

ORIGINAL ARTICLE



End-of-life chemotherapy use at a Finnish university hospital: a retrospective cohort study

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ABSTRACT

Background: Recent trends in the end-of-life (EOL) cancer care have suggested that the levels of treatment are becoming more aggressive. The aim of this single-center study was to evaluate the time from the last intravenous (IV) chemotherapy treatment to death and identify factors correlating with treatment closer to death.

Material and methods: The study included all patients diagnosed with cancer at Turku University Central Hospital between the years 2005 and 2013 ($N = 38,982$) who received IV chemotherapy during the last year of life ($N = 3285$). The cohort of patients and their respective clinical information were identified from electronic medical records. Statistical analysis was performed to assess and compare the treatment strategies, taking into account the patient's age, the year they were treated, and the type of cancer they were diagnosed with.

Results: A total of 11,250 cancer patients died during the observation time and one-third ($N = 3285$, 29.2%) of them had received IV chemotherapy during the last year of life. The time from the last IV chemotherapy regimen to death remained consistent across the follow-up time. During the last month of life, every third patient under the age of 50 years and only one-tenth of patients over the age of 80 years received IV chemotherapy. Hematological malignancies and lymphomas were treated closer to death when compared to other diagnostic groups.

Conclusions: During the period of 9 years, the pattern of EOL IV chemotherapy treatment remained stable. Every third patient died at tertiary care. Only 7.2% of patients who received IV chemotherapy during the last year of life were treated 14 days before death, which is in line with international recommendations. However, significant variation in EOL treatment strategies between different diagnosis and age groups were identified.

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Background

Multiple studies suggest that the trend for aggressive end-of-life (EOL) cancer care is increasing [1,2]. Proposed standard benchmarks for 'not overly aggressive cancer care' include <10% of patients receiving chemotherapy 14 days prior to death and <2% of patients starting a new chemotherapy regimen 30 days prior to death [3].

In Finland, the use of EOL chemotherapy among breast cancer patients has been studied [4], but the treatment patterns for other solid tumors and hematological malignancies remain unknown. When evaluating the quality of EOL care, aggressiveness of anti-cancer treatments must be assessed as potential adverse effects have a detrimental effect on the quality of life and aggressive EOL treatment also imposes considerable costs on health care systems [5].

Turku University Central Hospital is the main hospital in the Hospital District of Southwest Finland and one of the five university hospitals in Finland. It is responsible for cancer care for 0.47 million residents. In Turku University Central

Hospital, all documentation is systematically collected in electronic medical records providing a special opportunity to evaluate real world praxis by data mining. The tax-financed Finnish health care system provides cancer care for all residents of the district with minimal cost to the patients.

In the present study, we determined the time from the last intravenous (IV) chemotherapy to death in regard to patients' age, cancer type, treatment year and place of death. The study is based on data mining of real world data, consisting of electronic medical records of cancer patients treated in Turku University Central Hospital during the 9-year period of 2005–2013.

Material and methods

Data sources

Turku University Central Hospital is one of five academic hospitals in Finland and has a population of ~470,000 people, in

the Southwest part of Finland, comprising an area of 10,900 km². It is the single center providing cancer care in the region.

In Turku University Central Hospital, all crucial patient records are electronic and information including patient hospitalization, out-patient-clinic visits, ICD-10-codes, laboratory values, radiological exams performed, radiotherapies, and intravenously administered medications are systematically documented in patients' records. Additionally, medical records by clinicians, therapists and nurses are included. This extensive amount of data concerning all patients treated at the hospital has been collected from multiple operative IT-systems for secondary use and combined with patient IDs to form the hospital database.

Cohort selection

From the Turku University Central Hospital database, patients with a cancer diagnosis (ICD-10 C00–C97) between the years 2005 and 2013 were identified ($N=38,982$). During the time period, 11,250 cancer patients died and 3285 (29.2%) of the patients received IV chemotherapy during their last year of life. All the deceased cancer patients receiving IV chemotherapy during the last year of life were included in the study. Data regarding the patients' mortality and malignancy were confirmed from the database of Statistics Finland. Validation of data was performed manually to evaluate whether there were patients receiving chemotherapy for other diseases than cancer during their end of life. For the validation, electronic medical records of 100 patients, who were randomly selected by the computer, were manually revised and all (100%) of these patients had received chemotherapy for advanced cancer.

Design

Use of IV chemotherapy was evaluated in relation to the patients' age, gender, cancer diagnosis, treatment year and place of death. The patients were divided into five age groups: patients under 50 years ($N=308$, 9.4%), 50–59 years ($N=584$, 17.8%), 60–69 years ($N=1237$, 37.7%), 70–79 years ($N=923$, 28.1%), and over 80 years ($N=233$, 7.1%). Additionally, patients were divided into 15 diagnostic groups: (i) cancer of head and neck, (ii) esophageal and gastric cancer, (iii) pancreatic cancer, (iv) colorectal cancer, (v) other gastro-intestinal (GI) cancer, (vi) lung cancer, (vii) skin cancer, (viii) sarcoma, (ix) breast cancer, (x) gynecological cancer, (xi) prostate cancer, (xii) cancer of urinary tract, (xiii) hematological malignancies, (xiv) lymphoma and (xv) other cancer type (Table 1). When a deceased patient had more than one instance of malignancy, the patient was classified based on the most recent diagnosis before death. Finally, the patients were divided into three 3-year cohorts: 2005–2007 ($N=975$, 29.7%), 2008–2010 ($N=1129$, 34.4%) and 2011–2013 ($N=1181$, 36.0%). The use of IV chemotherapy was assessed at five time points during the last year of life: 1 year, 6 months, 3 months, 2 months, 1 month, and 2 weeks before death. The number of patients who died in the University

Table 1. Characteristics of patients receiving IV chemotherapy during the last year of life.

Characteristics	Median	
Age at death		
Female	66 years	
Male	66 years	
Time from the last treatment to death	111 days	
	$N=3285$	%
Gender		
Female	1547	47
Male	1738	53
Time from the last dose of IV chemotherapy to death		
6 months to 1 year	705	21.5
3 months to 6 months	834	25.4
1 month to 3 months	1159	35.3
2 weeks to 1 month	349	10.6
<2 weeks	238	7.2
Diagnosis groups		
Lung cancer	812	24.7
Hematological and lymphoma	479	14.6
Gynecological cancer	303	9.2
Breast cancer	295	9.0
Colorectal cancer	295	9.0
Pancreatic cancer	235	7.2
Gastric and esophagus	169	5.1
Prostate cancer	167	5.0
Other	530	16.1
Age groups (years)		
<50	308	9.4
50–59	584	17.8
60–69	1237	37.7
70–79	923	28.1
>80	233	7.1
Treatment year		
2005–2007	975	29.7
2008–2010	1129	34.4
2011–2013	1181	36.0

Hospital was evaluated for patients treated with IV chemotherapy in the five time points described above.

This retrospective registry-based study was done with the permission of the authorities of Turku University Central Hospital. According to the Finnish law, no ethics committee approval was needed.

Statistical analysis

Descriptive statistics were used to investigate patient characteristics. More specifically, continuous variables were reported as median and mean together with standard error. Categorical variables were reported as percentages. Time between the last dose of IV chemotherapy and death was analyzed using the Kaplan–Meier method. Differences in EOL IV chemotherapy treatment between different patient groups (based on age, year of death, or diagnosis) were examined using log-rank test (Figure 1). Finally, Cox regression analysis was performed to further investigate the association between EOL chemotherapy treatment and age, year of death and diagnosis. All statistical analyzes were performed using R version 3.1.3 [6].

Results

The cancer patient cohort consisted of 38,982 individuals of which 11,250 (28.9%) had died during 2005–2013. One-third

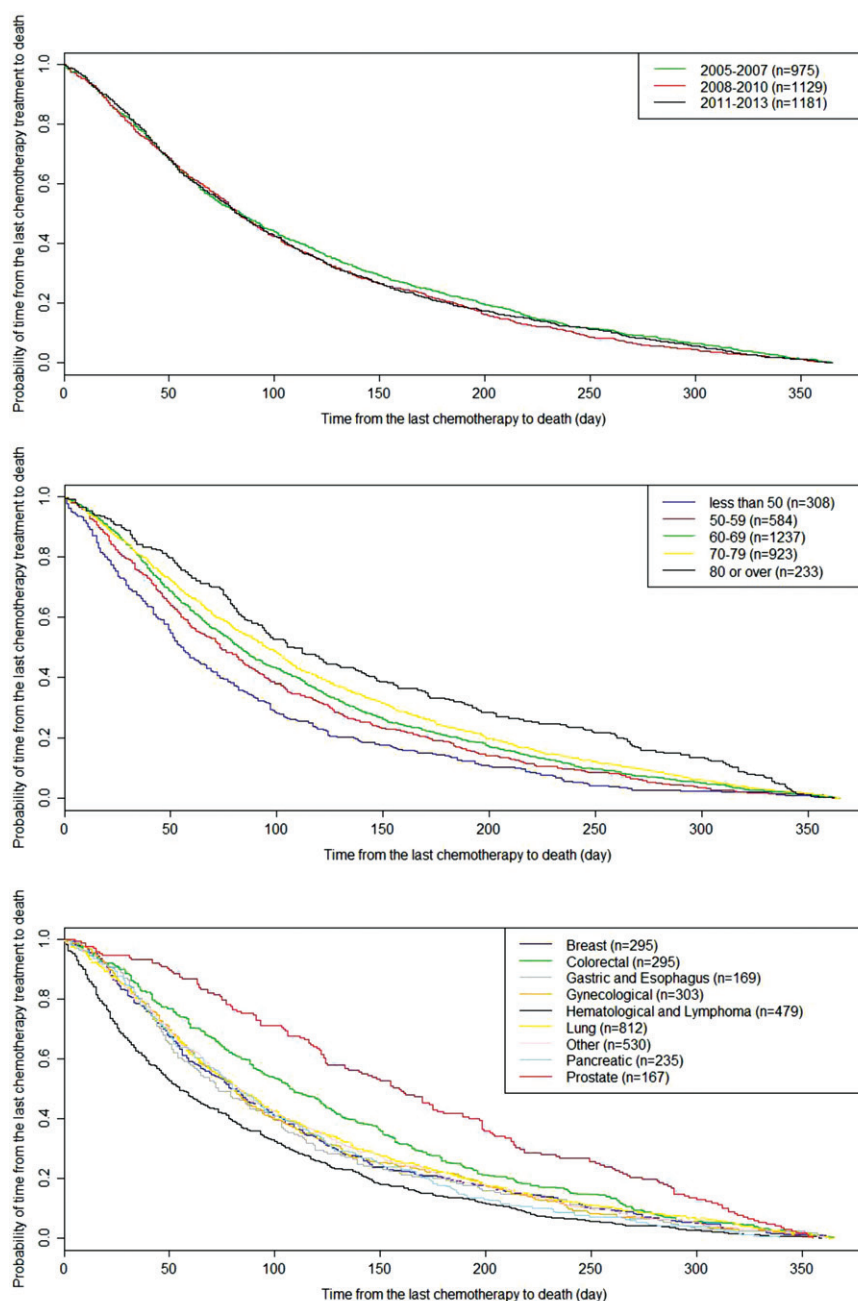


Figure 1. Time between the last dose of IV chemotherapy and probability of time from last chemotherapy treatment to death for (a) different years of death 2005–2013, (b) different age groups, and (c) largest diagnostic groups. The selected age groups and diagnostic groups differed significantly in overall comparisons ($p < .0001$), whereas no significant differences were observed between the follow-up intervals ($p = .20$).

($N = 3285$, 29.2%) of the deceased cancer patients received IV chemotherapy during the last year of life (Table 1).

Of the patients receiving IV chemotherapy during the last year of life, 7.2% were treated during the last 14 days of life. The percentages were higher for hematological malignancies (20.9%) and lymphomas (10.6%). The average time between the last dose of IV chemotherapy and death was 111 days ($SE = 1.6$) for those who received IV chemotherapy during the last year of life. For pediatric patients ($N = 23$), the average time between the last dose of IV chemotherapy and death was 70 days ($SE = 30.7$).

There were no significant differences between the studied follow-up intervals in regard to EOL IV chemotherapy

(Figure 1(a), $p = .20$). Thus, the time from the last IV chemotherapy dose to death remained stable over the years.

Time between the last dose of IV chemotherapy and death varied significantly according to the patient's age (Figure 1(b)). The differences between the age groups were statistically significant with the exception of the groups 50–59 and 60–69 ($p = .22$) and 60–69 and 70–79 ($p = .13$). Younger patients were treated closer to death than older patients ($p < .0001$). Of the patients <50 years of age, 31% received IV chemotherapy 1 month before death, while in the age groups 50–59, 60–69, 70–79 and >80 years, the corresponding percentages were 21, 16, 16 and 11%, respectively.

The use of IV chemotherapy varied significantly between the diagnosis groups (Figure 1(c), $p < .0001$). Patients with prostate cancer and cancer of the urinary tract were the least frequently treated groups among patients receiving treatment during the last year of life ($p < .05$). For patients with lymphoma or hematological malignancies, the time between last treatment and death was on average shortest ($p < .05$).

The Cox regression analysis was performed to study the combined effect of age, year of death, and diagnosis to days between last treatment and death. The analysis revealed similar results as described above showing that the significant factors in EOL IV chemotherapy treatment were age ($p < .001$) and certain cancer types: hematological malignancies ($p < .001$), lymphoma ($p < .001$), prostate cancer ($p < .001$), and cancer of urinary tract ($p = .020$). For the year of death, the effect was not statistically significant ($p = .55$).

One-third ($N = 1210$, 36.8%) of the patients who were treated during the last year of life received both IV chemotherapy and radiotherapy during the last year, although only five patients (0.2%) during the last 2 weeks of life.

From the patients who received IV chemotherapy during the last year of life, 31% died at the Turku University Central Hospital.

Discussion

In our epidemiologically descriptive study of all deceased cancer patients treated in Turku University Central Hospital during 2005–2013, 29.2% of the patients received IV chemotherapy during the last year of life. The time from the last IV chemotherapy treatment to death remained stable throughout the follow-up time of 9 years. Patients under the age of 50 years and patients diagnosed with hematological malignancy or lymphoma were more likely to receive IV chemotherapy during the last months and weeks of life. Significant differences were observed in the treatment strategies between different age and diagnostic groups.

ASCO (American Society of Clinical Oncology) has identified EOL chemotherapy as one of the five opportunities to improve care and reduce costs in oncology [7]. A treatment approach is considered overly aggressive when more than 10% of patients receive anti-cancer treatments during the last 14 days of life [3]. In the present study, of all the deceased cancer patients ($N = 11,250$) 2.1%, and of the deceased cancer patients treated during the last year of life ($N = 3285$) 7.2% were treated during the last 14 days, which is in line with the recommendations. The patients with hematological malignancies were treated more frequently during the last weeks of life, when compared to solid tumors, which is consistent with the findings by Hui et al. [8].

In previous population based studies, an increasing trend in the use of anti-cancer treatments during last year of life has been reported [2]; however, in the present study no such trend was observed. A large US study reported that the proportion of patients receiving chemotherapy was 27.9–29.5% [1] and in Sweden the percentage of patients receiving palliative chemotherapy was slightly higher, at 31% [9]. Comparison between the reports is, however, somewhat

challenging, as the health care systems, study designs, and inclusion criteria vary between the studies. Studies with different focuses that estimate the aggressiveness of the treatment at one month before death frequently reported higher percentages (22–56%) [9–14] than what was observed in the present study, with the exception of the Australian (19%), Swiss (12%) and Norwegian cohorts (10%) [15–17]. However if we include all deceased cancer patients instead of the ones treated during the last year of life, the percentage in our study is distinctly lower, 5.2%.

Previous study describing the intensity of anti-cancer treatments of breast carcinoma patients in Finland reported that approximately one-fifth of the patients received chemotherapy one month prior to death [4]. The study included breast cancer patients who had a contact to the health care system during the last 6 months of life. The present study confirms this finding, with 18.6% of breast cancer patients who were treated during the last year, receiving chemotherapy during the last month of life.

Alongside with age and diagnosis other factors including alternative available treatment options, stage of cancer at the time of diagnosis, and chemosensitivity of the tumor have been found to correlate with the use of chemotherapy during the last months of life [2,10,15,16]. Hematological malignancies are often chemosensitive, which has an influence towards more frequent treatment during the last months and weeks of life.

A patient receiving palliative chemotherapy will most likely require more admissions to the hospital, have a lower chance of dying at home, and may also have shortened survival time [9]. In our study, one-third of the patients who received chemotherapy during the last year of life died in a university hospital.

Median survival for many cancer patients is below 1 year and therefore patients may receive first-line chemotherapy during the last months of life. With some tumor types, chemotherapy may also prolong survival even with second, third or fourth line of chemotherapy. However, the general condition and the prognosis of the patient are to be considered when planning the treatment procedures because even among patients with good performance status, chemotherapy near EOL is not seen to improve the quality of life [18]. With younger patients it may be more difficult for clinician, patient and caregivers to relinquish cancer treatments. In addition, elderly patients may be more susceptible to adverse events of anti-cancer drugs, which may also explain our observation of younger patients being treated closer to death.

In Finland, cancer treatments are provided almost entirely by the public health-care system, and in Southwest Finland by Turku University Central Hospital. There may be, however, individual patients receiving treatment outside this unit. The study cohort was epidemiologically representative of the prominent oncological diseases found within the population. The 9-year follow-up allowed us to analyze the trends in the use of chemotherapy. The most significant limitation of the study was that the pharmacy data only included intravenously administered chemotherapy. In some cancer types, this may have an effect on the results, suggesting there are less

active treatment trends than actually occurring in real life. For example, in breast cancer and in colorectal cancer, orally administered capecitabine, in kidney cancer tyrosine kinase inhibitors (sunitib, sorafenib, etc.), and in lung cancer vinorelbine are used. Other limitations are that the date of the diagnosis of cancer or metastatic disease could not be identified from the electronic medical records and that the ICD codes used for identifying the cancer patients do not define the stage of the cancer. In the death certificates used for verifying the cause of death, the accuracy may vary. For a large series of patients, however, death certificates are the only source of data for evaluating the causes of death.

Conclusions

This study assessed the use of EOL chemotherapy in a Finnish university hospital offering chemotherapy for a population of almost half of a million, reflecting the established oncological treatment strategies. The time from the last treatment to death remained stable during the years 2005–2013. Every fifth patient received IV chemotherapy during the last month of life, while the corresponding portion for the patients under the age of 50 years was one-third and for the patients over the age of 80 years one-tenth. Use of chemotherapy during the last weeks or month in life should be critically evaluated as it, in most cases, is not likely to extend life. Cancer care near EOL was associated with death at tertiary care in 31% of patients. Instead, death at palliative ward or hospice or the possibility to die at home should be preferred.

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References

- [1] Earle CC, Neville BA, Landrum MB, et al. Trends in the aggressiveness of cancer care near the end of life. *JCO*. 2004;22:315–321.
- [2] Ho TH, Barbera L, Saskin R, et al. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. *JCO*. 2011;29:1587–1591.
- [3] Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Health Care*. 2005;17:505–509.
- [4] Asola R, Huhtala H, Holli K. Intensity of diagnostic and treatment activities during the end of life of patients with advanced breast cancer. *Breast Cancer Res Treat*. 2006;100:77–82.
- [5] Riley GF, Lubitz JD. Long-term trends in Medicare payments in the last year of life. *Health Serv Res*. 2010;45:565–576.
- [6] R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2015.
- [7] Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *JCO*. 2012;30:1715–1724.
- [8] Hui D, Didwaniya N, Vidal M, et al. Quality of end-of-life care in patients with hematologic malignancies: a retrospective cohort study. *Cancer*. 2014;120:1572–1578.
- [9] Nappa U, Lindqvist O, Rasmussen BH, et al. Palliative chemotherapy during the last month of life. *Ann Oncol*. 2011;22:2375–2380.
- [10] Braga S, Miranda A, Fonseca R, et al. The aggressiveness of cancer care in the last three months of life: a retrospective single centre analysis. *Psychooncology*. 2007;16:863–868.
- [11] Numico G, Trogu A, Cristofano A, et al. Active treatment given in the last weeks of life: poor quality cancer care or justifiable behavior? *Support Care Cancer*. 2014;22:2813–2819.
- [12] Greer JA, Pirl WF, Jackson VA, et al. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *JCO*. 2012;30:394–400.
- [13] Lee HS, Chun KH, Moon D, et al. Trends in receiving chemotherapy for advanced cancer patients at the end of life. *BMC Palliat Care*. 2015;14:4.
- [14] Pacetti P, Paganini G, Orlandi M, et al. Chemotherapy in the last 30 days of life of advanced cancer patients. *Support Care Cancer*. 2015;23:3277–3280.
- [15] Kao S, Shafiq J, Vardy J, et al. Use of chemotherapy at end of life in oncology patients. *Ann Oncol*. 2009;20:1555–1559.
- [16] Adam H, Hug S, Bosshard G. Chemotherapy near the end of life: a retrospective single-centre analysis of patients' charts. *BMC Palliat Care*. 2014;13:26.
- [17] Anshushaug M, Gynnild MA, Kaasa S, et al. Characterization of patients receiving palliative chemo- and radiotherapy during end of life at a regional cancer center in Norway. *Acta Oncol*. 2015;54:395–402.
- [18] Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy use, performance status, and quality of life at the end of life. *JAMA Oncol*. 2015;1:778–784.