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ORIGINAL ARTICLE

Aggressiveness of cancer treatment in patients hospitalized in a supportive care unit

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Abstract
Purpose This study aimed at determining the aggressiveness of chemotherapy (CT)in patients hospitalized in a supportive care unit (focusing on mortality, patient profiles, survival, readmissions, and CT near death).
Methods In a prospective cohort study, 247 consecutive patients were investigated at the admission (disease, treatments, oncologist's theoretical survival prognosis, internist's clinical global impression (CGI)). A 3-and 6-month follow-upwas performed. Survival was assessed up to 3 years.
Results Various cancer diagnoses were represented in polymorbid patients. Since disease onset, 69.6 % had received a first line of CT only; 147 patients (59.5 %) had CT at the admission; median CGI was 3 (range=0–10); and theoretical survival prognosis was <12 months in 65.2 %. In-hospitalmortality rate was 21 %. Odds of receiving CT was inversely associated with age (OR for patients ≥71 years vs. patients <50 years 0.19; 95 % CI 0.06–0.65; p=0.02) and number of previous CT lines (OR for patients with 2–4 lines vs. those with 1 line 0.14; 95 % CI 0.06–0.34; p=0.000). In the multiadjusted model, 6-monthsurvival remained associated with CT at the admission (HR 1.86; 95 % CI 1.31–2.65; p=0.001), CGI (per point HR 0.84; 95 % CI 0.73–0.96; p=0.013), and theoretical survival prognosis (per category HR 0.53; 95 % CI 0.44–0.66; p=0.000). Very few patients needed readmission related to CT's adverse effects. From admission and throughout follow-up, 24 patients (9.7 %) had received CT during their last 14 days of life.
Conclusion This study showed that a supportive care program can benefit a heterogeneous population as it contributes to assess clinical risks and benefits of CT and prevent aggressive care near death.

Keywords Supportive care · Chemotherapy · Advanced cancer · Aggressiveness of care · Integrated care

Introduction

Over the past years, oncological treatments have considerably changed the course of the disease with several new treatment options available. Patients and clinicians prioritize pain and symptom management for incurable cancer, but trends in oncology reveal that chemotherapy (CT)and acute care services are overused very near death [1]. In response to cancer becoming more of a chronic disease, supportive care in cancer has been developed as a means to achieve integrated care (http://www.mascc.org/).

In 2004, a supportive care program was implemented at the Geneva University Hospitals, in the division of general medical rehabilitation and in collaboration with the division of oncology. The multidisciplinary staff of the 12-bedsupportive care unit is headed jointly by an internist and an oncologist to take patients' polymorbidities into account. Collaboration is mainly based on daily rounds and weekly meetings which

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involve all care providers (physicians, nurses, dietetician, physical therapist, psychologist, and social worker). After an initial assessment, patient-tailoredcare is planned, according to the best practices and principles of supportive care, taking into account the various aspects of the patient's status (including function, fatigue, denutrition, and anxiety/depression). Daily rounds and weekly meetings offer the opportunity to adapt and coordinate care planning. This collaboration establishes the supportive care unit on a continuum that can extend from acute care wards to palliative care units and between stationary and ambulatory care services. This supportive care unit is part of a 1,200-bed urban public and teaching hospital which is the major primary care hospital for the area. Patients are referred by oncologists, from acute oncological units or ambulatory care of the hospital. The supportive unit addresses patients with an active and symptomatic pathology and comorbidities requiring integrated care (e.g., cardiac or renal insufficiency, decompensated diabetes, deconditioning/denutrition, or pain problems resistant to analgesic treatment).

Indeed, care coordination is essential: daily practice shows that caring for patients suffering from polymorbid conditions cannot be reduced to the addition of each disease. Lack of integrated care results in multiple procedures that may be useless and even redundant whereas integrated care can lead to less aggressive care at the end of life [2, 3]. When these dimensions are neglected, care providers may be inclined to focus on the disease rather than on the individual with the disease, leading to possible therapeutic overuse and possible losses of patients' functional autonomy [4]. In this context, we sought to determine the aggressiveness of cancer treatment in patients hospitalized in the supportive care unit. Only CT was considered. Regarding the definition of aggressiveness in the use of CT, five areas were investigated as follows: (a)mortality rate during hospitalization, (b) profile of patients receiving CT, (c) CT impact on survival, (d) CT use necessitating readmission, (e) use of CT near death [5].

Methods

We performed a longitudinal prospective cohort study enrolling all consecutive oncological patients hospitalized in the supportive care unit from April 1st, 2008, to October 31st, 2009. Patients were assessed in the first 48 h of their admission. Patients hospitalized in the unit are ≥18-year-old patients, presenting with a symptomatic oncological disease and/orwith adverse effects due to oncological treatments and/orwith somatic or psychological comorbidities necessitating hospital care in an internal medicine setting. Thus, patients hospitalized in the unit are addressed for treatment and subsequent return to their home. Patients requiring immunotherapy, intra-arterial, intra-thecal, or intra-pericardialCT are hospitalized in the acute oncological units.

Data were collected to characterize the patients and their disease and treatments. Charlson comorbidity index [6], laboratory data, type and stage of cancer, and length and status of the disease were extracted from the medical charts. Functional status was assessed by the performance status (PS)[7]. The internist in charge of the patient documented his/herclinical global impression (CGI)at the admission on a numerical rating scale from 0 (extremely poor) to 10 (excellent). At the same time, the oncologist in charge of the patient provided an estimation of the patient's theoretical survival prognosis (<3 months, 3–6 months, 6–12 months, 1–5 years, >5 years, complete remission) [8]. This prognosis was estimated after a full clinical staging according to the established guidelines of the European Society of Medical Oncology [8].

All patients were followed from admission up to 6 months, and the consequences of the oncological disease and its treatment were recorded (*During the hospital stay* CT adverse effects, transfer to acute care wards, discharge planning, and death; *During the 6-month follow-up* CT at 3 and/or6 months, emergency consultations related to CT's adverse effects at any point in time, CT during the last 14 days of life, or new CT line during the last 3 months of life, mortality, and place of death).

Survival was assessed up to March 30, 2013, through medical records and by inquiring the files of the Cantonal Population Office through the Geneva Cancer Registry.

The study protocol was approved by the hospital ethics committee in accordance with the ethical standards of the Helsinki Declaration. All included patients gave written informed consent.

Statistical analysis To assess determinants of CT provision, we used logistic regression analysis by considering as cases patients who were treated with CT at the admission and as controls those who were not. With univariate logistic regression, we identified which covariates were significantly associated to be a case. Then, to identify characteristics independently associated with cases, we performed a multivariate logistic regression entering in the model all the variables significant in the univariate analysis.

Three-month, 6-month, and 3-yearoverall survival curves were estimated according to the Kaplan-Meier product-limitmethod. A comparison between survival curves was done using the log-ranktest.

We used multivariate Cox regression models to evaluate the impact on 6-monthand 3-yearsurvival of CT after admission in the supportive care unit after adjusting for other prognostic factors. We evaluated overall survival, defined as the interval between the date of admission into the unit and the date of death from any cause.

All tests were two-sided. Statistical significance was established at $p<0.05$. Analyses were conducted using Statistical Package for Social Sciences (Version 15.0.1, SPSS Inc. Chicago, IL).

Results

During the study period, 247 patients were recruited (Table 1). Mean Charlson comorbidity index was as high as 7 (range=4–15), indicating that the patients suffered severe and/ormultiple conditions. The median score of the PS was 2. A wide range of cancer diagnoses were represented; 44 patients (18 %) suffered primary local diseases, 104 (42 %) local recurrences, and 99 (40 %) metastatic diseases. Median time since diagnosis was 5.9 months (range=0.1–122). Since disease onset, more than two third of the patients (69.6 %) had received a first line of CT only. In the previous 3 months, patients had received various oncological treatments. At the admission, the majority of the patients had a progressive disease (66.5 %); a number of them had no more CT (40.5 %) or were receiving a first line of CT (34.8 %). Taken together, 147 patients (59.5 %) had CT at the admission. Main toxicities of current CT were mostly of low grade (Table 2).

The median CGI of the internist at the admission was as low as 3 (range=0–10). The oncologist's theoretical survival prognosis was estimated below 12 months in more than two third of the patients (Table 1).

At *discharge*, 124 patients (50 %) went home; 47 (20 %) needed further hospitalization (convalescence home in 31 patients and palliative care ward in 16); 22 patients (9 %) were transferred to an emergency ward (e.g., severe sepsis, renal insufficiency); and 54 (21 %) died during the current hospital stay.

At *3 months after admission*, 138 patients (55.9 %) of the initial sample (N=247) were still alive; of those, 93 (67.4 %) belonged to the group who received CT at the admission; and the other 45 (32.6 %) belonged to the group without CT at the admission (Fig. 1a). Twenty-threepatients (9.3 %) of the initial sample were still receiving CT. During this period, 15 patients (6.1 %) needed readmission related to CT's adverse effects.

At *6 months after admission*, 106 patients (42.9 %) of the initial sample were still alive; of those, 69 (65.1 %) belonged to the group who received CT at the admission, and the other 37 (34.9 %) to the group without CT at the admission (Fig. 1a). At this time of the follow-up, three patients (1.2 %) of the initial sample were still receiving CT. Between the 3rd and the 6th month of follow-up, eight patients (3.2 %) needed readmission related to CT's adverse effects.

From admission and throughout the follow-upperiod, 24 patients (9.7 %) had received CT during their last 14 days of

Table 1 Socio-demographic and clinical characteristics of the patients

	Number (%)	Median (range)
Gender		
Men	124 (50)	
Women	123 (50)	
Age		67 (21–91)
Length of stay (days)		26 (4–121)
Charlson comorbidity index		7.00 (4–15)
Performance status (admission)		2 (0–4)
Primary cancer site		
Lung	56 (22.7)	
Gastrointestinal	51 (20.6)	
Urogenital	19 (7.7)	
Breast	31 (12.6)	
Head and neck	27 (10.9)	
CNS	11 (4.5)	
Hematological	13 (3.3)	
Other	39 (15.8)	
Length of disease (months)		5.9 (0.1–122)
Past chemotherapy treatment		
1 line	172 (69.6)	
2–4 lines	64 (25.9)	
5+ lines	9 (3.6)	
Oncological treatment before inclusion (<3 months)		
Chemotherapy	138 (55.9)	
Radiotherapy	76 (30.8)	
Surgery	45 (18.2)	
Hormonotherapy	28 (11.3)	
Immunotherapy	7 (2.8)	
Status of oncological disease		
Progressive	157 (66.5)	
Stable	27 (11.4)	
Partial remission	20 (8.5)	
Complete remission	3 (1.3)	
Not evaluable	29 (12.3)	
Current chemotherapy		
No chemotherapy	100 (40.5)	
1st line	86 (34.8)	
2nd line	36 (14.6)	
3rd to 8th line	25 (10.1)	
Current radiotherapy	65 (26.3)	
Current combined chemotherapy and radiotherapy	51 (20.6)	
Physician global impression (0=worst; 10=excellent)		3.0 (0–10)
Theoretical survival prognosis		
<3 months	43 (17.4)	
3 to 6 months	45 (18.2)	
6 to 12 months	73 (29.6)	
1 to 5 years	67 (27.1)	

Table 1 (continued)

	Number (%)	Median (range)
>5 years	5 (2.0)	
Complete remission	4 (1.6)	

life. A new CT line was introduced in 18 patients (7.3 %) during their last 3 months of life; and 16 (6.5 %) had been transferred to acute care settings in the 3 days before their death.

Three-year overall survival was 20.4 % for the patients receiving CT at the admission (95 % CI 13.7–27.2) and 11.8 % for those without CT at the admission (95 % CI 5.8–17.9; *p* log-ranktest=0.001). Overall, 206 patients deceased, 97 among those 100 who did not receive CT at the admission and 109 among those 147 who did (Fig. 1b).

Univariate logistic regression analysis showed that the probability of receiving CT at the admission in the supportive care unit was significantly associated with the oncologist's theoretical survival prognosis. It was inversely associated with age, higher number of CT lines received before the admission, and a longer duration of the disease (Table 3). In the multiadjusted logistic regression, older age (odds ratio [OR] of receiving CT for patients ≥71 years vs. patients <50 years 0.19; 95 % CI 0.06–0.65; p=0.02) and higher number of CT lines received before the admission (OR for patients with 2 to 4 lines vs those with 1 line: 0.14; 95 % CI 0.06–0.34; p=0.000] remained independently inversely associated with the probability of receiving CT at the admission (Table 3). The type of cancer (lung, gastrointestinal, urogenital, breast, head and neck, CNS, hematological, and others) was not associated with the presence or absence of CT at the admission.

The univariate Cox regression analysis showed that survival at 6 months was significantly associated with the PS, receiving CT at the admission, the internist's CGI, the oncologist's theoretical survival prognosis, and the type of cancer (Table 4). In the multiadjusted model, including all the variables that were significant in the univariate analysis, survival at 6 months remained significantly associated with receiving CT at the admission (HR 1.86; 95 % CI 1.31–2.65; p=0.001), the CGI (per point HR 0.84; 95 % CI 0.73–0.96; p=0.013), and the theoretical survival prognosis (per category HR 0.53; 95 % CI 0.44–0.66; p=0.000) (Table 4).

The 3-yearoverall survival was also modelled. Variables associated with survival in univariate models were the same as for the 6-monthsurvival. In the multivariate model, again, survival was significantly associated with receiving CT at the admission (HR 1.55; 95 % CI 1.15–2.09; p=0.004], the CGI (per point HR 0.90; 95 % CI 0.81–0.99; p=0.036), the theoretical survival prognosis (per category HR 0.61; 95 % CI 0.51–0.72; p=0.000], and the type of cancer (p=0.023) (as compared to patients with lung cancer, the HR of patients with gastrointestinal cancer was 0.60; 95 % CI 0.40–0.91; for those with head and neck cancer, HR was 0.53; 95 % CI 0.28–1.00; and for those with hematological cancer, HR was 0.24; 95 % CI 0.10–0.59).

Table 2 Number (%) of patients experiencing hematological and gastrointestinal toxicities from current chemotherapy by worst Common Toxicity Criteria (CTC) grading

CTC grade	1+2	3+4
WBC	30 (12.1)	12 (4.9)
Hemoglobin	56 (22.7)	5 (2.0)
Platelets	15 (6.1)	2 (0.8)
Fever (grades 3–4 neutrophils)		10 (4.0)
Infections (grades 3–4 neutrophils)		6 (2.4)
Infections (normal ANC or grade 1 or 2 neutrophils)	43 (17.4)	10 (4.0)
Mucositis	42 (17.0)	5 (2.0)
Nausea	51 (20.6)	9 (3.6)

No thrombocytopenic bleeding. Transfusion=8 patients (3.3 %)

Discussion

This study sought to determine the aggressiveness in the use of CT in patients hospitalized in a supportive care unit. The results showed that most of our patients suffered from various incurable malignancies, recently diagnosed. At the time of their admission in the unit, more than two third of them were receiving a first line of CT. In-hospitalmortality rate during the current stay was 21 %. Increased odds of receiving CT at the admission was inversely associated with age and higher numbers of previous CT lines. In this group of patients, CT appeared as a feasible (few high-gradetoxicities) approach to improve survival. In the multiadjusted model, survival at 6 months and 3 years was significantly associated with receiving CT at the admission. To the best of our knowledge, this is the first study reporting this positive balance of CT in a group of incurable patients. During the follow-up, only about 9 and 1 % of the patients still received CT at 3 and 6 months, respectively.

Less than 10 % had received CT during their last 14 days of life and even fewer had been transferred to acute care settings in the 3 days before their death or had experienced major toxicities from CT. Extensive cancer care has been pointed out as a problem in various countries with patients receiving CT near the end of life [5, 9, 10]. However, our results are in the lower range of such aggressive care as the proportions can range up to 33 % or even 43 % [1, 11]. They are in line with the suggestions of the "blueprint for a better cancer care system" which emphasizes the noxious effect of treatment overuse [12].

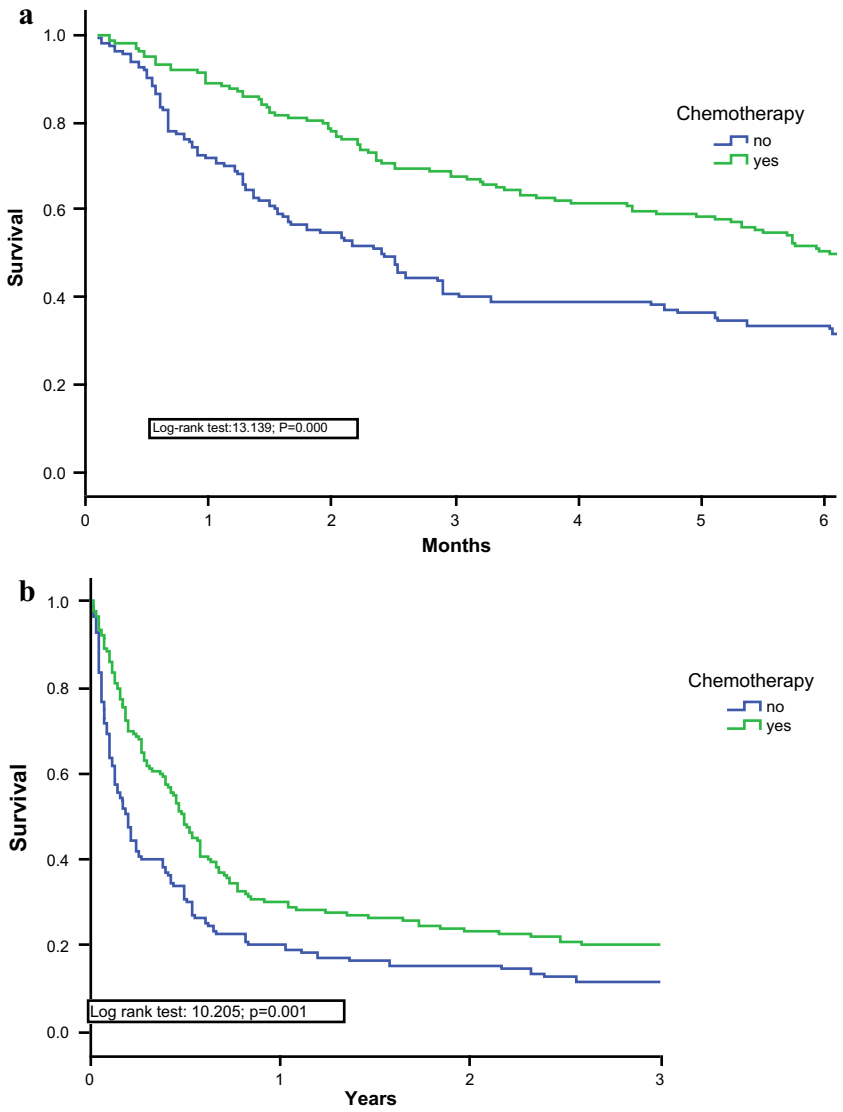

Fig. 1 **a** Six-month Kaplan-Meier survival curves in patients with and without chemotherapy at the admission in the supportive care unit. **b** Three-year Kaplan-Meier survival curves in patients with and without chemotherapy at the admission in the supportive care unit

The results also highlighted the predictive value of clinical judgment. Indeed, theoretical survival prognosis as estimated by the oncologist was significantly associated with the patient's survival at 6-monthand 3-year follow-upin the multivariate regression analyses. The clinical global impression of the internist also predicted the patient's survival at 6-months. These results may look like a contradiction, with the literature showing that doctors are mostly inaccurate when predicting patient survival, either overestimating [13, 14] or underestimating it [15]. While this study showed better predictions, some specificities of our setting need to be stressed. Throughout the study, theoretical survival prognosis was assessed at the admission by the same oncologist, experienced and trained to use standardized assessment procedures [8]. Both the theoretical survival prognosis and the clinical global impression were provided at the time of the admission of the patient; it may be hypothesized that the therapeutic relationship was not yet fully developed and that the results may have been different later on, showing more "medical activism" or emphasizing the patient-physiciancollusion that has been described to avoid discussing a possible death sentence [16]. Similarly, the CGI was provided independently of any decision of treatment and of any communication to the patient. It has been shown that doctors are often ambiguous when discussing treatment issues with the patient, e.g., leaving open misunderstandings between "treatments as possibly prolonging life" vs. "treatment as a cure" [16]. In our study, the timing and the setting of these assessments may thus account for at least part of the accuracy of the results.

Our results emphasize the value not only of clinical judgment which led to prescribe CT to those patients who could possibly benefit from the treatment, in terms of survival, but also of toxicities or of unexpected hospitalization. This is of importance as the decision to prescribe CT cannot rely only on characteristics such as age or comorbities [17].

Patients included in this study are representative of those requiring supportive care and hospitalized in the supportive

Table 3 Determinants of use of chemotherapy at admission in the supportive care unit. Univariate and multivariate logistic analysis

Variables	Odds ratio crude	95 % CI	*p*	Odds ratio adjusted[a]	95 % CI[a]	*p*[a]
Sex (women vs. men)	0.78	0.47–1.29	0.334			
Age			0.001			0.02
<50	1.00			1.00		
>50–70	0.96	0.42–2.18		0.71	0.23–2.25	
71+	0.37	0.16–0.84		0.19	0.06–0.65	
Charlson index (per additional point)	0.97	0.86–1.09	0.58			
Performance Status (per additional point)	0.74	0.56–1.00	0.048	0.99	0.86–1.67	0.293
Line of current chemotherapy (admission)			0.000			0.000
1	1.00			1.00		
2–4	0.24	0.13–0.45		0.14	0.06–0.34	
5+	0.06	0.01–0.51		–	–	
Clinical global impression (per point: 0–10)	1.13	0.99–1.29	0.069			
Theoretical survival prognosis (per category[b])	1.28	1.03–1.60	0.029	1.20	0.86–1.67	0.293
Length of disease (months)	0.99	0.98–1.00	0.036	1.01	0.99–1.3	0.204

[a] Odds are adjusted by age, Charlson index, Performance Status, line of current chemotherapy, Clinical global impression and length of disease

[b] Categories of prognosis: <3 months, 3–6 months, 6–12 months, 1 to 5 years, >5 years, and complete remission

care unit of the public and teaching hospital which is the major primary care hospital for the area. These patients presented heterogeneous characteristics. The age range was wide, although the median age suggested an elderly cohort of oncological patients; these patients were clearly polymorbid, suffering from various conditions other than oncological and affecting diverse organic systems; most of them presented with an advanced oncological disease, either progressive or metastatic; the oncological disease had been recently diagnosed however; and these patients were undergoing first-lineCT for a large part of them despite a theoretical survival prognosis of less than 6 months in more than a third of the

Table 4 Risk of death (HR) at 6 months of patients admitted in the supportive care unit according to clinical characteristics. Univariate and multivariate Cox regression analysis

Variables	Hazard ratio crude	95 % CI	*p*	Hazard ratio adjusted[a]	95 % CI	*p*
Sex (women vs. men)	0.98	0.71–1.36	0.895			
Age (per year)	1.01	0.99–1.02	0.440			
Charlson index (per point)	0.98	0.90–1.05	0.520			
Performance Status (per point)	1.37	1.12–1.67	0.002	0.98	0.80 – 1.21	0.879
Current chemotherapy (at admission, yes vs no)	1.82	1.31–2.52	0.000	1.86	1.31 – 2.65	0.001
Clinical global impression (per point: 0–10)	0.68	0.60–0.76	0.000	0.84	0.73 – 0.96	0.013
Theoretical survival prognostic (per change of category[b])	0.46	0.39–0.54	0.000	0.53	0.44 – 0.66	0.000
Length of disease (months)	1.01	1.00–1.01	0.156			
Cancer						
Lung	1.00		0.009	1.00		0.180
Gastrointestinal	0.60	0.37–0.96		0.65	0.40–1.06	
Urogenital	0.63	0.33–1.23		0.68	0.34–1.34	
Breast	0.87	0.51–1.48		1.13	0.64–2.01	
Head and neck	0.28	0.13–0.59		0.74	0.32–1.72	
CNS	0.62	0.28–1.38		0.57	0.24–1.35	
Hematological	0.21	0.07–0.68		0.31	0.09–1.02	
Other	0.84	0.51–1.39		1.09	0.63–1.88	

[a] Hazard ratios are simultaneously adjusted for performance status, current chemotherapy, clinical global impression, theoretical survival prognostic, and type of cancer

[b] Categories of prognosis: <3 months, 3–6 months, 6–12 months, 1 to 5 years, >5 years, and complete remission

cohort. The score of the ECOG-performancestatus indicated that the majority of the patients were capable of self-careand up and about more than 50 % of waking hours; as for the CT, most of the patients experienced low-gradetoxicities suggesting that the treatment was well tolerated. This heterogeneity in terms of age, comorbidities, and type and stage of cancer contrasts with the majority of clinical studies dealing with selected populations.

This heterogeneity increases the challenge of identifying patients for whom CT is both feasible and beneficial. An integrated model of care has been shown to improve treatment outcomes in selected types of cancer [2, 18–20]. In this study, care provided in the unit explicitly addressed the delivery of patient-tailoredcare but also coordination of care and treatment planning in the multidisciplinary team in order to avoid sequential decisions made in isolation by the various care providers. Our study shows that such a model may also benefit a heterogeneous polymorbid population by weighing carefully the risks and benefits of CT. It is noteworthy that survival up to 3 years remained significantly associated with receiving CT at the admission.

This study has limitations that need to be acknowledged. It was conducted in a single supportive care program in a tertiary care hospital thus limiting the generalization of the results to other settings. This study is a cohort study with no specific comparison group but we adjusted for variables important in the determination of the prescription of CT and for which we could control in the Cox analysis. However, we cannot exclude that other confounders for which we could not adjust may influence the results. Yet, the results of this study reflect "real life practice" insofar as all consecutive patients hospitalized in the supportive care program were included and followed-up. To assess the possibility to generalize our results in terms of the aggressiveness vs. benefits of CT, a randomized controlled design should be used, with an integrated model of care compared to standard oncologic care alone.

In conclusion, this study showed that an integrated model of care seems to benefit a heterogeneous population in that it contributes to assess the clinical risks and benefits of CT and in particular preventing aggressive care near death. In this group of polymorbid patients, such a model of care allowed to use CT with improved survival, few high-gradetoxicities, and few patients experiencing aggressive use of CT.

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Conflict of interest None.

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