Pathol. Oncol. Res. (2017) 23:139–144
DOI 10.1007/s12253-016-0111-4

ORIGINAL ARTICLE

To Treat or Not to Treat Metastatic Cancer Patients with Poor Performance Status: a Prospective Experience

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Received: 30 August 2015 / Accepted: 1 September 2016 / Published online: 7 September 2016

Abstract Administration of cytotoxic chemotherapy for patients with metastatic cancer and poor performance status is a daily clinical challenge. Guidelines only help to select a therapeutic regimen but do not offer a clear response whether or not the patients should be treated. We performed a prospective analysis in 139 metastatic patients with performance status > 1 according to the Eastern Cooperative Oncology Group scale. A decision was considered correct if patients treated with a medical anticancer treatment lived over 3 months or alternatively patients not treated had a survival under 3 months. The predominant tumor type was non-small cell lung cancer. Patients were chemotherapy naive in 87 cases (63 %). A new line of medical anticancer treatment was started in 107 cases (77 %). The median survival of the study population was 11 weeks (range, 1–53). 84 patients (60 %) died within 3 months while 55 patients (40 %) lived more than 3 months after decision. Treatment decisions were considered as appropriate in 81 cases (58 %). No patient was considered as undertreated. The analysis by pathology allowed to identify pathologies where decisions were correct in the majority of the cases (renal, urothelial and small cell lung cancers), pathologies where appropriate and inappropriate decisions were balanced (prostate, ovarian and breast cancers) and pathologies where decisions for treatment were excessive (non-small cell lung cancer and unknown primary). This prospective study was conducted as part of the evaluation of professional practices in our department. Administration of a medical anticancer treatment validated with patients with good performance status may be harmful for patients with poor performance status. The findings resulted in recommendations for daily practice in order to help physicians, especially for the "don't go" decisions. Until the identification of new prognostic factors for survival and/or the development of therapies making sensitive currently chemoresistant diseases, the initiation of a medical anticancer treatment outside standard situations should result from a consensual decision team or the inclusion in a clinical trial.

Keywords Metastatic cancer · Performance status · Cytotoxic chemotherapy · Supportive care · Therapeutic decision · Survival

Introduction

Performance status (PS) is the strongest prognostic factor of survival in patients with metastatic cancer. It measures the impact of comorbidities and tumor related symptoms on patients' activities in daily life and the capability of self care. According to the Eastern Cooperative Oncology Group (ECOG) scale, patients with poor PS are defined by a score ≥ 2 on a six-point scale worsening from 0 to 5 [1]. While medical oncology has been developed under the era of evidence-based medicine, with standard regimens and new drugs validated by randomised controlled trials, patients with poor PS are traditionally excluded from these studies. Few studies have been dedicated to patients with PS 2 or 3, some in lung cancer, but none has been reported in other tumor types for patients with PS 3 [2]. Therefore limits of reasonable efforts to initiate a medical anticancer treatment (MACT) are not clearly defined. Patients are often motivated to start or pursue therapy near the end of life while physicians may be

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not comfortable discussing prognosis and end-of-life issues or even may tend to avoid them. We are reporting a prospective experience in metastatic cancer patients with poor PS addressed to our department for therapeutic decision.

Patients and Methods

The study population is based on 139 consecutive patients with poor PS (2 to 4 according to the ECOG scale) who were hospitalised in the medical oncology department of the Saint Louis Hospital, Paris between the 1st November 2011 and the 31st July 2012. Therapeutic decisions were made in consensus by the oncologic team considering the proposal of the referral oncologist and the international guidelines. If an intravenous MACT was decided, the first cycle was administered immediately on the ward and the next ones according to the protocol and the PS of the patients either on the ward or in the day hospital. Patients resided between the cycles at home or in oncologic rehabilitation centres. If exclusive supportive care was decided it was organised either at home or in palliative care units, or assumed in our ward. In all cases patients were followed by the referral oncologist.

Survival was the main outcome. A decision was considered correct if patients who received a MACT lived up to 3 months or patients who were treated with best supportive care only had a survival under 3 months. A decision was considered incorrect in patients with opposite outcomes. Variables that can distinctively predict survival at 3 months were searched among the baseline characteristics. The validity of the Royal Marsden Hospital (RMH) prognostic score based on albumin, lactate dehydrogenase (LDH) and number of metastatic sites in predicting survival was tested [3].

Results

Initial patients' characteristics are summarised in Table 1. Overall, main features were middle age, the absence of significant comorbidity and a poor PS correlating with advanced disease and altered nutritional status. The predominant tumor type was non small cell lung cancer. Patients were chemotherapy naive in 87 cases (63 %).

A new line of MACT was started in 107 (77 %) cases: cytotoxic chemotherapy in 97 cases and oral targeted treatment in 10 cases, including hormonal therapy in 5 cases. Supportive care treatments only were decided in 32 cases (23 %). Among patients who received a MACT, the median number of administered cycles was 2 (range: 1–17). Cytotoxic chemotherapy was stopped for progressive disease or death in 63 patients, toxicity in 12 patients and at the request of the patients in 2 cases (despite clinical evidence of partial response). Targeted treatments were stopped for progressive disease or death in 3 cases and for toxicity in 1 patient. Ongoing targeted treatments included hormonal therapies in 5 patients with breast cancer and gefitinib in 1 patient with lung cancer.

The median survival of the study population was 11 weeks (range, 1–53). 84 patients (60 %) died within 3 months while 55 patients (40 %) lived more than 3 months after decision.

Table 1 Baseline characteristics of the study population

Characteristics	Number
Age, median (range)	64 (30–91)
Sex: F/M	68/67
Performance status (WHO scale)	
2	21
3	77
4	41
Performance status (Karnofsky score)	
60	12
50	44
40	41
30	42
Charlson score	
0	49
1	38
2	32
>2	20
Primary tumor	
Lung (non-small cell)	47
Breast	27
Ovary	13
Bladder	10
Unknown primary	10
Lung (small cell)	8
Prostate	8
Kidney	5
Other	11
Number of metastatic sites	
1	39
2	42
>2	58
N° of previous lines of medical anticancer treatment	
0	87
1	21
2	19
>2	12
Albumin (g/L; $N = 139$)	
Median (range)	33 (19–43)
Pre-albumin (g/L ; $N = 101$)	
Median (range)	0.15 (0.05–0.43)
Alkaline phosphatase (IU/L ; $N = 137$)	
Median (range)	115 (35–1198)
Lacticodehydogenase (IU/L ; $N = 129$)	
Median (range)	507 (198–6289)
Calcium (mmol/L ; $N = 137$)	
Median (range)	2.36 (2.0–4.34)
Hemoglobin ($N = 139$)	
Median (range)	10.9 (5.1–16.4)
Lymphocytes ($N = 134$)	
Median (range)	1020 (100–3220)
Royal Marsden prognostic score ($N = 129$)	
0	21
1	53
2	40
3	15

When considering all pathologies together, treatment decisions were considered as appropriate in 81 (58 %) cases. No patient was considered as undertreated since the 3 patients who lived more than 3 months without any MACT actually died in 17 to 18 weeks without any clinical improvement despite lege artis supportive care. Therefore the inappropriate decisions were restricted to the 55 patients who were treated with a MACT but did not live up to 3 months after starting therapy (Table 2). The separate analysis by pathology allowed to identify pathologies where decisions were correct in the majority of the cases (renal, urothelial and small cell lung cancers, Table 3a), pathologies where appropriate and inappropriate decisions were balanced (prostate, ovarian and breast cancers, Table 3b) and pathologies where decisions for treatment were excessive (non small cell lung cancer and unknown primary, Table 3c). The RMH prognostic score was applied to 129 patients but was not able to discriminate patients' outcome (Table 4).

Important baseline characteristics according to primary site are depicted in Table 5. Patients with renal carcinoma were chemo-naive in 2/5 cases, had a PS > 2 and a relatively preserved nutritional status (albumin <30 g/l in only 1 patient). Patients with urothelial carcinoma were chemo-naive in 6/10 cases, had a PS > 2 in all but one cases and a variable nutritional status (albumin <30 g/l in 4 patient). The survival was relatively favorable after chemotherapy combining gemcitabine and a platinum salt since 8 patients were treated out of 10 and 7 of them lived longer than 3 months. The only patient who did not live up to 3 months died of neutropenic sepsis after receiving MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy. Patients with SCLC were chemo-naive in 8/8 cases, had a PS > 2 in all but one cases and a preserved nutritional status (albumin >35 g/l in all patients). The survival was relatively favourable. All patients were treated by chemotherapy associating etoposide and a platinum salt. Early fatal complications were observed in 2 patients treated with an intensified regimen (cyclophosphamide, doxorubicin, etoposide, cisplatin).

Patients with ovarian carcinoma were chemo-naive in 9/13 cases, had PS >2 and a poor nutritional status (albumin < 35 g/l in all patients and < 30 g/l in 7 patients). Twelve out of 13 patients were treated and 7 of them lived longer than 3 months, 4 of them longer than 6 months. The early fatal complications in the other 5 cases were observed with later lines of chemotherapy (7th line topotecan and 3rd line topotecan in two patients, 4th line carboplatin in two cases) or serious comorbidities (ischemic cardiomyopathy at the age of 85 in one case). Patients with castration resistant prostate carcinoma were chemo-naive in 4/8 cases, had a PS > 2 in 5 patients and a relatively preserved nutritional status (albumin < 30 g/l in 2 patients). Seven out of 8 patients received chemotherapy. The 3 patients with PS 2 had a survival over 3 months independently whether they received docetaxel in first-line or cabazitaxel in second-line. All 4 patients with PS 3 had a survival less than 3 months whether they received docetaxel, cabazitaxel or mitoxantrone. Patients with breast cancer were chemo-naive in 10/27 cases, had a poor performance status (24 with PS > 2) and a relatively preserved nutritional status (albumin <30 g/l in 7 patients). The survival had a composite pattern. When hormonal therapy was possible, survival was good, even in patients with a Karnofsky score ≤30 and albumin level <30 g/l. Cytotoxic chemotherapy allowed a survival over 3 months exclusively when it was associated with a HER2 inhibition (in 3 cases) or given in 1st line (in 3 other patients).

Patients with NSCLC were chemo-naive in 33/47 cases and had a variable performance status (38 with PS > 2) and a relatively preserved nutritional status (albumin <30 g/l in 12 patients). Thirty-four patients were treated and 22 of them did not live up to 3 months. A subgroup analysis was performed (30 adenocarcinomas, 9 squamous cell carcinomas and 10 other NSCLC) and showed no difference in term of the correctness of the decisions between the 3 histologic subtypes. Patients with unknown primary were chemo-naive in 9/10 cases, had a PS >2 in all but one cases and a preserved nutritional status (albumin <30 g/l in 2 patients). Eight patients were treated with chemotherapy and only 1 of them lived longer than 3 months.

Patients with other malignancies had the following outcome: one patient with oesophageal adenocarcinoma was treated with chemotherapy and had a survival under 3 months. The two patients with endometrial carcinoma were treated and one of them lived longer than 3 months. The three patients with head and neck cancer were treated and two of them lived longer than 3 months. The three patients with undifferentiated thyroid carcinoma were treated but none of them lived up to 3 months. Both patients with sarcoma lived up to 3 months, one after cytotoxic chemotherapy and one with oral targeted treatment.

Table 2 Outcome according to treatment decision

Management	Survival ≥3 months	Survival < 3 months
Medical anticancer treatment	52	55
No medical anticancer treatment	3	29
Total	55	84

Discussion

Medical decision making on ceasing MACT remains a very complex, intimate and subjective process [4]. Chemotherapy is supposed to prolong survival or at least reduce symptoms. On the other hand, it may cause adverse effects and prevent

Table 3 Outcome according to primary site and treatment decision

3a	Kidney	≥3 months	<3 months	3b	Ovary	≥3 months	<3 months
	MACT +	0	0		MACT +	7	5
	MACT -	1	4		MACT -	0	1
	Total	1	4		Total	7	6
	Bladder	≥3 months	<3 months		Prostate	≥3 months	<3 months
	MACT +	7	1		MACT +	3	4
	MACT -	1	1		MACT -	0	1
	Total	8	2		Total	3	5
	SCLC	≥3 months	<3 months		Breast	≥3 months	<3 months
	MACT +	6	2		MACT +	11	9
	MACT -	0	0		MACT -	0	7
	Total	6	2		Total	11	16
3c	NSCLC	≥3 months	<3 months	3d	Other AC	≥3 months	<3 months
	MACT +	12	22		MACT +	4	6
	MACT -	0	13		MACT -	0	1
	Total	12	35		Total	4	7
	ACUP	≥3 months	<3 months				
	MACT +	1	7				
	MACT -	1	1				
	Total	2	8				

3a. Correct therapeutic decisions 3b. Partially correct decisions 3c. Excessive treatments 3d. Other carcinomas

MACT medical anticancer treatment, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *ACUP* adenocarcinoma of unknown primary, *AC* adenocarcinoma

patient from preparing for death and entering palliative care units. Therefore the daily challenge for the physician is to balance the pros and cons for every patient. Tumor sensitivity, survival prognostic parameters, predictable side effects of treatment as well as patients and families' desire are major features to consider. Ultimately, the decision may also involve the use of costly resources despite little chance of benefit.

As expected, this prospective experience included a patient population of poor prognosis, with a median survival of 11 weeks. Treatment decisions led to initiate a MACT in 77 % of the patients while only 40 % lived more than 3 months, suggesting an inadequate management, i.e. an over-treatment, in about half of them according to the study criteria. 42 (30 %) patients received a MACT in the last month of their life. These results are in line with the literature data, suggesting that up to a fifth of cancer patients are treated with chemotherapy in the last month of life without clear benefits. However most of available data are retrospective death-centered studies, population or institution based [4]. What reasons can explain our results?

Table 4 Outcome according to the Royal Marsden Hospital (RMH) prognostic score ($N = 129$)

RMH prognostic score	≥ 3 months	< 3 months
0	8	13
1	23	30
2	18	22
3	3	12
Total	52	77

First, about two thirds of the patients were naive of MACT. This characteristic may explain why physicians were more likely to give a MACT, even in diseases with well-known poor chemo sensitivity, such as non-small cell lung cancer or carcinoma of unknown primary. If a lack of effect on survival is expected, the rationale for treating patients may come from the hope of quality of life benefits. This issue was not directly addressed in the present study as we did not use questionnaires along the course of disease. However, only those patients who lived more than 3 months were able to improve by at least one level their PS on the ECOG scale. Second, the RMH prognostic score failed to accurately predict survival at 3 months in our study population. The main explanation probably lies in the fact that this score was originally dedicated to patient selection in phase I trials, and therefore built from patients with good PS (only 6 % of 212 patients had a PS > 1) [5]. These results suggest that albumin and LDH serum levels have a low prognostic value on survival in metastatic patients with poor PS, although other studies highlighted their potential interest [6]. In recent years, prognostic scores have been validated for patients in palliative care but focused on the last month of life [7]. With the aim to minimize the use of futile chemotherapy, specific prognostic characteristics would be important to

Table 5 Main baseline characteristics according to primary sites

Primary site	Number of patients	Number of chemo-naive patients	Number of patients with PS > 2	Number of patients with albumin < 30 g/L
NSCLC	47	33	38	12
Breast	27	10	24	7
Ovary	13	9	13	7
Bladder	10	6	5	4
ACUP	10	9	9	2
Prostate	8	4	5	2
Kidney	5	2	5	1

determine. Prospective studies incorporating new biomarkers such as circulating bone marrow derived progenitors are necessary to find more accurate prognosticators for survival [8].

The minimal life expectancy at the start of a new line of palliative chemotherapy is open to discussion. We proposed 3 months for the following reasons: 1) 3 months are sufficient to organise a meeting with a forgotten relative or moving to a preferred place, two potentially important end-of-life issues. 2) It is also the usual span to evaluate efficacy of chemotherapy in general, so it is affordable to reach that term once chemotherapy is started. 3) It was the cut off limit of the RMH study that we appreciate in particular [5].

Meanwhile these new prognostic factors and the development of more effective treatments, recommendations for daily practice from this prospective experience remain based on the potential treatment sensitivity of primary sites (Table 6). Initiating a MACT seems a reasonable option in chemo naive patients with bladder, breast, ovary and small-cell lung cancer whatever the PS. Patients with non-small cell lung and prostate cancer should be treated provided a PS ≤ 2. In other situations, no clear benefit is expected from a MACT. When considering the right decision, it is important to remember that i) age is not the most important issue for treatment results but PS is it [9, 10], ii) honesty doesn't take away hope [11], iii) recent reports claimed for an early intervention of palliative care teams during the course of metastatic diseases [12, 13].

Table 6 Proposal for the management of patients with poor performance status according to study results

Primary site	Treatment to consider
Bladder	Gemcitabine plus platinum salt
Breast	Cytotoxic chemotherapy only in first-line or if HER2 inhibition is feasible Hormone therapy beneficial in every cases
Kidney	No treatment
Non-small cell lung cancer	Chemotherapy for PS ≤ 2
Ovary	Paclitaxel plus carboplatin
Prostate	Chemotherapy for PS ≤ 2
Small cell lung cancer	Etoposide and platinum salt
Unknown primary	No treatment

Conclusions

This prospective study was conducted as part of the evaluation of professional practices in our department. Administration of a medical anticancer treatment validated with patients with good performance status may be harmful for patients with poor performance status. The findings resulted in recommendations for daily practice in order to help physicians, especially for the "don't go" decisions. Until the identification of new prognostic factors for survival and/or the development of therapies making sensitive currently chemo resistant diseases, the initiation of a MACT outside standard situations will result from a consensual decision team or the inclusion in a clinical trial.

Compliance with Ethical Standards

Funding The study did not get any funding.

Conflict of Interest Authors have no conflict of interest in respect of the article.

References

1. Oken MM, Creech RH, Tormey DC et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology group. Am J Clin Oncol 5:649–655
2. Liu S, Wang D, Chen B et al (2011) The safety and efficacy of EGFR TKIs monotherapy versus single-agent chemotherapy using third-generation cytotoxics as the first-line treatment for patients with advanced non-small cell lung cancer and poor performance status. Lung Cancer 73:203–210
3. Arkenau HT, Barriuso J, Ilmos D et al (2009) Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol 27:2692–2696
4. Braga S (2011) Why do our patients get chemotherapy until the end of life? Ann Oncol 22:2345–2348
5. Arkenau HT, Olmos D, Ang JE et al (2008) Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. Br J Cancer 98: 1029–1033
6. Barbot AC, Mussault P, Ingrand P, Tourani JM (2008) Assessing 2-months clinical prognosis in hospitalized patients with advanced solid tumors. J Clin Oncol 26:2538–2542
7. Maltoni M, Scarpi E, Pittureri C et al (2012) Prospective comparison of prognostic scores in palliative care cancer populations. Oncologist 17:446–454
8. Massard C, Borget I, Le Deley MC et al (2012) Prognostic value of circulating VEGFR2+ bone marrow-derived progenitor cells in patients with advanced cancer. Eur J Cancer 48:1354–1362

9. Yun YH, Kwak M, Park SM et al (2007) Chemotherapy use and associated factors among cancer patients near the end of life. Ann Oncol 72:164–171
10. Braga S, Miranda A, Fonseca R et al (2007) The aggressiveness of cancer care in the last three months of life: a retrospective single center analysis. Psychooncology 16:863–868
11. Harrington SE, Smith TJ (2008) The role of chemotherapy at the end of life: "When is enough, enough?". JAMA 299:2667–2678
12. Temel JS, Greer JA, Muzikansky A et al (2010) Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 363:733–742
13. Greer JA, Pirl WF, Jackson VA et al (2012) Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. J Clin Oncol 30:394–400