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RESEARCH ARTICLES

Limited impact of palliative chemotherapy on survival in advanced solid tumours in patients with poor performance status

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Abstract
Aim Oncologists should carefully weigh up the risks and benefits of palliative chemotherapy in patients with advanced solid tumours (AST) and poor general status from the standpoint both of medical and ethical issues and of healthcare resources required. This study is intended to assess the impact on overall survival of palliative chemotherapy in patients with AST and admitted to hospital as a result of their poor ECOG status.
Materials and methods We performed a retrospective analysis of 92 hospitalised patients with AST, ECOG 3–4, who were treated with palliative chemotherapy. Uni- and multivariate statistical analyses were conducted to determine the impact of clinical and disease variables (number of previous chemotherapy lines, presence of comorbidities, presentation of anorexia-cachexia syndrome, delirium, dyspnoea, ascitis, brain metastases, T-cell count, albumin, haemoglobin and LDH) on survival in this patient population.
Results Mean age was 54 years (range 15–80). No chemotherapy had been given for advanced disease in 74%, 13% had received one line, 6% 2 lines and 7% ≥3 lines. Median survival, i.e., after initiation of chemotherapy to death, in these patients was 33 days (range 1–1390). The median of chemotherapy cycles was 1. In the multivariate analysis, no previous chemotherapy, and absence of anorexia-cachexia syndrome and of comorbidities was associated with significantly improved survival in patients. Forty-nine percent of patients died within 30 days of therapy, 28% died between days 30 and 90, and only 23% of patients lived longer than 90 days. Grade 3–4 toxicities mainly entailed blood disorders, namely anaemia 8%, neutropenia 13% and thrombocytopenia 8%. Six patients (5%) developed sepsis after therapy; of these, 3 died from this toxicity, 1 patient suffered cardiac toxicity, one patient leukoencephalopathy and 1 patient acute pulmonary thromboembolism.
Conclusion Palliative chemotherapy given to patients with AST and ECOG 3–4 with short life expectancy provided no benefit for survival. As a result, we may be over-treating these patients and contributing to poor-quality care.

Keywords Advanced solid tumours · Palliative chemotherapy · Poor performance status

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Introduction

New anti-cancer therapies have been introduced over the past few years that have increased both options for therapy and expectations in patients with advanced solid tumours (AST). At the same time, the use of chemotherapy in end-stage cancer patients has increased [1, 2]. Even after failure of various anti-cancer treatment regimens, patients and their relatives often still want further cancer therapy in an attempt to delay inevitable death. Up to 20% of patients are given palliative chemotherapy during their last weeks of life [2].

However, it is questionable whether this has a positive effect by increasing survival and decreasing patients' symptoms, or whether palliative chemotherapy with unproven efficacy is overused and leads to increased toxicities that, in turn, inevitably involve more emergency department visits, a higher number of hospital admissions and essentially a worse quality of life for these patients at the end stage of life [1–3].

The aim of this study was to evaluate the impact of palliative chemotherapy on survival in patients with incurable AST, admitted to hospital as a result of their poor ECOG 3–4 performance status.

Materials and methods

Patient selection

This was a retrospective study in patients over 18 years diagnosed with incurable AST (excluding germ cell tumours and lymphomas) and poor general status as defined by the Eastern Cooperative Oncology Group performance status score (ECOG 3–4) who also received palliative chemotherapy during their admission to Hospital Virgen de la Victoria in Malaga (Spain) between January 2005 (date when a computerised registry of all chemotherapy applied in our hospital was launched) and May 2009.

Palliative chemotherapy was defined as chemotherapy given with no curative intent but to improve disease-related symptoms and to increase patient survival. Survival in patients was measured from the date chemotherapy was given to death.

The following information was collected both for the clinical record for each patient and for palliative chemotherapy received: age, gender, tumour type and histology, date of metastatic disease diagnosis, previous chemotherapy lines received, major comorbidities, signs and symptoms in patients (anorexia-cachexia, delirium, dyspnoea on minor effort or at rest, ascitis, presence of brain metastases), as well as test parameters (WBC count, albumin, haemoglobin, platelets, LDH), kind of response to chemotherapy, date of palliative chemotherapy, cause and date of death, and date and latest follow-up status for the patient.

Statistical methods

For statistical analysis, the following variables were accepted as prognostic factors of poor survival in AST patients: number of previous chemotherapy lines, presence of comorbidities, presence of anorexia-cachexia syndrome, delirium, dyspnoea, ascitis, brain metastases, abnormal WBC count, albumin, haemoglobin and LDH.

Data analysis was performed with SPSS software version 13, with a general descriptive analysis of the variables included in the study. Qualitative variables were described according to absolute and relative frequency distributions. Quantitative variables were evaluated using central trend measures (mean and median) and scatter measures (standard deviation). A chi-square test was used to estimate distribution and significance of frequencies. We used the Kaplan-Meier method to estimate survival, which gave rise to a survival curve. We examined overall survival and its correlation with different prognostic factors through a univariate analysis, applying the log-rank test. Multivariate analyses with Cox's proportional hazards model were subsequently performed.

Results

Between January 2005 and May 2009, a total of 92 patients with incurable AST, ECOG 3–4 and admitted to the Medical Oncology Department at the Virgen de la Victoria Hospital in Malaga received palliative chemotherapy. The clinical characteristics of patients are shown in Table 1. The median age was 54 years (range 15–80).

No previous chemotherapy for metastatic disease had been given in 74% of patients, while 13% had received one line, 6% two lines and 7% three or more previous lines of chemotherapy.

The median number of days between the last course of chemotherapy and death was 33 (range 1–1390) (Fig. 1). A median of one chemotherapy line was given. Within the first seven days of palliative chemotherapy 15% of patients died (3 died as a result of toxicity), 49% of patients died within 30 days of treatment and 28% of patients died between days 30 and 90. Only 23% of patients lived longer than 90 days.

One patient (1%) achieved complete response, 4 (4%) partial response, 4 (4%) stable disease and 80 (88%) had disease progression. Response could not be assessed in 3 patients (3%) who died from secondary toxicity during the first week following therapy.

In the multivariate analysis, enhanced survival of patients had a significant association only with having received no prior chemotherapy, and the absence of anorexia-cachexia syndrome and of comorbidities (Table 2).

Grade 3–4 toxicities were mainly haematological: anaemia 8%, neutropenia 13% and thrombocytopenia 8%. Cardiac toxicity developed in 6 patients (5%), one patient suffered leukoencephalopathy and a further patient developed acute pulmonary thromboembolism. There were 3 toxic deaths due to post-chemotherapy sepsis and neutropenia.

Discussion

Oncologists should carefully weigh up the risks and benefits of palliative chemotherapy in patients with AST and poor general status from the standpoint of both medical

Table 1 Patient characteristics *N*=92

Age 54 years (r: 15–80)	ACS Yes: 58 (63%) No: 34 (37%)	
Tumour type Lung: 35 (38%) Breast: 16 (17%) TUO: 11 (12%) Gynaecological: 7 (8%) Gastric: 6 (7%) Colorectal: 4 (4%) Head & neck: 5 (5.5%) Kidney & urinary tract: 5 (5.5%) Other: 3 (3%)	Comorbidities Yes: 15 (16%) No: 77 (84%) Dyspnoea Yes: 43 (14%) No: 49 (53%) Ascitis Yes: 13 (14%) No: 79 (86%)	
ECOG ECOG 3: 79 (85%) ECOG 4: 13 (15%)	Brain metastases Yes: 8 (9%) No: 84 (91%)	
Staging III: 7 (8%) IV: 85 (92%)	Delirium Yes: 2 (2%) No: 90 (98%)	
Number of previous CT lines 0 lines: 68 (74%) 1 line: 12 (13%) 2 lines: 5 (6%) ≥3 lines: 7 (7%)	Laboratory tests *WBCs* ≤11,000: 64 (70%) >11,000: 28 (30%)	*Haemoglobin* ≥10 g/dl: 55 (60%) <10 g/dl: 37 (40%)
	Albumin >3.5 g: 11 (12%) <3.5 g: 41 (45%) NT: 40 (43%)	*LDH* Normal: 16 (17%) >ULN: 76 (83%)

TUO, tumour of unknown origin; CT, chemotherapy; ACS, anorexia-cachexia syndrome; ECOG 3, patients with symptoms who are bedridden or need to sit for over 50% of their waking hours; ECOG 4, patients with symptoms who are bedridden 24 h a day; NT, no test available; ULN, upper limit of normal

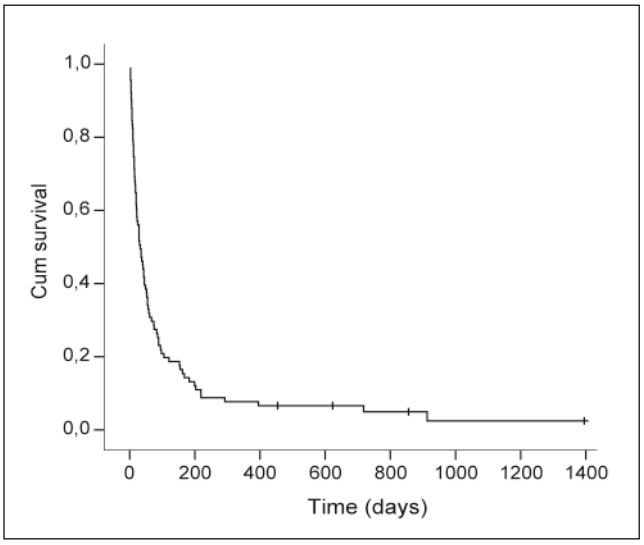

Fig. 1 Overall survival

Table 2 Multivariate analysis of OS and clinical–pathological characteristics

Variable	Hazard ratio (95% CI)	*p* value
No. of previous CT lines (0 vs. ≥1)	0.41 (0.23–0.76)	0.004
Comorbidities	0.42 (0.18–0.97)	0.04
Anorexia-cachexia	0.47 (0.26–0.85)	0.01
Dyspnoea	0.76 (0.43–1.3)	0.3
Ascitis	1.5 (0.71–3.29)	0.2
Brain metastases	1.2 (0.53–2.9)	0.6
WBC	1.1 (0.6–2)	0.6
Albumin	0.9 (0.58–1.6)	0.9
Haemoglobin	1.2 (0.77–2.1)	0.3
LDH	0.9 (0.5–1.6)	0.7

CI, confidence interval; CT, chemotherapy

and ethical issues as well as of the healthcare resources used in treatment.

Median survival in our patients from receiving palliative chemotherapy up to their death was only 33 days. Most of these (74%) received first-line chemotherapy for metastatic disease. Only 23% of patients lived longer than 90 days after palliative chemotherapy. These results point to the poor impact on survival of palliative chemotherapy in most of our hospitalised patients with AST and ECOG 3–4.

Given that a patient's general status is one of the main prognostic factors in advanced cancer [4, 5], several different scales are used to measure performance status, the most common being the Palliative Performance Scale (PPS) and the Eastern Cooperative Oncology Group Performance score (ECOG). Previous trials have reported a correlation between poor ECOG status and shorter survival as well as a limited response to chemotherapy [6–10].

Reports in many different tumour types show that palliative chemotherapy brings about a statistically significant improvement in overall survival or in the patients' symptoms compared with best supportive care. These studies, unlike our own, did not include ECOG 3–4 status patients. Even so, differences in overall survival were only modest with limited clinical repercussions [11–15]. Connor et al. [16] associated the use of palliative chemotherapy with deleterious effects for patients. This major study on patients receiving either supportive care without chemotherapy or chemotherapy without supportive care showed that survival was significantly longer in patients with lung and pancreatic cancer receiving supportive care but only marginally so for colon cancer. There were no differences in terms of survival in breast or prostate cancer patients. Furthermore, chemotherapy causes adverse effects, leading to increased emergency department visits, hospital admissions and healthcare costs [1–3]. In our patient group, 17 (18%) developed grade 3–4 haematological toxicity and 8 patients (9%) suffered some severe non-haematological toxicity (bacteriaemia, pulmonary thromboembolism, leu-

koencephalopathy). Three of our patients died as a result of toxicity from treatment for post-chemotherapy sepsis and neutropenia.

The likelihood of benefiting from palliative chemotherapy is lower in patients with poor prognosis [1]. So, why do oncologists continue to prescribe more palliative chemotherapy at the very end of terminal patients' lives?

1. Clinical estimates of patient survival by cancer specialists are often inaccurate and tend to overestimate prognosis [17]. However, these specialists can be fairly certain of impending death within the last three months of life, regardless of treatment. A close relationship between the oncologist and patient, however, may limit both the objectivity and the accuracy of a patient's prognosis. In these circumstances, we may call on a colleague to make a more objective appraisal of prognosis [18, 19].

2. Patients and their relatives often demand aggressive treatment, based on their lack of knowledge and on denial to accept disease prognosis and real treatment options, as well as on unrealistic expectations regarding their disease status [20, 21]. Patients are willing to accept greater or lesser toxicities in exchange for even a minor survival benefit in their attempt to avoid dying at any cost [1, 22]. In this situation, it is often easier to recommend another line of chemotherapy instead of providing painful and difficult explanations of why we do not consider active cancer therapy is indicated [22–25]. Certain cancers, i.e., breast, colon, ovarian or small-cell lung are chemosensitive and may respond to palliative chemotherapy. However, the absence of response after 1 cycle should alert the oncologist to treatment failure and steps should be taken to interrupt therapy. We need to consider whether such an aggressive attitude really does alleviate patients' symptoms. And, even though we are giving up therapy, we should insist that we are not abandoning the patient and that palliative care may in fact be the best treatment option.

3. Finally, some patients may be receiving experimental chemotherapy. However, patients with poor general status and short life expectancy are not ideal candidates for inclusion in Phase I clinical trials on new drugs either for the patient him/herself or for the clinical development of the drug [26].

Our study does have certain limitations. Firstly, this was a retrospective study from a single centre with a relatively small number of patients. Clearly, a larger, multicentre trial would be required to confirm our results. Given the retrospective nature of the study, no quality of life test was performed that may well have provided very useful additional qualitative information. No analysis was conducted either on the direct or indirect costs of palliative chemotherapy compared with a cohort of patients receiving best supportive care.

In conclusion, no benefit in survival was seen in giving palliative chemotherapy to patients with AST admitted to hospital because of their ECOG 3–4 status and short life expectancy. These patients may be over-treated and this may contribute to poor-quality care. Measures involving best supportive care may well keep symptoms under better control than palliative chemotherapy in these patients.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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