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La cessation de la chimiothérapie pour le traitement de l'adénocarcinome pancréatique avancé: recherche de facteurs prédictifs de mort imminente.

THESE

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par

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La cessation de la chimiothérapie pour le traitement de l'adénocarcinome pancréatique avancé: recherche de facteurs prédictifs de mort imminente.

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Dans cette étude rétrospective, nous reportons des données relatives à la chimiothérapie chez des patients atteints d'adénocarcinome pancréatique avancé, avec attention à la durée du temps qui passe entre le dernier traitement et la mort. En outre, nous analysons des paramètres cliniques et de laboratoire, enregistrés à la dernière chimiothérapie, avec le but d'identifier des facteurs de risque pour un décès proche.

L'analyse rétrospective est effectuée sur des patients avec adénocarcinome pancréatique avancé, qui ont bénéficié au moins d'une ligne de chimiothérapie. Nous avons enregistré les données concernant la chimiothérapie (régimes, lignes et date de la dernière administration) et avons choisi et enregistré des facteurs cliniques et de laboratoire, qui étaient récoltés à la dernière chimiothérapie (performance status, présence d'ascite, hémoglobine, leucocytes, plaquettes, bilirubine totale, albumine, LDH, protéine C-réactive et Ca19-9). Des analyses statistiques (univariée et multivariée) sont effectuées pour étudier la relation entre ces facteurs et le temps de survie, à la recherche de facteurs prédictifs de mort imminente.

Nous avons analysé les données de 231 patients: hommes/femmes, 53/47%; métastatique/localement avancé, 80/20%; âge médian 66 ans (gamme 32-85). Tous les patients sont décédés à cause de la progression de la maladie. La survie globale médiane est 6.1 mois (95% CI 5.1-7.2). Lors de la dernière chimiothérapie, le performance status est 0-1 pour 37% et 2 pour 63% des patients. Cinquante-neuf pour cent des patients reçoivent une ligne de chimiothérapie, 32, 8 et 1% reçoivent des chimiothérapies de deuxième, troisième, quatrième ligne, respectivement. L'intervalle entre la dernière administration de chimiothérapie et le décès est <4 semaines pour 24%, 4-12 semaines pour 47% et >12 semaines pour 29% des patients. La survie médiane à partir de la dernière chimiothérapie jusqu'au décès est 7.5 semaines (95% CI 6.7-8.4). L'ascite, la leucocytose, des valeurs élevées de bilirubine, LDH, protéine C-réactive et Ca19-9, et des valeurs abaissées d'albumine sont associés à une survie plus courte à l'analyse univariée; néanmoins, aucun de ces facteurs n'est corrélé à la survie de façon significative à l'analyse multivariée.

Nous en concluons qu'une proportion significative de patients avec adénocarcinome pancréatique avancé reçoit la chimiothérapie dans le dernier mois de vie, et que les paramètres cliniques et de laboratoire enregistrés à la dernière chimiothérapie ne prédisent pas une survie plus courte.

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ORIGINAL ARTICLE

Chemotherapy in patients with advanced pancreatic cancer: too close to death?

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Abstract
Purpose We evaluated the attitude in using chemotherapy near the end of life in advanced pancreatic adenocarcinoma (PAC). Clinical and laboratory parameters recorded at last chemotherapy administration were analyzed, in order to identify risk factors for imminent death.
Methods Retrospective analysis of patients who underwent at least one line of palliative chemotherapy was made. Data concerning chemotherapy (regimens, lines, and date of last administration) were collected. Clinical and laboratory factors recorded at last chemotherapy administration were: performance status, presence of ascites, hemoglobin, white blood cell (WBC), platelets, total bilirubin, albumin, LDH, C-reactive protein (C-rp), and Ca 19.9.
Results We analyzed 231 patients: males/females, 53/47 %; metastatic/locally advanced disease, 80/20 %; and median age, 66 years (range 32–85). All patients died due to disease progression. Median overall survival was 6.1 months (95 % CI 5.1–7.2). At the last chemotherapy delivery, performance status was 0–1 in 37 % and 2 in 63 %. Fifty-nine percent of patients received one chemotherapy line, while 32, 8, and 1 % had second-, third-, and fourth line, respectively. The interval between last chemotherapy administration and death was <4 weeks in 24 %, ≥4–12 in 47 %, and >12 in 29 %. Median survival from last chemotherapy to death was 7.5 weeks (95 % CI 6.7–8.4). In a univariate analysis, ascites, elevated WBC, bilirubin, LDH, C-rp and Ca 19.9, and reduced albumin were found to predict shorter survival; however, none of them remained significant in a multivariate analysis.
Conclusions A significant proportion of patients with advanced PAC received chemotherapy within the last month of life. The clinical and laboratory parameters recorded at last chemotherapy delivery did not predict shorter survival.

Keywords Pancreatic cancer · Palliative chemotherapy · End of life · Aggressiveness

Introduction

Pancreatic adenocarcinoma (PAC) is one the most lethal malignancies and the fourth leading cause of cancer-related death in USA in 2010 [1]. Prognosis for patients with locally advanced or metastatic disease is poor. In advanced PAC, chemotherapy increases survival compared to best supportive care (BSC). However, the lack of standardized protocols of BSC represents a methodologic limitation in interpreting this finding [2, 3]. In 1997, gemcitabine was found to improve both median overall survival (OS, 5.65 vs 4.41 months, p0 0.0025) and clinical benefit response (23.8 vs 4.8 %, p0 0.0022) compared to 5-fluorouracil [4]. Gemcitabine-based regimens failed to demonstrate a significant or clinically relevant improvement in OS over gemcitabine alone. Recently, the FOLFIRINOX regimen significantly improved OS over single-agent

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gemcitabine (11.1 vs 6.8 months, $p<0.001$) in patients with metastatic disease, good performance status (PS), and normal bilirubin [5]. Currently, there is no accepted standard for gemcitabine refractory patients. An OS advantage has been reported using an oxaliplatin-based regimen compared to BSC [6].

To date, the use of palliative chemotherapy is increasing due to the availability of more drugs and a wider range of indications [7]. Many oncologists consider chemotherapy near the end of life (EoL) as aggressive and typically unnecessary. On the other hand, patients have to face the difficult decision of chemotherapy near the EoL: such treatment may prolong survival and/or reduce their symptoms; however, it may cause adverse effects, such as increasing toxicity, preventing patients from preparing to die, accelerating hospitalization and emergency department visits, precluding entry into palliative care services, and increasing costs. The time when it is more appropriate to discontinue chemotherapy is often a difficult decision, given that patients', family members', and physicians' attitude is substantially different. Prescription of new anticancer therapies or the prolonging of the ongoing treatments near the EoL emerged as one of the most relevant factors poorly influencing the quality of care [8]. In unresectable PAC, some prognostic factors such as Ca 19.9 value, stage of disease, and treatment modality are identified as independent factor to worsen OS [9]. In addition, PS, peritoneal carcinomatosis, and C-reactive protein (C-rp) were identified as prognostic factors in gemcitabine refractory patients [10].

Most of data relating to the use of chemotherapy at the EoL arise from trials involving patients with various cancer types. Here, we aimed to describe the patterns of the use of chemotherapy in a cohort of patients with advanced PAC who died due to disease progression. In particular, the study's objective was to determine the proportion of patients receiving chemotherapy according to the time between the last chemotherapy administration and death, and treatment line. Moreover, in order to identify survival predictors in this specific setting, we analyzed clinical and biochemical variables recorded at the last delivery of chemotherapy and their independent value as prognostic factors for survival.

Patients and methods

Study population

Inclusion criteria in this retrospective study conducted at the Oncology Institute of Southern Switzerland were: (1) biopsy diagnosed as locally advanced or metastatic PAC and treated was analyzed for this study; (2) patients underwent at least one line of palliative chemotherapy; and (3) patients died due to progressive disease. Approval for the study was obtained from the institutional review board of the Oncology Institute of Southern Switzerland. All patients provided an informed consent.

Data collection

The Oncology Institute of Southern Switzerland database provided all patients' clinical charts and all the following data: (1) *patients characteristics at diagnosis*: age, gender, Eastern Cooperative Oncology Group (ECOG) PS, stage of disease, primary tumor location, number of metastatic sites, Ca 19.9, and weight loss; (2) *treatment characteristics*: number of chemotherapy lines, chemotherapy regimens, and time of last administration of chemotherapy before death (divided in three periods: <4 weeks, 4 to 12 weeks, and >12 weeks), according to the chemotherapy line; and (3) *clinical and laboratory parameters recorded at the last administration of chemotherapy*: ECOG PS, presence of ascites, white blood cell (WBC), hemoglobin (Hb), platelets (PLT), total bilirubin, albumin, LDH, C-rp, and Ca 19.9. These variables were selected because they have been found to be of prognostic significance in patients with terminal cancer [11]. The relationship between chemotherapy patterns and clinical and laboratory parameters, recorded at the last chemotherapy delivery, and survival time were examined using uni- and multivariate analyses.

Statistical analysis

For descriptive purposes, continuous variables were summarized as medians, and categorical variables as proportions with 95 % CI. Inferential comparisons were carried out by t or Mann–Whitney U test according to data determined by the Kolmogorov–Smirnov test. Fisher exact test was utilized to assess significance among categorical variables. Statistical significance was determined as $p<0.05$ with a two-sided test. OS was calculated from diagnosis to death. Survival from last chemotherapy delivery to death was calculated. Both survival variables were analyzed with the Kaplan–Meier method, while comparisons among subgroups were performed with log rank test. For survival analysis purposes, all variables were dichotomized. Statistically significant and borderline significant variables ($p<0.1$) were included in the Cox regression analysis. All statistical analyses were performed using SPSS software package version 15 (SPSS Inc, Chicago, IL).

Results

From 1993 to 2010, 231 patients with advanced PAC were identified (Table 1). The median age was of 66 years and 53 % were males. Tumor was localized to the head in 55 %

Table 1 Patients characteristics at diagnosis

	N (%)	Median OS	*p* value	95 % CI
Patients	231 (100)			
Median age (range)	66 years (32–85)			
Sex				
Males	123 (53)	6.14		4.74–7.54
Females	108 (47)	6.27	0.30	4.60–7.94
PS (ECOG)				
0	68 (30)	9.3		5.61–12.98
1–2	163 (70)	4.9	<0.001	3.79–6.12
Setting				
Metastatic	185 (80)	5.7		4.71–10.39
Locally advanced	46 (20)	7.5	0.24	4.54–6.95
Tumor location				
Head	126 (55)	6.7		5.62–7.84
Body–tail	105 (45)	4.9	0.84	3.49–6.43
Liver metastases				
Yes	147 (67)	4.8		3.56–6.22
No	84 (37)	7.7	0.009	5.77–9.66
Sites of metastases				
1	191 (83)	6.7		5.61–7.85
≥2	40 (17)	3.7	0.068	1.72–5.69
Weight loss				
Yes	107 (46)	5.38		4.27–6.49
No	124 (54)	6.73	0.47	5.55–7.91

OS overall survival (in months), *PS* performance status (ECOG)

of patients, and most of the patients presented with metastatic disease. The median value of CA19.9 was 532 (range 0–972,000), while the median OS was 6.1 months (95 % CI 5.1–7.2).

The status of chemotherapy lines before death is summarized in Table 2. In details, first line was the only treatment in approximately 60 % of patients (single-agent gemcitabine in 70 %, gemcitabine-based combinations or fluoropyrimidine in 30 %). About one third of patients received second line (either fluoropyrimidine- or gemcitabine-based regimens), while 9 % were treated with third- and fourth line (either single agents or within phase I trials).

The median survival from last chemotherapy administration to death was 7.5 weeks (range 0.43–75.5; 95 % CI 6.7–8.4). Approximately 24 % of patients received last chemotherapy within 4 weeks before death (Table 3); among them, the last dose of chemotherapy was given within 2 weeks before death in 7 %. With respect to chemotherapy during the last month of life, two periods of time (from 1993 to 2003 and from 2004 to 2010) were observed separately: 32 out of 108 (30 %) patients were treated in the first period, compared to 27 out of 123 (22 %) patients in the second one. Thirty-six out of 55 (65 %) patients who died within 4 weeks before the last chemotherapy administration were in first line.

Observing the last chemotherapy delivery, ECOG PS was 0–1 in 38 % and 2 in 62 %, respectively. Ascites was present in 41 % of cases. Furthermore, median values for laboratory parameters were: WBC 7.9×10^9/L, Hb 10.5 g/dl, PLT 212×10^9/L, total bilirubin 12.7 μmol/L, albumin 33 g/L, LDH 440 U/L, C-rp 37 mg/L, and Ca 19.9 2,125 U/mL. At univariate analysis, presence of ascites, elevated WBC, bilirubin, LDH, C-rp, and Ca 19.9 and reduced albumin were found to predict shorter survival. However, none of them emerged as independent predictors of survival at multivariate analysis (Table 4).

Table 2 Last line of chemotherapy before death

Chemotherapy line	No. of patients (%)
First	137 (59.3)
Second	74 (32)
Third	18 (7.8)
Fourth	2 (0.9)

Table 3 Number of patients treated according to the time between the last administration of chemotherapy and death

Time (weeks)	No. of patients (%)
<4	55 (23.8)
4–12	109 (47.2)
>12	67 (29)

Table 4 Characteristics at last administration of chemotherapy: uni- and multivariate analysis

	N (%)	Median OS	Univariate		Multivariate	
			p value	95 % CI	*p* value	HR
Age						
<66 years	112 (48)	7.5		6.12–9.01		
≥66 years	119 (52)	7.5	0.69	6.29–8.84		
PS (ECOG)						
0–1	85 (37)	8.2		6.27–10.29		
2	139 (63)	6.8	0.19	6.12–9.01		
Ascites (*n*0226)						
Yes	92 (41)	6.0		4.32–7.67		
No	134 (59)	8.5	0.055	6.85–10.29	0.173	0.609
WBC (*n*0219)						
$<11\times10^9$/L	161 (73)	8.2		6.80–9.76		
$\geq11\times10^9$/L	58 (27)	4.4	0.003	3.22–5.62	0.649	1.213
Hb (*n*0217)						
<10 g/dL	34 (16)	8.0		5.75–10.24		
≥10 g/dL	183 (84)	7.4	0.72	6.38–8.47		
PLT (*n*0219)						
$<400\times10^9$/L	190 (87)	7.5		6.60–8.53		
$\geq400\times10^9$/L	29 (13)	7.0	0.83	3.73–10.26		
Bilirubin (*n*0207)						
<34 mol/L	189 (91)	7.7		6.94–8.48		
≥34 mol/L	18 (9)	4.4	0.002	3.83–5.01	0.498	1.472
Albumin (*n*0145)						
<35 g/L	88 (61)	6.7		5.27–8.15		
≥35 g/L	57 (49)	7.8	0.023	5.14–10.57	0.693	0.854
LDH (*n*0183)						
<500 U/L	121 (66)	7.7		5.73–9.69		
≥500 U/L	62 (34)	6.0	0.025	3.79–8.20	0.145	1.761
C-rp (*n*0148)						
<5 mg/L	16 (11)	13.5		4.05–23.09		
≥5 mg/L	132 (89)	6.5	0.005	5.36–7.77	0.092	3.945
Ca 19.9 (*n*0121)						
<1,000 U/mL	44 (36)	8.3		3.95–12.61		
≥1,000 U/mL	77 (64)	8.1	0.035	6.17–10.10	0.300	0.671

OS overall survival (in weeks), *PS* performance status (ECOG), *WBC* white blood cell, *Hb* hemoglobin, *PLT* platelets, *C-rp* C-reactive protein

Discussion

The role of chemotherapy near the EoL is a complex issue. Its administration at life's end involves a proper oncological assessment, a focused attention toward the patient's goals of care, and a balancing of perspectives of the patient and treating oncologist. While there is no accepted medical definition of futile care, chemotherapy may be overused in terminally ill cancer patients, despite its little chance of benefit. Most of available data on this matter are offered by retrospective population or institution-based death-centered studies [12–19]. Within this body of evidence, the concept of futility could particularly apply in advanced PAC, an overly aggressive neoplasm, which rapidly tends to be unresponsive to chemotherapy.

The main goal of our study was to report the patterns of chemotherapy use in patients who died for advanced PAC. Out of the 231 patients analyzed, a substantial proportion (24 %) of them received chemotherapy in the last month of life. There are limited data in this specific setting. In a lesser extent but increasing over time (from 8.1 to 16.4 % in 1992–1994 and 2004–2006, respectively), also others reported a significant use of chemotherapy in the last month [20]. In our study, according to the analysis of two different periods of time including a rather balanced number of patients, we can speculate that both the implementation of early

symptoms control strategies and the improved communication between oncologists, palliative care givers, patients, and their families may account for the inverse trend in use of chemotherapy during the last month of life. Another explanation of the inverse trend is that many oncologists are reluctant to prescribe chemotherapy at the EoL, especially in aggressive neoplasms [21].

In our study, 65 % of patients who died within 4 weeks before last chemotherapy administration were in first line. In a way, this finding is somewhat cumbersome and underlies the need of more accurate tools for adequate patient selection. Moreover, 7 % of patients received chemotherapy in the last 2 weeks of life. Related to this, health care systems who do not provide overly aggressive care would be ones in which less than 10 % of patients receive chemotherapy in the last 14 days of life [22]. Conversely, in our cohort, almost 30 % of patients did not receive chemotherapy during the last 3 months of life, which could reflect the effort to both optimize the chemotherapy use and supportive resources.

Similar to other solid neoplasms, chemotherapy prolongs survival also in advanced PAC [2]. Therefore, the crucial issue is not if but rather until when chemotherapy should be administered. Multiple factors may account for the increased use of chemotherapy near the EoL, and the mutual physician–patient relationship heavily influences the final therapeutic process. From the patient's perspective, keeping up faith and hope is an important defensive mechanism, in where chemotherapy "fights" against the disease. Moreover, if patients with advanced cancer are given truthful prognostic and treatment information, even if they are bad, their hope to fight cancer is kept alive [23].

However, doctors may interfere with hopefulness by offering patients with a wide range of outcomes over which patients usually choose the most favorable one [24]. Many patients choose chemotherapy to have a small clinical benefit, and its adverse effects become a minor concern for patients [25]. Physicians also play a critical role for the assessment of late-stage chemotherapy. Doctors' survival predictions are not always accurate, and overestimation of survival by at least 4 weeks has been reported in 27 % of cases [26–28]. Emotionally difficult and painful discussions between physicians and patients on prognosis are also a delicate factor in determining the therapy. Managing the transition to palliative care when chemotherapy is failing is difficult, particularly due to barriers in communication between patients and doctors. For instance, the oncologist may respond to patient and/or family distress by agreeing to an additional round of chemotherapy, which turns out to be the optimal solution rather than "doing nothing." Although this may temporarily solve the problem, it evades the real issue of cancer progression and displaces any EoL planning. At times, chemotherapy is temporarily suspended until the patient "gets stronger." This approach does allow an oncologist to avoid critical issues, including death, treatment failure, and loss of hope for survival, enabling patients and families to realistically plan their limited time left [29]. Yet, the most important determinant for the decision is the medical oncologist [30]: those without communication skills are more likely to prescribe third- and fourth-line chemotherapy, impacting negatively on the quality of life of the patient and its costs [31].

Objective indicators near the EoL may help to establish a realistic survival estimate, in order to prevent inappropriate therapies and to avoid unnecessary toxicity to the patient. Thus, we aimed to identify clinical and laboratory parameters that could predict shorter survival and, consequently, indicate whether it is more appropriate for the patients to terminate chemotherapy. While early-stage tumor prognosis is typically based on histopathological findings and tumor stage, prognosis for advanced malignancies necessitate additional parameters. Review of literature indicates that the PS and indices of activity and functional autonomy are major predictors of outcome. In addition, signs and symptoms that often characterize the terminal phase (anorexia, cachexia, weight loss, dysphagia, difficulty in swallowing, xerostomia dyspnea, and delirium or cognitive impairment) have a prognostic impact. Among the laboratory parameters, low pseudocholinesterase, high vitamin B12, high bilirubin, elevated C-rp, lymphocytopenia, and leukocytosis have also a prognostic significance [32]. Among the 11 clinical and laboratory parameters analyzed in our study, a positive correlation of poor survival was identified in presence of ascites, low serum albumin, and elevated leucocyte count, bilirubin, LDH, C-rp, and Ca 19.9. However, none of these parameters were found to be independent prognostic factors at multivariate analysis.

In a systematic review of 53 trials involving patients with uncurable cancer, some factors associated with survival were organized into four categories according to attributes of the host, the tumor, the treatment, and the interactions between the host, tumor, and treatment (symptoms, quality of life, PS, and laboratory tests). PS, anemia, thrombocytopenia, hypoalbuminemia, and elevated serum levels of both alkaline phosphatase and LDH were associated with shorter survival [33]. Similar data were reported by others in end-stage disease [11]. Particularly for advanced PAC, pretreatment serum CA 19-9 concentration is an independent prognostic factor for survival [34]. Interestingly, in a recently published prospective study in terminally ill cancer patients, the PS, LDH, lymphocyte count, serum albumin, and time from initial diagnosis to diagnosis of terminal disease were found to be independent prognostic factors of survival and formed the basis of a nomogram [35].

The retrospective feature of our study represents a major limitation, as it relies on the accuracy of the hospital records.

For instance, patients' symptoms, which are considered another potential factor influencing the use of palliative chemotherapy, were not included in the analysis as they were not properly collected. Another limitation of this study is the lack of information on other validated indicators for care quality at EoL, namely the intensive care unit admission, emergency department visits, inpatients hospital admissions, and underuse of palliative care service [8, 22].

In conclusion, our study identified that a significant proportion of patients with advanced PAC received chemotherapy near the EoL. As data in this setting are limited, we believe that our experience offers the opportunity to reexamine how care is delivered at the EoL in this specific condition. Implications of these findings for everyday practice are that every patient must be individually assessed before each chemotherapy administration. Prognostic tools are needed in order to help oncologists whether the patient is fit enough for further chemotherapy and likely to survive long enough to benefit from the treatment, but realistically it is difficult to set up. More importantly, efforts are underway to early integrate palliative services into a comprehensive cancer care plan, in order to optimize the quality and outcome of EoL care.

Conflict of interest There are no conflicts of interest to declare.

References

1. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics. Cancer J Clin 60:277–300
2. Sultana A, Smith CT, Cunningham D et al (2007) Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 25:2607–2615
3. Cherny NJ, Abernethy AP, Strasser F et al (2009) Improving the methodologic and ethical validity of best supportive care studies in oncology: lessons from a systematic review. J Clin Oncol 27:5476–5486
4. Burris HA 3rd, Moore MJ, Andersen J et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
5. Conroy T, Desseigne F, Ychou M et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
6. Pelzer U, Schwaner I, Stieler J et al (2011) Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer 47:1676–1681
7. 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
8. Earle CC, Park ER, Lai B et al (2003) Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol 21:1133–1138
9. Park JK, Yoon YB, Kim YT et al (2008) Survival and prognostic factors of unresectable pancreatic cancer. J Clin Gastroenterol 42:86–91
10. Nakachi K, Furuse J, Ishii H et al (2007) Prognostic factors in patients with gemcitabine-refractory pancreatic cancer. Jpn J Clin Oncol 37:114–120
11. Viganó A, Bruera E, Jhangri GS et al (2000) Clinical survival predictors in patients with advanced cancer. Arch Intern Med 160:861–868
12. Earle CC, Ayanian JZ (2006) Looking back from death: the value of retrospective studies of end-of-life care. J Clin Oncol 24:838–840
13. Näppä U, Lindqvist O, Rasmussen BH et al (2011) Palliative chemotherapy during the last month of life. Ann Oncol 11:2375–2380
14. Emanuel EJ, Young-Xu Y, Levinsky NG et al (2003) Chemotherapy use among Medicare beneficiaries at the end of life. Ann Intern Med 138:639–643
15. O'Brien ME, Borthwick A, Rigg A et al (2006) Mortality within 30 days of chemotherapy: a clinical governance benchmarking issue for oncology patients. Br J Cancer 95:1632–1636
16. Andreis F, Rizzi A, Rota L et al (2011) Chemotherapy use at the end of life. A retrospective single centre experience analysis. Tumori 97:30–34
17. 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. Psychooncology 16:863–868
18. Goncxalves J, Goyanes C (2008) Use of chemotherapy at the end of life in a Portuguese oncology center. Support Care Cancer 16:321–327
19. Keam B, Oh DY, Lee SH et al (2008) Aggressiveness of cancer-care near the end-of-life in Korea. Jpn J Clin Oncol 38:381–386
20. Sheffield KM, Boyd CA, Kuo Y-F et al (2011) End-of-life care in Medicare beneficiaries dying with pancreatic cancer. Cancer 117:5003–5012
21. Behl D, Jatoi A (2010) What do oncologists say about chemotherapy at the very end of life? Results from a semiquantitative survey. J Palliat Med 13:831–835
22. Earle CC, Neville BA, Ladrum MB et al (2005) Evaluating claims-based indicators of the end-of-life cancer care. Int J Qual Health Care 17:505–509
23. Smith TJ, Dow LA, Virago E et al (2010) Giving honest information to patients with advanced cancer maintains hope. Oncology 24:521–525
24. Helft PR (2005) Necessary collusion: prognostic communication with advanced cancer patients. J Clin Oncol 23:3146–3150
25. Matsuyama R, Reddy S, Smith TJ (2006) Why do patients choose chemotherapy near end of life? A review of the prospective of those facing death from cancer. J Clin Oncol 24:3490–3496
26. Christakis N, Lamont E (2000) Extent and determinants of error in doctors' prognoses. Br Med J 320:469–473
27. Vigano A, Dorgan M, Buckingham J et al (2000) Survival prediction in terminal cancer patients: a systematic review of the medical literature. Palliat Med 14:363–374
28. Glare P, Virik K, Jones M et al (2003) A systematic review of physicians' survival predictions in terminally ill cancer patients. Br Med J 327:195–200
29. Maguire P (1985) Barriers to psychological care of the dying. Br Med J (Clin Res Ed) 291:1711–1713
30. Kao S, Shafiq J, Vardy J, Adams D (2009) Use of chemotherapy at end of life in oncology patients. Ann Oncol 20:1555–1559
31. Thorne SE, Bultz BD, Baile WF et al (2005) Is there a cost to poor communication in cancer care?: a critical review of the literature. Psychooncology 14:875–884
32. Maltoni M, Caraceni A, Brunelli C et al (2005) Prognostic factors in advanced cancer patients: evidence-based clinical

recommendations—a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 23:6240–6248
33. Hauser CA, Stockler MR, Tattersall MHN (2006) Prognostic factors in patients with recently diagnosed incurable cancer: a systematic review. Support Care Cancer 14:999–1011
34. Hess V, Glimelius B, Grawe P et al (2008) CA 19-9 tumor marker response to chemotherapy in patients with pancreatic cancer enrolled in a randomized controlled trial. Lancet Oncol 9:132–138
35. Feliu J, Jiménez-Gordo AM, Madero R et al (2011) Development and validation of a prognostic nomogram for terminally ill cancer patients. J Natl Cancer Inst 103:1613–1620