive systemic treatment in EOL.

First draft submitted: 3 February 2023; Accepted for publication: 20 February 2024; Published online: 29 February 2024

Keywords: chemotherapy • end-of-life • immunotherapy • oncological treatment • quality of life • target therapy

Active systemic treatment in end of life (EOL) has recently been identified by the American Society of Clinical Oncology as one of the most widespread, wasteful and unnecessary practices in clinical oncology, and it has been included in the 'first five' clinical practices to change for better cure and management of oncological patients [1].

In the USA, it is estimated that up to 50% of patients diagnosed with advanced cancer will receive systemic therapy during their last months of life [2], with approximately 20 and 9% of cases receiving treatment in the last 3 and 1 month of life, respectively [3]. In recent years, advancements in supportive therapy and the introduction of new therapeutic options such as targeted therapy and immunotherapy have led to improved survival rates and reduced toxicities, resulting in increased administration of anticancer therapy at EOL [4]. Patients who are more likely to receive EOL chemotherapy are young, Caucasian, married, have good performance status (PS) and have no major comorbidities [5,6].

The primary objectives of anticancer treatment for recurrent and/or metastatic patients should be symptom palliation, maintenance of the best possible quality of life (QoL) and prolonging survival. However, literature indicates that systemic treatments administered in terminally ill patients do not necessarily improve survival and are associated with increased toxicity [7].

Discontinuing treatment at EOL poses significant challenges for medical oncologists, both because it is not always a straightforward clinical decision and because of difficulties in communicating with patients and their families. Over 50% of patients may find it challenging to discuss their EOL needs or the possibility of death with their referring physicians [8]. Moreover, patients and their relatives often have unrealistic expectations about their prognosis, leading them to choose active systemic treatment over best supportive care [9], especially when they have not received sufficient information about the efficacy of anticancer therapy, the risks of side effects and the potential impact on QoL. Furthermore, patients who receive systemic treatment within 2 weeks of death are less likely to be admitted to hospice, resulting in death occurring in an acute care setting [10]. Nonetheless, information on the actual proportion of patients receiving systemic treatments and the factors influencing this treatment decision in

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a real-life setting remains limited. To the best of our knowledge, data from patients receiving immunotherapy are also limited.

Consequently, this study was designed to assess the proportion and characteristics of patients with advanced solid neoplasms who received antineoplastic treatment, including immunotherapy, in the EOL period, with the goal of identifying factors that may influence this decision-making process.

Methods

Study setting

This was an exploratory, monocentric, retrospective, nonprofit study. Data were collected from patients with a histologically proven diagnosis of solid neoplasm who had made at least one outpatient visit for anticancer therapy to the Medical Oncology Unit, Spedali Civili of Brescia (Italy), from 1 January to 31 December 2018. To be included in the study, patients had to be deceased by 31 December 2019. Patients with gynecological and brain neoplasms were excluded since they are managed in units other than Medical Oncology. The current authors' unit is a European Society for Medical Oncology-designated reference center for palliative and simultaneous care. The study protocol was approved by the Institutional Review Board of the Coordinating Center in Brescia on 31 March 2020 (Brescia Ethics Committee, Spedali Civili [study No. 4001–EoL Study]). The study was conducted in accordance with the Declaration of Helsinki for clinical studies.

Data collection

Anonymized data for all patients who met the criteria were collected in an electronic case report form. EOL was considered the last 3 months of life. The following data were retrieved: age at death, sex, primary cancer site, presence of caregiver(s), Eastern Cooperative Oncology Group PS and availability of simultaneous palliative care, defined as the presence of referral to palliative care service with a clear and established program of supportive care. The last two variables were recorded during oncological assessments at the onset of the last 3 months and the final month of life.

Anticancer therapy was defined based on whether the patient started a new therapy in the last 3 months of life (EOL period), continued an ongoing therapy until death or both. The type of treatment received (chemotherapy, hormone therapy, immunotherapy or targeted therapy) before EOL and the number of systemic treatment lines before EOL were collected. Toxicities grade >3 experienced with systemic treatments before EOL and creatinine and transaminase alteration in the same period were also analyzed according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0). Outcome data, namely, best response and progression-free survival (PFS) to the line of therapy received before EOL, were also collected.

Statistical analysis

Data were analyzed using descriptive statistics. Statistical differences were analyzed using the chi-square test for categorical variables or the Mann-Whitney U test for continuous or ordinal variables. To test biochemical, clinical and pathological parameters as possible predictors of anticancer therapy administration during the last months of life, a logistic regression analysis related to EOL therapy was performed to assess odds ratios (ORs) and 95% CIs both in the univariate and multivariate analysis. Only factors that obtained $p < 0.05$ in univariate analysis were entered into the multivariate analysis. Statistical significance was set at $p < 0.05$. SPSS v23.0 software was used for statistical analyses (SPSS Inc., IL, USA).

Results

Patient characteristics

As depicted in Supplementary Table 1, 486 patients we included, with 277 (57%) being male, and the median age at death was 66.4 years (range: 20–86 years). The primary tumor site was the lungs (29.2%), followed by the upper gastrointestinal tract (19.7%), colon/rectum (12.3%) and breast (10.7%), as shown in Supplementary Table 1. The median PS was 2 during the last 3 months and 3 during the last month of life.

Regarding the type of anticancer therapy administered before EOL, chemotherapy was the most common (68.3%), followed by immunotherapy (14.9%), targeted therapy (11.7%) and hormone therapy (4.5%). Patients had received a median of 1 (range: 0–12) prior line of anticancer therapy, with a median PFS of 5 months (range: 0–50). Progression of disease according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) was the best response to the last-administered treatment in over half of cases (54.8%). Most patients (88.1%) did not

Table 1. Univariate and multivariate analysis of variables predicting probability of therapy during end of life.

Variable	n	Therapy		Univariate analysis		Multivariate analysis	
		No	Yes	OR (95% CI)	p-value	OR (95% CI)	p-value
Eastern Cooperative Oncology Group performance status:							
Last month	235	3.17 (0.61)	2.71 (0.84)	0.385 (0.248–0.597)	<0.001		
Last 3 months	223	2.09 (0.91)	1.47 (0.90)	0.471 (0.342–0.650)	<0.001	0.419 (0.241–0.726)	0.002
Palliative care:							
Last month:	321				<0.001		
No		12 (6.7%)	30 (21.1%)	1			
Yes		167 (93.3%)	112 (78.9%)	0.264 (0.130–0.535)			
Last 3 months:	227				<0.001		0.029
No		44 (31.2%)	62 (72.1%)	1		1	
Yes		97 (68.8%)	24 (27.9%)	0.176 (0.097–0.317)		0.355 (0.140–0.897)	

experience severe toxicity in the last anticancer treatment line. Almost all patients included in the study had a caregiver (86.1%), and activation of palliative care service was registered in 53.3% of patients in the last 3 months and 86.9% in the last month of life.

EOL therapy

Treatments performed during EOL are summarized at the end of Supplementary Table 1. In total, 281 of 486 patients (57.7%) received no EOL anticancer therapy. Among the remaining 205 (42.3%) patients, 54 (11.1%) started a new line of therapy in the last 3 months and 54 (11.1%) continued systemic treatments in the last month, while 97 patients (19.9%) continued a therapy started within the EOL period until the last month of life. Regarding the type of anticancer therapy administered in EOL, chemotherapy was chosen in 65.9% of cases, followed by targeted therapy (18%), immunotherapy (13.7%) and hormone therapy (2.4%).

Predictors of EOL therapy

Univariate logistic regression analysis revealed that a better PS in the last 3 months and last month were significantly associated with continuing or starting an active treatment in EOL (last month OR: 0.39; 95% CI: 0.25–0.60; $p < 0.001$; last 3 months OR: 0.47; 95% CI: 0.34–0.65; $p < 0.001$). In addition, a lack of activation of palliative care was significantly associated with EOL therapy (last month OR: 0.26; 95% CI: 0.13–0.54; $p < 0.001$; last 3 months OR: 0.18; 95% CI: 0.10–0.32; $p < 0.001$). Only the last 3-month PS (OR: 0.42; 95% CI: 0.24–0.73; $p = 0.002$) and palliative care activation (OR: 0.36; 95% CI: 0.14–0.90; $p = 0.029$) maintained independent significant associations with EOL therapy in the multivariate logistic regression model (Table 1).

All other variables analyzed failed to show promise as potential predictors of EOL active therapy (Supplementary Table 2). In particular, age at death ($p = 0.536$), number of previous lines of therapy ($p = 0.108$), PFS and overall response rate of the previous line ($p = 0.602$ and 0.806, respectively) were not associated with continuing or starting an active treatment in EOL.

Discussion

Antineoplastic therapies in the final period of life in patients with advanced cancer aim to relieve symptoms, temporarily control the disease and prolong survival [11]. However, balancing clinical benefits with potential side effects can be challenging, potentially worsening patient QoL, contrary to the initial aim [10,12].

This study was designed to investigate the rate of patients receiving systemic therapies at EOL in a cohort of patients with advanced cancer, either metastatic or recurrent, not amenable to curative treatment and treated with chemotherapy, targeted agents or immunotherapy. In our series, more than 40% of patients received therapies in the last month or initiated new therapy in the last 3 months of life.

Other studies have reported a range of EOL treatments, mainly chemotherapy, for ranging between 5 and 55% of patients. This wide interval depends on different definitions of the EOL period, inclusion criteria and publication year, since a reduction of systemic therapy in the last period of life has been reported in recent years [6]. A strength of this paper is that it provides a comprehensive overview of EOL treatment approaches, considering all real-world strategies available for physician choice. However, the use of active treatments during the EOL period is

considered malpractice due to its association with increased rates of hospital admissions, mechanical ventilation and cardiopulmonary resuscitation. Moreover, it may hinder effective discussions about advanced care planning and preferred site of death [2,6,13]. Likewise, an active treatment administered when the probability of obtaining a benefit is limited would reduce QoL [2].

Regarding the administration of new anticancer agents, such as immune checkpoint inhibitors (ICIs) and targeted therapies, which may have changed the treatment landscape due to their perceived reduced burden of adverse events, 14% of patients treated during the EOL period received immunotherapy in this study. Glish *et al.* reported about 30% of patients received an ICI in the last 30 days of life [14], with increased prescriptions in frail patients, with PS $\geq$2 and with a higher burden of disease, thus confirming that this treatment is considered less invasive and has a perceived greater benefit. Similarly, Parikh *et al.* showed increased ICI use in metastatic urothelial cancer in the last months of life, mainly due to higher numbers of patients with poor PS [15]. We refer to the 'Lazarus effect' to indicate a sustained response in a frail patient. In hopes of achieving this result, therapy, particularly less toxic therapy, is being administered to patients who would otherwise be candidates for supportive care only [16–18]. However, there is a huge margin of uncertainty about this, and poor PS is one of the most important predictive factors of worse outcomes with immunotherapy. Conversely, patients treated with ICIs present an increased rate of in-hospital death (56 vs 29%; p = 0.002) and a decreased rate of hospice admission (45 vs 69%; p = 0.007) [14]. Given these considerations regarding immunotherapy, it is probably not a matter of minor toxicity load but rather a different toxicity profile; also, the expectations of physicians, patients and caregivers of this therapeutic approach may sometimes be higher than the results obtained in real-life settings.

When examining the factors influencing the decision to initiate therapy in the final months of life, this study identified only PS and the presence of an active palliative care service as prognostic indicators. Interestingly, other factors such as age, PFS from the last treatment and previous toxicities did not play a significant role. This suggests the challenge of identifying common characteristics among patients treated with different drugs and various primary cancers.

Furthermore, in this study, patient received a median of one line of systemic therapy before the last one received during EOL, with a range of 0–12. This may suggest a trend toward prioritizing the most effective drugs as the first-line option, but also that it is common for certain patients to discontinue therapies prematurely and succumb to worsening clinical conditions and early disease progression.

Previous studies have outlined characteristics of patients more likely to receive active therapy in the EOL: younger age, married status, insurance coverage, higher education, fewer comorbidities, good PS and treatment in larger volume centers [19]. However, there is not a clear and precise alignment between these factors and the benefits derived from systemic therapy. Hence, it is crucial to define factors associated with clinical benefit from systemic therapies to better tailor treatment choices for patients with limited life expectancy. In the realm of immunotherapy, ongoing studies aim to identify potential biomolecular and genomic predictors of activity and toxicity. These endeavors hold promise in assisting clinicians in making more informed therapeutic decisions in the future.

Additionally, the presence of a palliative care service was associated with reduced EOL treatment, a correlation consistent with findings from other studies [20,21]. Early integration of palliative care alongside oncological care has benefits such as increased hospice access, longer overall survival and improved QoL [13,21]. On the contrary, in a center with high integration between active and simultaneous palliative care, there may be a greater tendency to start active treatment at the EOL due to better management of possible treatment-related adverse events. Close collaboration between physicians managing active oncologic care and palliative care specialists is essential. The concept of simultaneous care underscores this cooperation, where active treatments may take precedence during the initial phase of disease relapse, while palliative care becomes more prominent in the EOL period. Both approaches should be integrated since disease relapse may not be amenable to salvage treatments.

Study limitations

The main limitations of this study include its retrospective nature, relatively limited number of patients, heterogeneous population in terms of primary cancer type and presence of variables with missing data. In addition, the retrospective nature of the analysis prevented the possibility of defining the reasons for the choice of administering systemic treatments, as taken by each treating physician. Therefore, we acknowledge that the results obtained can only be considered hypothesis-generating and speculative in nature.

Conclusion

In recent years, about 40% of patients with cancer continue to be treated during EOL. Although limited by its retrospective nature, these data strengthen the need for a call to action to improve EOL care for patients with cancer. To avoid the administration of useless therapy, advanced care planning and the validation of predictive factors are crucial to identify patients more prone to benefit from active treatments. Another key point to refine EOL care is implementing early palliative care activation as simultaneous care. Finally, we must keep patient wishes in mind by encouraging an open dialogue between patient, clinician and caregiver.

Summary points

- This work was designed to investigate the proportion of patients receiving systemic palliative therapies at the end of life (EOL) in a monocentric retrospective cohort of patients with advanced cancer.
- More than 40% of patients received therapies in the last month or initiated a new therapy in the last 3 months of life, highlighting the need for improved EOL care for patients with cancer.
- This study provides a comprehensive overview of EOL systemic treatment approaches, with chemotherapy as the most widespread EOL treatment.
- Regarding the identification of factors influencing the decision to initiate therapy in the EOL, only performance status and the presence of an active palliative care (PC) service were identified as prognosticator factors influencing this choice.
- In this study, PC service was associated with less EOL treatment administration.
- To avoid the administration of useless therapy, advanced care planning and the validation of predictive factors are crucial to identify patients more prone to benefit from active treatments.
- The current data support the importance of close cooperation between oncologic care physicians and PC experts, suggesting that PC support should play a major role together with active oncological treatment starting from the very first phase of disease relapse.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0092

Author contributions

Conceptualization: P Bossi; methodology: M Zamparini; formal analysis and investigation: all; supervision: A Berruti; writing original draft preparation: C Gurizzan and A Esposito; writing review and editing: all.

Financial disclosure

The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

P Bossi is on the advisory boards of Merck, Sanofi-Regeneron, Merck Sharp & Dohme, Sun Pharma, Angelini, Molteni, Bristol-Myers Squibb, GSK and Nestlè outside the submitted work. He has received conference honoraria from Merck, Sanofi-Regeneron, Merck Sharp & Dohme, Sun Pharma, Angelini, Molteni, Bristol-Myers Squibb, GSK and Nestlè outside the submitted work. A Berruti has received grants and personal fees from Janssen Cilag and Astellas and personal fees from Bayer outside the submitted work. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Writing assistance was provided by Aashni Shah, Mattia Zamboni (Polistudium SRL, Milan, Italy) and was supported by internal funds.

Ethical conduct of research

The study protocol was approved by the Institutional Review Board of the Coordinating Center in Brescia, Italy on the 31 March 2020 (Brescia Ethics Committee, Spedali Civili [study No. 4001–EoL Study]). In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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