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Reduced use of chemotherapy at the end of life in an integrated-care model of oncology and palliative care

Roberto Magarotto, Gianluigi Lunardi, Francesca Coati, Paola Cassandrini, Vincenzo Picece, Silvia Ferrighi, Luciana Oliosi, and Marco Venturini

Oncology Department, Ospedale Sacro Cuore-Don Calabria, Negrar (VR), Italy

ABSTRACT

Aims and Background. When there is little hope of a clinical benefit, too delayed a withdrawal from chemotherapy might be detrimental for a patient's quality of life. We evaluated appropriately timed cessation of chemotherapy in our Oncology Department after integration of a Supportive and Palliative Care Unit.

Methods. We carried out a review of deceased patients in our department from January 2006 to December 2009. Activities of the Supportive and Palliative Care Unit started in late 2007. We analyzed the characteristics of patients near the end of life and chemotherapy use within 30 days of death as an aggressiveness of cure index.

Results. During the considered period, 361 hospitalized patients died: 69 in 2006, 77 in 2007, 97 in 2008 and 118 in 2009; 102 never received chemotherapy. Sixty-one of the remaining 259 patients died within 30 days of the last drug administration. The percentage of patients receiving chemotherapy in their last 30 days fell from 19% in 2006 and 20% in 2007, to 16% in 2008 and 14% in 2009.

Conclusions. Supportive and Palliative Care Unit integration decreased chemotherapy use in the last 30 days of life. A careful evaluation of prognostic factors of advanced cancer patients and provision of appropriate supportive and palliative cares can reduce the use of futile anticancer chemotherapy and preserve a patient's qualify of life.

Introduction

Modern oncology includes, as a benchmark, the stop of chemotherapy in the last weeks of life in order to improve clinical practice. The National Cancer Policy Board of the USA has defined poor-quality care "when practices of known effectiveness are being under-utilized, when practices of known ineffectiveness are being over-utilized, and when services of equivocal effectiveness are being utilized in accordance with provider rather than patient preferences"[1].

Recently, some papers reported various percentages of the use of chemotherapy at the end of life in oncology patients. In an Australian study concerning two academic teaching oncology units with inpatients and home-based palliative care facilities[2], 18% of patients received chemotherapy in their last four weeks of life. In an Italian study, this incidence was 23%, taking into account patients in care at the Medical Oncology Unit of the University Hospital of Bologna and assisted at home by a non-profit association experienced in home care[3]. In the USA, Hui *et al.*[4,5] reported that 17% of patients admitted to an acute palliative care unit received chemotherapy (11% chemotherapy and 6% targeted agents) and had a median survival of 22 days. In another North American study, utilizing the Surveillance Epidemiology and End Results (SEER) data on the use of palliative chemotherapy in a terminal phase[6], the incidence was 18.5%. Other data reported 29% in a French study covering the years 2008-2009[7], 16% in a Canadian study for patients in the last 2 weeks of life[8], and 20% in a Finnish study of advanced breast cancer patients who continued with chemotherapy in the last month of life[9].

Key words: chemotherapy, end of life, palliative care.

Conflict of interest statement: None.

Correspondence to: Roberto Magarotto, MD, Oncology Department, Sacro Cuore-Don Calabria Hospital, Via Sempreboni 5, 37024 Negrar (VR), Italy.
Tel +39-045-6013549;
fax +39-045-6013411;
e-mail
roberto.magarotto@sacrocuore.it

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The reasons for this over-treatment are many. For instance, clinicians often overestimate prognosis in cancer patients who are approaching death. As claimed by the authors of a systematic review on this topic, "this optimism may have serious implications for patients in terms of inappropriate applications of disease-controlling treatment and delays in referral to palliative care"[10]. Another reason is the reticent information provided by physicians about the reality of disease that does not permit emergence of the patient's perspective, often very different from that presumed. Only receiving realistic information, about the different options of care and the likelihood of successful treatment or adverse effects, can the patient decide to undergo useless therapies[11]. Finally, integration between oncology and supportive and palliative care services is still poor and is often managed by separate non-communicating staff.

The present study analyzes the data of patients who died of advanced cancer in our Oncology Department, the chemotherapy time course, and the possible factors that help the prediction of an individual patient's life expectancy.

The primary aim of the study was to evaluate trends over time of the aggressiveness of cancer care near the end of life in our Oncology Department before and after the integration of a Supportive and Palliative Care (SPC) Unit by assessing the frequency of chemotherapy in the last days of life.

Methods

We used a retrospective cohort design for the study. We identified all patients who died from January 2006 to December 2009 at the Oncology Department of Sacro Cuore-Don Calabria Hospital (Negrar, Verona, Italy). In late 2007, the Department was officially implemented with the SPC Unit of Medical Oncology. The unit was dedicated to the care of patients symptomatic for advanced disease and patients near the end of their life. The unit, which conformed to the integrated-care model[12], was fully active at the beginning of 2008.

We collected and analyzed data regarding 361 patients at their last hospitalization. Patients had to have previously received chemotherapy at our department or to be in follow-up at our clinic without previous chemotherapy. Patients not previously followed by us had to have been evaluated by our oncologists about therapeutic and prognostic chances before admission.

Available information on patients near death were: age, gender, primary cancer type, sites of metastasis, performance status, blood chemistry and hematology, presence of anorexia and/or dyspnea, physician expected survival time, number of lines of chemotherapy, date of the last chemotherapy, prevalent cause of death.

The Palliative prognostic (PaP) score was evaluated, according to Pirovano *et al.*[13], at the beginning of the last cycle of chemotherapy.

We defined tumor chemosensitivity according to Kao *et al.*[2] and then classified tumors as highly sensitive (breast, small-cell lung, ovary, colorectal, hematological, testis, bladder, esophagus, head and neck) or poorly sensitive cancers (CNS, liver, kidney, pancreas, melanoma, stomach, prostate, thyroid, non-small cell lung, pleura, uterus). Based on drugs used, we classified chemotherapy either as cytotoxic (CT) or as targeted therapy (TT).

We recorded data by STATA software by means of which they were subsequently analyzed for descriptive statistics.

Results

Patients with advanced cancer who died in the study period were 361 (Table 1): 69 in 2006, 77 in 2007, 97 in 2008 and 118 in 2009. Median duration of hospitalization was 10 days (range, 1-67). Median patient age was 69 years (range, 25-97) and median ECOG performance status was 3. Fifty-nine percent of patients was males.

The prevalent solid tumor types were lung cancer (24%), breast cancer (13%), colorectal cancer (12%), pancreatic cancer (6%), gastric cancer (6%), bladder cancer (4%), ovarian cancer (4%), prostate cancer (4%), sarcoma (3%), kidney cancer (3%), and biliary tract cancer (3%). Prevalent metastatic sites, except for lymph nodes, were liver (50%), lung (31%), bone (28%), brain (14%), peritoneum (13%), pleura (6%) and adrenal gland 6%.

Table 1 - Characteristics of patients

	Years					
	2006-2007		2008-2009		Total	
	n = 146	%	n = 215	%	n = 361	%
Sex						
Men	85	58	127	59	212	59
Women	61	42	88	41	149	41
Age						
Median (range)	69 (34-98)		70 (25-94)		69 (25-98)	
<69 years	83	57	110	51	193	53
≥70 years	63	43	105	49	168	47
Primary tumor						
Gastroenteric	40	27	72	34	112	31
Genitourinary	32	22	28	13	60	17
Hematologic	6	4	7	3	13	4
Lung and pleura	30	21	58	27	88	24
Breast	23	16	24	11	47	13
Others	15	10	26	12	41	11
CT sensitivity						
High sensitivity	64	44	99	46	163	45
Low sensitivity	78	53	111	52	489	52
UKN sensitivity	4	3	5	2	9	2

In 316 patients (88%), the cause of death was clearly related to metastastic disease and the predominant causes of death were cardio-circulatory collapse in cachexia (29%), respiratory insufficiency (24%), liver failure (23%), endocranic hypertension (5%) and kidney failure (5%). In the remaining 45 patients (12%), death occurred for the following main causes: 11 patients of pulmonary embolism (24%), 9 patients of ictus cerebri (20%), 4 of hemorrhagic shock (9%), 3 patients of antibiotic-resistant pneumonia (7%), 2 patients of sepsis not correlated to neutropenia (4%), 3 patients of cardiac arrhythmia (7%) and 2 patients of heart attack (4%). Four patients died for septic shock in neutropenia correlated to chemotherapy (9%). A total of 102 patients (28%) died without ever having received chemotherapy [20 (29%) in 2006, 19 (25%) in 2007, 23 (24%) in 2008, and 40 (34%) in 2009].

Sixty-one patients died within 30 days of the last drug administration of chemotherapy, which consisted in CT for 58 patients and TT in 3 patients. The median age of this subgroup was 66 years (range, 34-84). The tumor sites were lung and breast in 20% of these patients, colon in 12%, pancreas in 7%, sarcoma and gastric cancer in 5% and others in smaller percentages. In particular, the 3 tumor sites for TT were colon, kidney and soft tissue sarcoma.

Prevalent causes of death were hepatic failure (36%), collapse in cachexia (30%), and pulmonary embolism (10%). Sudden death occurred in 3 patients (5%), and 4 patients (7%) died for toxicity from chemotherapy. All the 3 patients in TT died for collapse in cachexia.

The chemosensitivity of treated tumors in patients who died within 30 days of the last chemotherapy was low in 49% of patients and high in 51%. Seven patients were on therapy with oral drugs, whose administration had been prescribed more than 30 days before death.

To evaluate differences in this last cohort of patients after integration of the SPC Unit, we grouped data for the years 2006 and 2007 and for the years 2008 and 2009. Table 2 summarizes principal data of the 61 patients.

Twenty-nine patients out of 146 (20%) died in the years 2006-2007 and 32 out of 215 (15%) in the years 2008-2009, but the difference did not reach statistical significance (chi-squared test, $P = 0.215$). Figure 1 shows in detail the percentage for each year. A high number of lung and pleura cancers in the years 2008-2009 determined an increment in the percentage of male patients and of first-line chemotherapy. We analyzed the ECOG performance status at the last chemotherapy administration. Four patients (14%) out of 29 in the period 2006-2007 had ECOG performance status 1 or 2, whereas no patient had values below 2 in the period 2008-2009. The same percentage of patients (75%) had ECOG performance status 3 or 4 in the two periods. Tumor chemosensitivity and PaP score were not substantially different between the two periods.

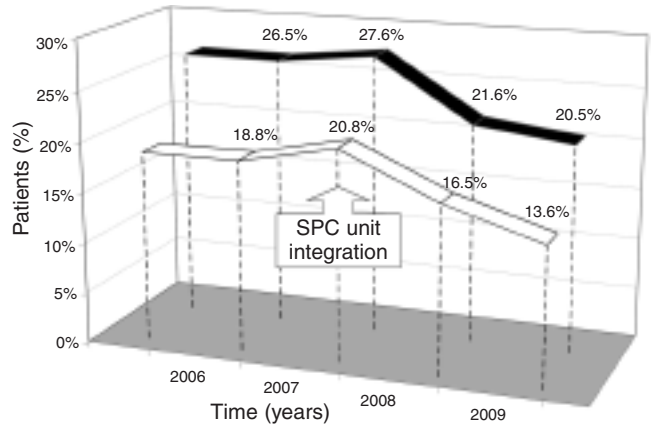

Figure 1 - By year percentage of dead patients who received chemotherapy during the last 30 days of their life (white line, percentage with respect to all patients; black line, percentage with respect to only patients who received chemotherapy). SPC, supportive and palliative care.

Discussion

We retrospectively evaluated the use of chemotherapy in patients near the end of their life and compared aggressiveness of cancer care before and after integration of the SPC Unit in our Oncology Department, conforming to the integrated-care model[12]. According to the literature, we considered overly aggressive care when the last chemotherapy regimen started within 30 days of death[1].

With the integrated care, we obtained a decrease from 20% to 15% of patients who received chemotherapy in the last 30 days of life. Several factors may be at the basis of the result reached after SPC Unit integration. For instance, the availability of the SPC Unit gave to the oncologist the continuity of care for the patient without recurring to useless chemotherapy. At the same time, patients and family members did not perceive the shift to palliative care as abandonment but as the better solution for a new step of the disease.

Finally, timely appropriate cessation of chemotherapy could be due to a more collegial discussion of the patient's prognosis among oncology and palliative physicians. Clinicians involved in palliative care and oncology should effectively work together in caring for patients with serious cancers. One important aspect of this cooperation is the difficulty in deciding to remove chemotherapy near the end of life. Patient's health, age, type of cancer, organs involved as well as the goals and adverse effects of treatment are important issues to take into account.

The real benefits of chemotherapy, i.e., the length of survival or the reduction of symptoms, should be thoroughly evaluated and compared to options such as hospice or palliative care. In fact, in some cases, chemotherapy might not prolong but rather shorten

life. For instance, a study of matched patients who received hospice care and no chemotherapy *versus* those who did not receive hospice care but had chemotherapy showed that survival was significantly longer for hospice patients with lung cancer and pancreatic cancer, marginally longer for colon cancer, and no different for patients with breast and prostate cancer[14]. Similar data were recently reported in non-small-cell lung cancer patients[15]. Patients receiving early palliative care had less aggressive care at the end of life and longer survival and significant improvements in both quality of life and mood compared to those patients who received standard care.

In our study, even after the integration of the SPC Unit, patients treated in their last month of life were in many cases (66%) at their first line of chemotherapy, given with the aim to obtain a palliative effect. However, these patients did not have to receive chemotherapy, because they had little chance of benefit and more chance of adverse effects, because 47% of them had poorly responsive tumors and 75% had a performance status of 3 or 4.

In our opinion, the use of the PaP score did not give useful adjunctive information to predict prognosis in our very advanced cancer patients. Only a small fraction of patients (Table 2) belonged to group C, i.e., patients with very poor chances to live more than 30 days. Most patients belonged to group B, i.e., patients with a 30-day probability survival between 30 and 70%, a score that is not very useful for the clinician who is uncertain about a patient's survival. This is probably due to the subjective "clinician prediction of survival score" contained in the scale and which accounts for about 50% of the total score. Therefore, performance status seems to remain a better objective score for the clinician to decide the path to take.

Of note is that the number of patients who received at the end of their life palliative care after the Unit integration increased from 146 in the years 2006-2007 to 215 in the years 2008-2009. This increment reflects the increased continuity of supportive care given by the Unit in very advanced cancer patients. This continuity of care probably led the terminally ill patients, or their family, to choose the same available interdisciplinary structure able to cope with their physical, psychological, spiritual and religious needs.

Palliative care has been defined by WHO as "the prevention and relief of suffering in all its forms: physical, psychological, social and spiritual"[16]. This definition implies that palliative care is applicable across the spectrum of cancer, from the moment of diagnosis throughout all courses of illness, and not merely at the end of life. An international effort to calibrate the oncology of the new millennium is the integration of palliative care in the vision of comprehensive cancer care[17-19].

There has been a considerable progress to have a routinely and readily available comfort-focused care in hospitals and health systems. The target is the implementation of simultaneous care: "progressive palliative care, not crisis management at the end of life"[20]. In Italy, the AIOM (*Associazione Italiana di Oncologia Medica*) believes that "the mission of medical oncology should follow the non-abandonment culture, guaranteeing quality of life and continuity of care to all cancer patients at every step of the disease, always considering the patient and not the disease the most important target"[21].

The European Society for Medical Oncology (ESMO) has a specific program for integration of Oncology and Palliative care[22] and, since 2003, 73 cancer centers have been recognized as Integrated Centers of Oncology and Palliative Care. ESMO recognized our SPC Unit as a center of excellence in palliative care for cancer patients in September 2009.

Table 2 - Characteristics of patients who received chemotherapy during the last 30 days of their life

	Years					
	2006-2007		2008-2009		Total	
	n = 29	%	n = 32	%	n = 61	%
Sex						
Men	13	45	22	69	35	57
Women	16	55	10	3	26	43
Age						
Median (range)	64 (34-84)		67 (50-80)		66 (34-84)	
<69 years	21	72	20	62	41	67
≥70 years	8	28	12	38	20	33
Primary tumor						
Gastroenteric	8	28	8	25	16	26
Genitourinary	5	17	2	6	7	11
Hematologic	3	10	2	6	5	8
Lung and Pleura	3	10	9	28	12	20
Breast	6	21	6	19	12	20
Others	4	14	5	16	9	15
CT sensitivity						
High sensitivity	14	48	15	47	29	48
Low sensitivity	15	52	17	53	32	52
Line of CT						
1st	13	45	21	66	34	56
2nd-3rd	13	45	9	28	22	36
more than 3rd	3	10	2	6	5	8
ECOG performance status						
0-1	4	14	0	0	4	7
2	3	10	8	25	11	18
3-4	22	76	24	75	46	75
PaP score						
A (30 days survival probability >70%)	7	24	7	22	14	23
B (30 days survival probability 30-70%)	20	69	20	62	40	66
C (30 days survival probability <30%)	2	7	5	16	7	11

In summary, integration of the SPC Unit in the oncology department decreased the number of patients who died within 30 days of the last chemotherapy and probably introduced better supportive treatments. However, even after integration of the Unit, clinicians continued to give chemotherapy to very advanced cancer patients, notwithstanding poor tumor chemosensitivity or low patient performance status. Namely, most of these patients never received previous treatments and chemotherapy was likely administered as an attempt to obtain palliative care. With the aim to increase quality of life in patients near their end of life, future efforts are required to select those patients who have very advanced cancer but who never received previous treatments, to direct them towards more appropriate palliative care instead of useless palliative chemotherapy.

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