Annals of Oncology 28: 1612–1617, 2017
doi:10.1093/annonc/mdx172
Published online 4 May 2017

ORIGINAL ARTICLE

Clinical validation of a prognostic tool in a population of outpatients treated for incurable cancer undergoing anticancer therapy: PRONOPALL study

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Note: This study was previously presented at the 47th Congress of the American Society of Clinical Oncology, 3–7 June 2011, Chicago, USA; at the Congress of the Multinational Association of Supportive Care in Cancer, 23–25 June 2011, Athens, Greece; at the 36th Congress of the European Society for Medical Oncology, 23–27 September 2011, Stockholm, Sweden; 50th Congress of the American Society of Clinical Oncology, 30 May–3 June 2014, Chicago, USA.

Background: In 2008, a study of the characteristics of hospitalised patients led to the development of a prognostic tool that distinguished three populations with significantly different 2-month survival rates. The goal of our study aimed at validating prospectively this prognostic tool in outpatients treated for cancer in terminal stage, based on four factors: performance status (ECOG) (PS), number of metastatic sites, serum albumin and lactate dehydrogenase.

Patients and methods: PRONOPALL is a multicentre study of current care. About 302 adult patients who met one or more of the following criteria: life expectancy under 6 months, performance status ≥ 2 and disease progression during the previous chemotherapy regimen were included across 16 institutions between October 2009 and October 2010. Afterwards, in order to validate the prognostic tool, the score was ciphered and correlated to patient survival.

Results: Totally 262 patients (87%) were evaluable (27 patients excluded and 13 unknown score). Median age was 66 years [37–88], and women accounted for 59%. ECOG PS 0–1 (46%), PS 2 (37%) and PS 3–4 (17%). The primary tumours were: breast (29%), colorectal (28%), lung (13%), pancreas (12%), ovary (11%) and other (8%). About 32% of patients presented one metastatic site, 35% had two and 31% had more than two. The median lactate dehydrogenase level was 398 IU/l [118–4314]; median serum albumin was 35 g/l [13–54]. According to the PRONOPALL prognostic tool, the 2-month survival rate was 92% and the median survival rate was 301 days [209–348] for the 130 patients in population C, 66% and 79 days [71–114] for the 111 patients in population B, and 24% and 35 days for [14–56] the 21 patients in population A. These three populations survival were statistically different ($P < 0.0001$).

Conclusion: PRONOPALL study confirms the three prognostic profiles defined by the combination of four factors. This PRONOPALL score is a useful decision-making tool in daily practice.

Key words: prognostic tool, palliative care, lactate dehydrogenase, serum albumin, Performance Status (PS ECOG), survival at 2 months

Introduction

Withdrawing chemotherapy for end-stage metastatic cancer patients in palliative care is a difficult decision-making process in a context of serious illness. Furthermore, with new medications continuously becoming available, opinion is stacked against this choice [1]. In societal terms, in spite of an increase in palliative and supportive care, patients and their relatives have a growing fear of this ultimate question of stopping chemotherapy. Oncologists themselves may play a role in forging ahead regardless by offering a new line of palliative chemotherapy. However, a clinical deterioration or laboratory results may argue against this decision. The oncologist sometimes overestimates patients life expectancy and then patients receive chemotherapy. Prognostic tools have been described previously (palliative prognostic score, palliative prognostic index) but they were underused in routine practice because of their complexity and of some subjective items which defined them. There is abundant literature on the subjective assessment of prognosis [2–4], and we wish to introduce some objective decision-making tools to the process.

Patients often receive very little information about their prognosis, and they also place unrealistic hopes in the progress of medicine, which means that they very often ask for any kind of treatment in order to be taking some action [5] even if there is only a minimal benefit [6].

The value of stopping chemotherapy is rarely addressed in the international literature. Since 2003 and on a number of occasions, F Goldwasser and others (P Vinant, C Bouleuc etc.) have made the point that 'the consultation when we announce the end of chemotherapy will be all the more difficult if all prior consultations have placed an excessive importance on chemotherapy' [7]. 'It is therefore crucial to broaden the scope of care from the outset, from the earliest consultations, going beyond antitumour treatments alone so that when they are withdrawn the patients do not see this as an abandonment' [8]. Moreover, the timeframe between the end of palliative chemotherapy for a solid tumour and death in 2002 for 1064 adult patients was reported in a Portuguese study: 168 days [9]. Of the patients included, 29 (7%) had received at least 30 days of chemotherapy and 36 (9%) had received only a single cycle of palliative chemotherapy.

According to ANAES (the French agency for accreditation and evaluation in healthcare) in December 2002: 'palliative care is active, continuous, flexible, and coordinated care delivered by a multidisciplinary team. Its purpose is, within a global and personalised approach, to prevent or relieve physical symptoms including pain amongst others, to anticipate the risks of complications, and to take into account psychological, social and spiritual needs, while respecting the dignity of the person cared for. Palliative care seeks to avoid unreasonable investigations and treatments and does not intentionally cause death'.

In 2008, Barbot et al analysed multiple parameters and isolated four items [Karnofsky index, number of metastatic sites, serum albumin and serum lactate dehydrogenase (LDH)] to produce a prognostic score [10]. This score ranged from 0 to 10 and allowed three populations of hospitalised patients to be distinguished, for which the 2-month survival rates were 8% (population A: score 8–10), 43% (population B: score 4–7) and 92% (population C: score 0–3). For the patients who presented a high score (population A), the questions from the continuation of the active treatment, the maintenance or not at home, and response to the patient and family's request for support arise. The Observatory dedicated to Cancer that forms part of the OMEDIT (Observatory for Medicines and Medical Devices and Treatment Innovations) in the Brittany and Pays de Loire regions investigated the validity of this prognostic score (PRONOPALL score) in outpatients using a prospective multicentre study.

Patients and methods

Inclusion and exclusion criteria

Inclusion criteria were the following:

- Adult patient (≥18 years old) with incurable solid cancer at the palliative care stage, for which they intend to have treatment, originating in the lung, breast, colon, pancreas, prostate, ovary or kidney.
- Proposed anticancer treatment other than hormone therapy [chemotherapy, tyrosine kinase inhibitor (TKI) and monoclonal antibodies].
- Presents with at least one of the following criteria:
  - Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≥ 2;
  - Oncologist estimates life expectancy at under 6 months;
  - Disease progression on the previous chemotherapy regimen.

Exclusion criteria was unavailable serum LDH or albumin (not possible to calculate the score).

The patients were recruited prospectively in both public and private hospitals in the regions of Brittany and Pays de Loire (France). They were for the most part outpatients and seen in clinics.

The Ethics Committee for the Western region II (Angers) approved this study into current care on 27/08/2009. The patients signed an informed consent form to participate in the study.

Purpose of the study

The main purpose of the study was to investigate prospectively the validity of a prognostic tool which could help with making treatment decisions.

Evaluation

The variables making up the score were the following (Table 1):

- ECOG PS (0 or 1, 2, 3 or 4)
- Number of metastatic sites: (0 or 1, ≥ 2)
- Serum LDH level (<600 IU/l or ≥ 600 IU/l)
- Serum Albumin (<33 g/l or ≥ 33 g/l)

Their weightings were defined according to Barbot's study. LDH and albumin cut-off have been defined previously by univariate Cox survival regression analyses [10, 11]. The ECOG PS replaced the Karnofsky PS used in Barbot's study [10] because it was more commonly used by clinicians at present. C Ma et al have constructed empirically a conversion table to convert PS scores among the ECOG, KPS and Palliative Performance Scale (PPS) measures, using a large sample of patients with advanced cancer [12]. For the KPS, the categorisation of 100 (PS 0), 80–90 (PS 1), 60–70 (PS 2), 40–50 (PS 3) and 10–30 (PS 4) had the highest hit rate (75%). So projection has been proposed for PRONOPALL prognostic tool. Moreover, I De Kock et al. have shown that the ECOG was convertible to the KPS in the Palliative Performance Scale (PPS) even if the relationship was not as strong as the one between KPS and PPS [13]. Their results could also facilitate comparisons between different performance and prognostic tools.

Each value was given a score according to Barbot's study (Table 1). The sum of the scores was the prognostic score PRONOPALL calculated at patient's inclusion. Based on the results obtained, three distinct populations were defined: A, B and C, with respectively a poor prognosis (A, high score 8–10), an intermediate prognosis (B, intermediate score 4–7) and a good prognosis (C, low score 0–3).

Data collection

The clinical data were extracted from medical records. The results of each laboratory were obtained from blood tests that had either already been carried out or were due to be carried out, but within a maximum of 15 days of the date of inclusion. No specific sample was asked. The following data were captured: PS, expected survival, previous treatment response, type of primary cancer, locations of metastatic sites, serum LDH level and albumin (absolute value with reference range).

Statistical methodology

The data were presented in percentage form for the qualitative variables and by the mean (standard deviation) and extreme values for the quantitative variables. Survival time is defined as the time between inclusion and death. Survival curves (Kaplan Meier) based on the score were drawn up for sub-populations according to prognosis group. Alive patients have been censored.

Variables previously described making up the prognostic tool were analysed for univariate comparisons using a log-rank test. Multivariate survival analysis was performed using the Cox proportional hazards model. Prognostic performance was assessed. Prognostic accuracy was derived from ROC analysis, using the c-index with 95% confidence interval.

The number of subjects needed was simulated using SAS V9. According to guidelines relative to validation samples, a minimum 100 events were required, and ideally 200 events were expected.

Table 1. Calculating the PRONOPALL score

Variable	Allocation of points			Score
ECOG PS	PS 0-1	PS 2-3	PS 4	
	↓	↓	↓	=. . ./4
	score = 0	score = 2	score = 4	
Number of metastatic sites	nb ≤ 1	nb ≥ 2		
	↓	↓		=. . ./2
	score = 0	score = 2		
LDH (IU/L)	LDH < 600	LDH ≥ 600		
	↓	↓		=. . ./1
	score = 0	score = 1		
Albumin (g/L)	≥ 33	< 33		
	↓	↓		=. . ./3
	score = 0	score = 3		
	Total score			=. . ./10

ECOG PS, Eastern Cooperative Oncology Group Performans Status; LDH, Lactate dehydrogenase.

Results

From November 2009 to October 2010, 302 patients were included across 16 centres. Two centres included 74% of all patients. The inclusions were made during clinic appointments in 80% of cases. 40 patients (13%) were excluded because it was not possible to calculate their prognostic score and because inclusion criteria were not met (supplementary Figure S1, available at *Annals of Oncology* online).

The analysis therefore included in 262 patients who met at least one of these criteria (more than one criterion may be met) distributed as follows:

- ECOG PS ≥ 2: 143 patients (55%);
- Life expectancy estimated by the oncologist at under 6 months: 133 patients (50%);
- Progression on previous chemotherapy regimen: 208 patients (80%).

The prognosis estimated by the oncologist at inclusion was correct in only 69% of cases when the patient had a life expectancy below 6 months and in 59% of cases for a life expectancy of over 6 months (data not shown).

The variables of the population are described in Table 2. The median age of the eligible patients was 66 years [37–88], women accounted for 59%. 258 patients presented with metastases and four locally advanced cancer.

ECOG PS was as follows: 0 for 52 patients (20%), 1 for 67 patients (26%), 2 for 97 patients (37%), 3 for 37 patients (14%) and 4 for 9 patients (3%).

The numbers of metastatic sites were distributed as follows: four patients had none (2%), 85 patients had one (32%), 91 patients had two (35%) and 82 patients had more than two (31%).

As an absolute value, the median serum LDH level was 398 IU/l [118–4314]. About 73 patients (28%) presented a level in excess of 600 IU/l. Median serum albumin level was 35 g/l [13–54]. About 93 patients (36%) presented a level below 33 g/l.

Based on the calculation formula, the prognostic score PRONOPALL split patients into three distinct populations (Table 3):

- Score 8–10: 21 patients (8.0%) or population A (poor prognosis);
- Score 4–7: 111 patients (42.4%) or population B (intermediate prognosis) ;
- Score 0–3: 130 patients (49.6%) or population C (good prognosis).

Table 2. Patients characteristics

Variables	Description	Number	%
Sex	Female	155	59
	Male	107	41
Age	Below or equal to 75 years	200	76
	Over 75 years	62	24
Inclusion	Consultation	210	80
	Hospital admission	52	20
Localization	Breast	77	29
	Bowel	73	28
	Lung	34	13
	Ovary	29	11
	Pancreas	28	11
	Prostate	16	6
	Kidney	5	2
Metastases	No	4	2
	Yes	258	98
	Lungs	88	34
	Liver	144	56
	Lymph nodes	83	32
	Brain or meninges	27	11
	Bones	92	36
	Other (39 peritoneal, 19 pleural, 14 adrenal, 12 skin, 5 gastrointestinal, 3 spleen, 3 ovaries, 2 pelvic, 2 subcatenous, 1 testicle, 1 mediastinal, 1 parietal and 1 lymphatic vessel)	104	40
Prior palliative treatment		208	80
	Progression after initial response	91	44
	Progression without response	107	51
	Treatment response not known	10	5
Treatment planned (one or more per patient)	IV chemotherapy	192	73
	Monoclonal antibodies	25	10
	Oral chemotherapy	70	27
	Treatment not known	2	1
1 Treatment received after inclusion		243	93
2 Treatments received after inclusion		89	34

IV, intravenous.

At the time of, 241 patients were deceased, 19 patients were alive and 2 patients were lost to follow-up. The causes of death of the 241 patients were as follows: progression for 219 patients (91%); other: 2 (1%) (1 pulmonary embolism and 1 post-operative cardiac arrest) and undocumented: 20 (8%).

Figure 1 shows the three significantly different survival curves. The median survival reported for each population was as follows: population A: 35 days CI 95 [14–56], population B: 78 days [71–114] and population C: 301 days [209–348] (Table 3). The PRONOPALL score showed significant correlation with survival: $P < 0.0001$ (Log-rank test: $chi^2 = 96.1$). The 2-month and 6-month survival rates are presented in Table 3.

Fifteen patients (6%) out of 262 had a score that did not correlate with their survival. There was an underestimation of survival for five cases in population A, the poor prognosis group, and an overestimation for 10 cases in population C, the good prognosis group (data not shown).

Univariate analysis showed that the number of metastatic site was no more a significant factor in survival ($P = 0.89$). Bad PS (ECOG PS), low serum albumin and LDH > 600 IU/l had always a negative influence on survival ($P < 0.0001$) (supplementary Figure S2, available at *Annals of Oncology* online).

Multivariate Cox regression analyses confirmed the lack of independent prognostic value of the item based on the number of metastatic sites. Removal of this factor did not improve the overall prognostic accuracy.

The prognostic performance of the score, evaluated by comparing the low-score C population to A and B, at 2 months and 6 months, had sensitivity 89.4% and 69.4%, specificity 60.9% and 76.9%, positive predictive value 41.2% and 76.9%, negative predictive value 66.7% and 71.5%, overall accuracy 66.7% and 71.5%, respectively.

Vales of the c-index and 95% CI, computed from the ROC analysis of survival at 2-months and at 6-months, were 0.81

Table 3. Description of the PRONOPALL scores obtained and the three populations with different prognosis and analysis of the relationship between the Pronopall score (quantitative) and survival

	Pronopall score	Number	%
Population A	10	2	1
	9	3	1
	8	16	6
Population B	4	33	13
	5	32	12
	6	18	7
	7	28	11
Population C	3	27	10
	2	73	28
	1	4	2
	0	26	10
Pronopall population	A (8–10)	B (4–7)	C (0–3)
Number	21	111	130
%	8	42	50
Two-month survival	24 ± 9%	66 ± 5%	92 ± 2%
Six-month survival	5 ± 5%	27 ± 4%	66 ± 4%
Median survival (days CI95)	35 [14-56]	78 [71-114]	301 [209-348]

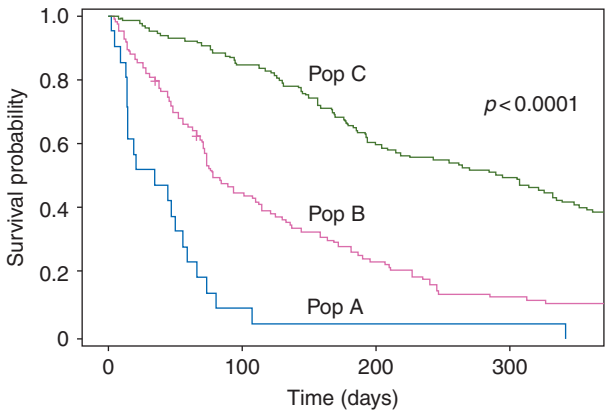

Figure 1. Pronopall group survival curves. PRONOPALL score split patients into three distinct populations: Score 8–10, population A (poor prognosis); Score 4–7, population B (intermediate prognosis); Score 0–3, population C (good prognosis).

[0.75–0.87] and 0.78 [0.72–0.83] respectively (supplementary Figure S3, available at *Annals of Oncology* online).

Discussion

Errors in the evaluation of prognosis are broadly previously described [2–4] which underlines difficulties met to evaluate correctly survival. However, since the 1980s, some of the pioneers of palliative care have validated a number of prognostic tools. These tools, as a true *memento mori* in our modern times, are sometimes considered as a source of mistrust. As such, PRONOPALL is a robust clinical prognostic tool with two biological items that has been validated in two different populations.

In comparison to Barbot's study [10], the 2 months survival rate was quite similar for populations B and C. For population A, difference (8% versus 24%) could be explained that PRONOPALL population is mostly included during consultation (not hospitalized patients).

The number of metastatic site was no more a significant factor in survival maybe because of the difference of population: broadly outpatients versus hospitalized patients which probably induced a better prognosis. Whereas removal of this factor would lead to a simplified score in this population, it seems preferable to adopt a unified scoring strategy which performs accurately in both out- and in-patients populations.

This prognostic tool produced very encouraging results since only 15 patients (6%) out of 262 had a score that did not correlate with their survival (underestimation of survival for 5 poor prognosis cases and overestimation for 10 good prognosis ones). The variations in serum albumin connected to comorbidities and highly progressive diseases (lung and pancreatic cancers) may explain these occasional errors. PRONOPALL also offers the advantage of being able to be recalculated, particularly after albumin levels have returned to normal.

In some cases, the tool may also be useful for evidencing the prognosis of a patient who shows clinical features in the short term that point to a very poor prognosis. In high score patient, this knowledge is helpful for the clinicians to offer him a therapeutic break and to improve part of palliative care. This score can be achieved very regularly to follow patient's evolution.

One of the limitations of the Pronopall score is the intermediate grey area of scores between 4 and 7: we therefore wish to undertake a dynamic evaluation study in which calculations are repeated regularly.

The Pronopall study was conceived with the intention of reducing investigations and treatments for patients whose life expectancy can be counted in weeks, and whose needs should be met principally by palliative care teams. This approach is supported by results from studies carried out by Bakitas *et al.* [14], and Zimmermann *et al.* [15], which showed that palliative care improves quality of life and the Temel *et al.* study [16], which demonstrated that early introduction of this care improves quality of life, mood and overall survival of patients. Palliative care must be introduced as early as possible outside the knowledge of the score.

Moreover, Wright's team showed in a prospective study with a cohort of 386 patients that using chemotherapy in the terminal stage during the final months of life was associated with an increased risk of cardiopulmonary resuscitation and/or mechanical ventilation as well as death in an intensive care unit [17].

At the palliative care stage, the main purpose is to support the patient and their relatives, and a good understanding of the prognosis is fundamental to success. The Pronopall tool could offer this two-part advantage: alerting the care team to the palliative management pathway if it has not been solicited before and instigating a more enlightened discussion of the suitability of an anticancer treatment [18].

It seems essential, in the context of runaway increases in the cost of drugs, to devise tools for making ethical and appropriate decisions in order to safeguard fairness and an access to care for all.

This prognostic score will be used in current practice in a next trial.

Conclusion

The validation of the Pronopall score allows to identify three populations with clearly distinct prognosis. Calculating this score may be a factor in a deeper reflection for teams managing this population of patients, and it may allow them to avoid superfluous investigations and unsuitable indications for chemotherapy, which would have a significant medical and economic impact for society. The prognostic tool could encourage early steps towards a palliative care pathway for the patient and their relatives.

Acknowledgements

The authors thank the patients, institutions, clinicians, medical staff, the clinical research associates, the Regional health agencies of Brittany and the Pays de la Loire. Special thanks to Sory Traoré (former statistician) and Aude de Fallois, (former CRA of Observatory of Cancer BPL).

Funding

None declared.

Disclosure

The authors have declared no conflicts of interest.

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