

Chemotherapy at the End of Life – The Reality of an Oncological Centre

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Abstract: Background: In advanced and incurable cancer disease, chemotherapy may be recommended if it improves the quality of life, even if it does not increase survival. However, in an end-of-life setting, the use of chemotherapy is controversial, with less clear indications and more individualized decisions. This study aimed to evaluate patients who received chemotherapy within the last three months of life, an indicator of the quality of care provided. Methods: We analyzed data from patients receiving chemotherapy in the last 3 months of life and who died from January 2018 to December 2020, in our Oncology Department. Results: It was found that 391 patients received chemotherapy in the last 3 months of life. Most had metastatic disease at diagnosis (71%, n=276) and were treated in a first-line setting. A more detailed analysis revealed that 50% (n=193) underwent treatment in the last month and 22% (n=42) in the last week of life. Most patients died due to disease progression, with 79% of deaths occurring in the hospital. Conclusions: This work puts into figures the reality of an Oncology Centre, revealing the investment made in fighting the disease and providing greater longevity to patients, with quality of life.

Keywords: Chemotherapy, End of Life, Last Month of Life, Palliative Care

1. Introduction

According to European and international guidelines, in a patient with advanced and incurable oncological disease, chemotherapy may be a recommended treatment, if it increases the quality of life, even if it does not increase survival [1]. However, the decision to proceed with chemotherapy at this stage of life is not easy, mainly due to the management of risks and benefits for the patient - if on one hand we can get some relief from symptoms caused by the disease, on the other hand we can enhance the emergence of new symptoms, related to treatments' adverse effects, which may, even temporarily, worsen the general condition of the patient. Therefore, this decision must be shared with

the patient [2].

The use of chemotherapy at the end-of-life phase is a controversial topic, in which criteria and indications become less clear, and decisions more individualized [3].

The main objective of this study was to evaluate the amount of patients undergoing chemotherapy treatments in the last three months of life, an important indicator of the quality of care provided in this very particular stage of life. It was also intended to understand which pathologies were more prevalent and evaluate some factors related to quality of life at the end of life, such as performance status, symptoms presented by the patient and place of death.

2. Methods and Materials

Observational, retrospective, cross-sectional study on the population of patients diagnosed with solid neoplasms, undergoing chemotherapy treatments at our oncology department from January 2018 to December 2020. From this group, patients who died in that period, having undergone

treatment in the last 3 months of life, were selected. Patients diagnosed with hematological malignancies were excluded. Data were obtained by consulting the clinical file as well as the National Oncological Registry platform. Data were collected in an Microsoft Excel file created for this purpose and, later, analyzed using the IBM SPSS Statistics version 24 software. Table 1 shows the variables collected in this study.

Table 1. Variables obtained referring to patients who underwent chemotherapy treatments in the last three months of life.

VARIABLE	CODIFICATION
00 – Identification	Random number
01 – Age	Years
02 – Gender	0 – Feminine 1 – Masculine
03 – Performance Status	0 – Fully active, able to carry on all pre-disease performance without restriction. 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. 2 – Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours. 3 – Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. 4 – Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
04 – Oncological Diagnosis	0 – Esophageal cancer 1 – Gastric cancer 2 – Colorectal cancer 3 – Pancreatic cancer 4 – Lung cancer 5 – Prostate cancer 6 – Breast cancer 7 – Head and neck cancer 8 – Central nervous system cancer 9 – Gynecological cancer 10 – Other urological neoplasms (kidney, bladder) 11 – Biliary tract cancer 12 – Occult primary neoplasms 13 – Others
05 – Staging	I-IV
06 – Chemotherapy	Name of the chemotherapy drug
07 – Line of treatment	0 – 1 st line 1 – 2 nd line 2 – 3 rd line 3 – Subsequent lines
08 – Time, in months, from the start of treatment to the date of death	Months
09 – Time, in months, from the last cycle to the date of death	Months
10 – Place of death	0 – Hospital 1 – Hospice 2 – Home
11 – Cause of death	0 – Disease progression 1 – Treatment-related complications 2 – Other 3 – Unknown
12 – Number of episodes of admission to the emergency room	Number
13 – Number of episodes of hospitalization	Number
14 – Referral to the Palliative Care Service	0 – No 1 – Yes
15 – Decision of best supportive care	0 – No 1 – Yes

3. Results

From January 2018 to December 2020, 7425 new cases of solid neoplasms were registered, of which 9% (n=696) died in the same period, despite the treatments performed.

It was found that 391 received chemotherapy treatments in the last 3 months of life. Of these, 65% (n=255) were male, with a mean age of 63 years and the majority (81%, n=317) had an ECOG performance status (PS) of 0-1.

Regarding oncological disease, the most frequent diagnoses were lung cancer in 33% of cases (n=128), gastric cancer in 14%

(n=53) and colorectal cancer in 12% of cases (n=47), as shows table 2. As for staging, 71% (n=276) of patients had metastatic disease.

Table 2. Distribution of patients according to oncological diagnoses.

oncological diagnoses	n° of patients
Esophageal cancer	12 (3%)
Gastric cancer	53 (14%)
Colorectal cancer	47 (12%)
Pancreatic cancer	28 (7%)
Lung cancer	128 (33%)
Prostate cancer	9 (2%)
Breast cancer	5 (1%)
Head and neck cancer	19 (5%)
Central nervous system cancer	31 (9%)
Gynecological cancer	20 (5%)
Other urological neoplasms (kidney, bladder)	16 (3%)
Biliary tract cancer	12 (3%)
Occult primary neoplasms	6 (2%)
Others	5 (1%)
TOTAL	391 (100%)

Most patients (66%, n=258) underwent chemotherapy with doublets, in a first-line setting. The main regimens used were carboplatin/pemetrexed, carboplatin/etoposide, carboplatin/paclitaxel and cisplatin/5-FU; in monotherapy, the most used drug was gemcitabine. As mentioned, most patients underwent first-line treatment, with only 9% (n=24) undergoing treatment in a context of three or more subsequent lines.

A more detailed analysis revealed that 28% of patients (n=193) underwent treatment in the last month and 6% (n=42) in the last week of life. This subgroup of patients was quite representative of the total study population, with similar prevalence in terms of cancer diagnosis, staging and treatment.

Of these 193 patients, 53% died from disease progression and 20% due to treatment-related complications such as febrile neutropenia. Most deaths occurred in the hospital (79%, n=153). In the last month of life, patients had an average of two episodes of admission to the emergency department and one episode of hospitalization. Best supportive care was decided for 21% of patients (n=40) and of these, only 13% (n=25) were referred to the palliative care unit.

4. Discussion

Cancer is the second leading cause of death in the world, after cardiovascular disease [4]. In fact, Oncology has been an area of great expansion in recent decades, not only due to the higher incidence and prevalence of oncological diseases, but also due to the great advances in available treatments, which is reflected in an increase in patients' survival.

At the same time, concerns have arisen about the aggressiveness of care provided in the end-of-life setting. The use of chemotherapy at end-of-life, particularly in the last month, is considered an aggressive measure and should be avoided [5]. One of the largest studies in Portugal to assess the factors associated with the aggressiveness of end-of-life care [6], revealed that advanced age, breast cancer and metastatic disease are associated with a lower risk of aggressiveness,

while the existence of other comorbidities, gastrointestinal and hematological neoplasms were considered risk factors in this context. This study also showed that, in Portugal, 7 out of 10 patients with cancer in the end of life stage were subjected to some type of aggressiveness in the care provided, such as chemotherapy treatments in the last month of life, a higher number of hospitalization episodes and higher number of deaths in the hospital environment.

Literature shows that lung and colorectal neoplasms are most commonly associated with chemotherapy treatments in the last month of life [5]. Results similar to those obtained in our study, in which, of the 193 patients who received chemotherapy in the last month of life, 36% (n=69) and 12% (n=23) had a diagnosis of lung and colorectal cancer, respectively.

Despite being a much discussed topic and with growing interest, there is little concrete data on how to act in this very particular phase of life [7]. In a palliative setting, the goals of treatment may be a little different as chemotherapy can be used to relieve the symptoms caused by the disease and increase patient's performance status and quality of life. However, treatments are not free from risks and toxicities, which means that chemotherapy itself can worsen the patient's general condition, especially regarding the associated side effects: greater asthenia, nausea and vomiting, infectious complications, with greater morbidity and patient frailty. A study showed that the use of chemotherapy in the last month of life had no significant impact on patient survival, and was even associated with worse outcomes in terms of quality of life, especially for patients with better performance status [8]. Therefore, the risks and benefits of treatment at this stage should be carefully analyzed and shared with the patient and their family.

Although it is known the prognosis of cancer diseases, it is impossible to know in advance when a patient will die. Studies show that, in general, physicians tend to overestimate the prognosis of patients. One of the main predictors of poor prognosis is performance status [9]. Other factors can be taken into account: line of treatment, signs of clinical deterioration, presence of adverse effects related to the treatment. There are also validated prognostic scales used mainly in palliative care, which can be applied so that this prediction is as close to reality as possible – Morita's Palliative Prognostic Index, Maltoni's Palliative Prognostic Score or the most recent, Gold Standards Framework Prognostic Indicator Guidance [10].

Questions about starting or not a chemotherapy treatment, proceed to the next cycle, differentiate symptoms caused by the disease from symptoms caused by the treatment, are very fine limits and, in clinical practice, make some decisions more difficult. The fact that there are no guidelines to guide the cessation of chemotherapy treatments, makes the decision extremely challenging [11]. In our study, no prognostic modifying factors were identified that could help the decision to continue or not with treatments, whether factors related to the disease or the patient. Although we know that age, performance status, comorbidities, aggressiveness of the disease, sensitivity of the tumor to chemotherapy and previous treatments carried out are factors to take into account, in

general, decisions are essentially based either on clinical judgment or on the patients' wishes [12, 13].

Studies show that the incidence of chemotherapy treatments in the last month of life in patients with advanced cancer varies from 11.7% to 52%, as resumed in table 3 [14-17]. Despite being very wide percentages, as they come from different studies, with different samples and different

variables analyzed, it allows us to have an idea of what happens in other cancer centres. According to our study, 28% of patients underwent chemotherapy treatment in the last month of life. Even though this is in line with the literature, it is a considerable percentage and that should make us reflect on what we can change in our practice to provide the best possible care to our patients.

Table 3. Summary of reports in the literature concerning chemotherapy at the end of life.

Study (place/author, year)	N° of Patients in the Study	% of Patients Receiving Chemotherapy in the Last Month	Gender	Median Age	Oncological Diagnoses	Line of Treatment	Cause of Death	Other Information
Our study Portugal / Fontes / 2018-2020	193	28%	Masculine, 65% Feminine, 35%	63	Lung, 33% Gastric, 14% Colorectal, 12% Brain, 9%	1 st line, 66% 2 nd line 26% ≥ 3 lines 9%	Disease progression, 64% Treatment-relate d complications, 14%	Only 13% of patients were referred to palliative care.
Shangai / Zhang / 2007-2017	542	15,7%	Masculine, 54% Feminine, 46	67	Lung, 19.8% Gastric, 16.7% Colorectal, 15.7% Breast, 11.9%	—————	—————	One of the main reasons for undergoing treatment was the patient's and family's willingness and hope to try to fight the disease.
Lebanon / Assi / 2014	130	43,2%	Masculine, 51,5% Feminine, 48.5%	65	Gastrointestinal, 31.5% Lung, 16.9% Genitourinary, 13.1% Hematological, 11.5%	1 st line, 32,8% 2 nd line 34,4% ≥ 3 lines 32,8%	Disease progression, 54,6% Sepsis, 22,3%	71,5% of patients spent more than 14 days of the last month of life in hospital.
Portugal / Martins-Branc o 2010-2015	92 155	6,7% (last 14 days of life)	Masculine, 62% Feminine, 38%	73	Lung, 15,9% Colorectal, 10,2% Gastric, 8,7% Prostate, 8,5%	—————	—————	In Portugal, 7 out of 10 adults who died of cancer underwent aggressive treatments, compromising their quality of life.
France / Rochigneux / 2010-2013	279 846	19,5%	Masculine, 58% Feminine, 42%	75	Gastrointestinal, 33,7% Lung, 22,7% Breast, 9,3% Urological, 5,5%	—————	—————	Patients treated at centers without Palliative Care Units were more likely to receive chemotherapy at the end-of-life.
Sweden / Nappa / 2008	1 200	23%	Masculine, 56% Feminine, 44%	65	Gastric, 33% Lung, 22% Colorectal, 15% Gynecological, 8%	1 st line, 47% 2 nd line 25% ≥ 3 lines 28%	—————	
USA / Wilkerson / 2018-2019	92	12% (last 14 days of life)	Masculine, 55% Feminine, 45%	68	Lung, 30% Hematological, 18% Pancreatic, 12% Colorectal, 5%	1 st line, 52% 2 nd line 30% ≥ 3 lines 18%	—————	28% of patients were referred to palliative care in the last week of life.
Italy / Pacetti / 2010-2012	162	24,3%	Masculine, 64,8% Feminine, 35,2%	68	Lung, 30,3% Colorectal, 19,1% Pancreatic, 15,4% Head and neck, 8,6%	1 st line, 43,8% 2 nd line 32,1% ≥ 3 lines 24,1%	Disease progression, 64,8%	—————
Turkey / Urvay / 2015-2019	182	52%	Masculine, 56,8% Feminine, 43,2%	59	Lung, 37,8% Gynecological, 13,6% Colorectal, 10,5% Pancreatic, 8,4%	1 st line, 37,8% 2 nd line 22,2% ≥ 3 lines 40%	Disease progression, 32% Treatment-relate d complications, 22%	70% of patients had an episode of hospitalization in the Intensive Care Unit in the last month of life.
Switzerland / Adam / 2006-2007	119	11,7%	Masculine, 60% Feminine, 40%	75	Gastrointestinal, 37% Lung, 30% Gynecological, 10% Hematological, 8%	—————	—————	—————
Italy / Andreis / 2007-2009	102	16%	Masculine, 50% Feminine, 50%	62	Colorectal, 48% Breast, 22% Other (pancreas, lung, gastric), 30%	1 st line, 30% 2 nd line 55% ≥ 3 lines 15%	Disease progression, 71%	—————

Study (place/author, year)	N° of Patients in the Study	% of Patients Receiving Chemotherapy in the Last Month	Gender	Median Age	Oncological Diagnoses	Line of Treatment	Cause of Death	Other Information
Portugal / Braga / 2003	319	37%	Masculine, 39% Feminine, 61%	61	Breast, 31,7% Gynecological, 14,7% Lung, 11,9% Head and neck, 9,7%	_____	_____	14% of patients started a new treatment regimen in the last month of life.

Patients are often willing to bear the side effects related to treatment, hoping to achieve some control of the disease and relief from symptoms, even those such as fear, anxiety, depression. Our study revealed that, despite the vast majority of patients having undergone treatment in a first-line setting, most died due to disease progression, which makes decisions to initiate or not treatment even more difficult for both health professionals and patients. The key is that the care provided in this delicate stage of life, which can last for days, weeks or even months, is individualized, centered on the patient and their will, and provided in a multidisciplinary way, with a doctor, nurse, palliative care service, psychologist and, eventually, religious services. What patients value most in end-of-life care is the trusting relationship with their doctor, feeling a continuum of care, avoiding extraordinary measures of life and being mostly at home and with their family [18-20]. The importance given by patients and their families to the need for chemotherapy treatments is sometimes an obstacle to adequate care and has to be worked on and demystified [19, 21]. The fear of withdrawing hope from patients at this fragile stage of life is also a barrier to decision-making. In regard to this, it is essential to share information with the patient, clear and realistic information about the clinical situation, so that the patient understands the inevitability of a fatal outcome and that the eventual cessation of treatment does not imply the cessation of care or investment in his well-being. In fact, less aggressive approaches and more directed towards the care and comfort of the patient are associated with a better quality of life and, at times, greater survival. Patients with earlier follow-up by a palliative care team have fewer hospitalizations and die more often at home [22]. It is known that the ability to provide this care is a strong indicator of quality of life.

Although it wasn't its focus, this study confirmed the great need for investment in palliative care, which by definition is the care provided to patients with chronic, progressive and incurable disease, with the objective of prevent and relieve physical and psychosocial suffering of patients and their families [23]. Only 27% (n = 106) of patients who underwent chemotherapy in the last three months of life were referred to palliative care unit and 13% (n = 25) of the ones treated in the last month of life. The causes are multiple, from the difficulty in responding to requests, as it is a service still lacking in terms of the human resources available for the volume of patients in need, to the unpredictability of the patient's fatal outcome, or in other cases, due to the fact that referral happens at a stage too late for the patient to benefit from it. Although not limited to Oncology, there is a growing need to include palliative care in the management of cancer patients, which should be integrated early into patient management, in parallel with

ongoing active treatments [24]. Survival in this study was eight months for patients who underwent treatment in the last three months of life and six months for those who underwent treatment in the last month of life, which shows us not only the aggressiveness of the disease, but also the need for multidisciplinary patient management, focused not only in treating but also in caring.

Some limitations of this study are related to the fact that it is a retrospective study, which makes it more difficult to do a more detailed analysis of some indicators, as with regard to quality of life. In the future, it would be interesting to evaluate other variables, namely the symptoms of patients and understand whether they improved or not with the instituted treatments, as well as comparing this group of patients with a similar group of patients who did not undergo chemotherapy at the end of life and evaluate symptoms, admissions to emergency room, hospitalizations and referral for palliative care.

5. Conclusion

The demographic evolution of the population and the scientific evolution of Oncology translate into an increase in the number of cancer patients, but also an increase in the available therapeutic options. However, this does not always mean overcoming the disease. In fact, one of the great difficulties is knowing how to adapt knowledge to the patient situation, knowing when and how to invest, but also knowing when to stop with fruitless measures and nurse. This is genuinely one of the greatest arts in health care.

There are always things to improve, but there are also good actions and good results that must be shared.

This work puts in numbers the reality of an Oncology Department, revealing the investment made in fighting the disease and providing greater longevity to patients. There is no right way. There is a game of probabilities, shared decisions, good clinical sense and, above all, there is the will to fight. These are daily battles that we can't always win, but together with our patients, we fight back the disease.

References

- [1] Zhang Z, Chen ML, Gu XL, et al. (2018) Palliative Chemotherapy Near the End of Life in Oncology Patients. *Am J Hosp Palliat Care* 35 (9): 1215-1220. DOI: 10.1177/1049909118763338.
- [2] Barbera L, Seow H, Sutradhar R, et al. (2015) Quality Indicators of End-of-Life Care in Patients With Cancer: What Rate Is Right? *J Oncol Pract.* 11 (3): e279-e287. DOI: 10.1200/JOP.2015.004416.

- [3] Earle CC, Neville BA, Landrum MB, et al. (2004) Trends in the Aggressiveness of Cancer Care Near the End of Life. *J Clin Oncol* 22: 315-321. DOI: 10.1200/JCO.2004.08.136.
- [4] Roser M, Ritchie H, et al. (2017) Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* vol 390: 1151–210.
- [5] Assi T, Rassy E, Tabchi S. (2016) Treatment of cancer patients in their last month of life: aimless chemotherapy. *Support Care Cancer* 24, 1603–1608. DOI: 10.1007/s00520-015-2959-3.
- [6] Martins-Branco D, Lopes S, Canario R, et al. (2020) Factors associated with the aggressiveness of care at the end of life for patients with cancer dying in hospital: a nationwide retrospective cohort study in mainland Portugal. *ESMO Open* 2020; 5: e000953. DOI: 10.1136/esmoopen-2020-000953.
- [7] Rochigneux P, Raoul JL, Y. Beaussant Y. (2016) Use of chemotherapy near the end of life: what factors matter? *Annals of Oncology* 28: 809–817, 2017. DOI: 10.1093/annonc/mdw654.
- [8] Prigerson HG, Bao Y, Shah MA. (2015) Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. *JAMA Oncol* 1 (6): 778-784. DOI: 10.1001/jamaoncol.2015.2378.
- [9] Nappa U, Lindqvist O, Rasmussen BH, Axelsson B. (2011) Palliative chemotherapy during the last month of life. *Annals of Oncology* 22: 2375–2380. DOI: 10.1093/annonc/mdq778.
- [10] Stone PC, Lund S. (2007) Predicting prognosis in patients with advanced cancer. *Annals of Oncology* 18: 971–976. DOI: 10.1093/annonc/mdl343.
- [11] Wilkerson DH, Santos JL, Tan X, Gomez TH. (2021) Too Much Too Late? Chemotherapy Administration at the End of Life: A Retrospective Observational Study. *American Journal of Hospice and Palliative Medicine* 38 (10): 1182-1188. DOI: 10.1177/1049909120966619.
- [12] Pacetti P, Paganini G, Orlandi M, et al. (2015) Chemotherapy in the last 30 days of life of advanced cancer patients. *Support Care Cancer* 23 (11): 3277-80. Doi: 10.1007/s00520-015-2733-6.
- [13] Kao S, Shafiq J, Vardy J, Adams D. (2009) Use of chemotherapy at end of life in oncology patients. *Ann Oncol*. 20 (9): 1555-1559. DOI: 10.1093/annonc/mdp027.
- [14] Adam H, Hug S, Bosshard G. (2014) Chemotherapy near the end of life: a retrospective single-centre analysis of patients' charts. *BMC Palliat Care* 13, 26. DOI: 10.1186/1472-684X-13-26.
- [15] Andreis F, Rizzi A, et al. (2011) Chemotherapy use at the end of life: A retrospective single centre experience analysis. *Tumori*; 97 (1): 30-4. PMID: 21528660.
- [16] Braga S, Miranda A, Fonseca R, et al. (2007) The aggressiveness of cancer care in the last three months of life: A retrospective single centre analysis. *Psycho-Oncology* 16: 863–868. DOI: 10.1002/pon.1140.
- [17] Urvay S, Civelek B, Ozaslan E et al. (2020) Chemotherapy at the end of life. *Journal of Palliative Care* 1-5; 36 (2): 73-77. DOI: 10.1177/0825859720946505.
- [18] Heyland DK, Dodek P, Rocker G, et al. (2006) What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ*. 174 (5): 627–633. DOI: 10.1503/cmaj.050626.
- [19] Earle CC, Park ER, Lai B, et al. (2003) Identifying Potential Indicators of the Quality of End-of-Life Cancer Care From Administrative Data. *Journal of Clinical Oncology*, Vol 21, No 6, pp 1133-1138. DOI: 10.1200/JCO.2003.03.059.
- [20] Luta X, Maessen M, Egger M, et al. (2015) Measuring Intensity of End of Life Care: A Systematic Review. *PLoS ONE* 10 (4): e0123764. DOI: 10.1371/journal.pone.0123764.
- [21] Braga S. (2011) Why do our patients get chemotherapy until the end of life? *Ann Oncol*. 22 (11): 2345-2348. DOI: 10.1093/annonc/mdr416.
- [22] Triplett DP, LeBrett WG, Bryant AK, et al. (2017) Effect of Palliative Care on Aggressiveness of End-of-Life Care Among Patients With Advanced Cancer. *Journal of Oncology Practice* 13, no. 9 (September 01, 2017) e760-e769. DOI: 10.1200/JOP.2017.020883.
- [23] World Health Organization (August, 2020). Palliative Care. <https://www.who.int/news-room/fact-sheets/detail/palliative-care>.
- [24] Ferrell BR, Temel JS, Temin S et al. (2017) Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 35 (1): 96-112. DOI: 10.1200/JCO.2016.70.1474. Alimehmeti, I. (2021). Efficacy and Safety of AZD1222, BNT162b2 and mRNA-1273 vaccines against SARS-CoV-2. *Albanian Journal Of Trauma And Emergency Surgery*, 5 (1), 791-796. doi: 10.32391/ajtes.v5i1.178.