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A new, simple and objective prognostic score for phase I cancer patients

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ABSTRACT

Aim: To ensure safety and optimise efficacy, careful patient selection for participation in oncologic phase I trials is warranted. Therefore, we did a validation study on existing phase I prognostic scores, and subsequently aimed to make an even more simple prognostic score.

Patients and methods: We retrospectively analysed characteristics and clinical outcome of 122 patients who participated in eight different phase I studies in our centre. A literature search was performed for existing prognostic scores which were validated in our dataset. Additionally, a simple prognostic score able to predict overall survival (OS), progression free survival (PFS), 90-d mortality and duration of participation was developed.

Results: In our population the median OS was 31 (range 4–241) weeks, median PFS was 10 (range 3–119) weeks. Thirteen patients (11%) died within 90-d and median participation duration was 11 (range 1–119) weeks. Two out of five existing prognostic scores could be validated in this dataset for OS. Based on multivariate analyses a new, objective and simple score, consisting of LDH, sodium and haemoglobin, was tested. High score (2–3 points) compared to low score (0–1) significantly predicted OS (HR 1.878, $p = 0.003$), PFS (HR 1.156, $p = 0.038$), participation duration (HR 1.858, $p = 0.004$) and 90-d mortality (OR 4.200, $p = 0.022$).

Conclusion: We propose a new prognostic model, using LDH, sodium and haemoglobin, helpful to predict OS, PFS, participation duration and 90-d mortality. Larger multicentre studies are needed to validate this score.

1. Introduction

Phase I studies are primarily designed to determine the tolerability and toxicity profile of a new agent or a new combination of drugs. Characteristic for oncological phase I trials are the small number of patients participating, the uncertainty of toxicity and effectiveness, the study strain for the participants due to the large logistic commitment and multiple safety control visits. Patients participating within these studies are vulnerable patients with advanced cancer who have been through all available standard therapies. The question whether or not to offer a specific patient the chance to participate in a phase I trial is not easy to answer. In order to ensure safety and to minimise risk, the widely accepted inclusion

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and exclusion criteria for phase I trials include a life expectancy of more than 12 weeks, a performance score according to the World Health Organisation (WHO) criteria of Eastern Cooperative Oncology Group (ECOG) 0–1 (Karnofsky score $\geqslant$ 70) and normal organ function. These are, however, rather suggestive and not very sophisticated criteria, making them not very instrumental in the careful selection of phase I participants.

A prognostic score which can estimate overall survival (OS), progression free survival (PFS) and 90-d mortality could contribute to a proper selection. Recently a number of prognostic scores have been published in the literature.[1–5] Most of these used comparable factors in order to differentiate between patients with more and less favourable prognosis. Used prognostic factors were hypo-albumin (<38 g/L), lymphocyte count below 700/mm^3, lactate dehydrogenase (LDH), lowered ECOG score, a positive history of thromboembolism or cisplatin use, the presence of liver metastases and elevated platelets counts ($\geqslant 440 \times 10^9$/L).[1–6] Of note, only one of these scores, the score proposed by Arkenau et al. has been validated.[1] This score consists of an elevated LDH (>upper limit of normal (ULN)), lowered albumin (<35 g/L) and number of metastatic sites (>2).[6] Patients in the high risk group (score 2–3) had a significantly lower OS than patients in the low risk group (score 0–1). Their reported phase I survival risk score was determined in a population comprising 35% patients with urological cancers, with a significant better overall survival due to a high number of prostate cancer patients compared to the non-urological cancer patients (98 versus 26 weeks, <0.0001). The score was validated in an independent dataset in which only 8% of the patients had urological tumours and still the score proved to be able to predict treatment outcome.[1]

We aimed to compare the clinical outcome of our single centre phase I population with the literature, to validate the existing prognostic scores in our dataset and to propose a prognostic score contributing to optimal patient selection. Preferably, this score must be clinically applicable, simple, objective and able to estimate OS, PFS, participation duration and 90-d mortality.

2. Materials and methods

2.1. Patients and data collection

Dutch patients who participated in eight different phase I studies between July 2004 and August 2008 at the Radboud University Nijmegen Medical Centre were identified. All patients fulfilled the study specific selection criteria and had objective progressive disease prior to study entry. In each case we recorded the following patient characteristics: age, gender, cancer type, cancer histology, number of metastatic sites, number of previous treatments, performance status, weight loss prior to start, albumin, haemoglobin (Hb), leucocytes, lymphocytes, thrombocytes, LDH, C-reactive protein (CRP), sodium, potassium, calcium, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (AF). The duration of survival, PFS and participation duration were documented. Also 90-d mortality was documented. To determine severe toxicity, we recorded the presence of serious adverse events (SAEs) and treatment related deaths.

2.2. Statistical considerations

First, existing prognostic scores as identified in the literature were validated in our dataset on OS, PFS and participation duration using a Cox regression model and on 90-d mortality using a logistic regression model. Only those scores composed of variables available in our data set were tested. Scores using more than two risk groups were modified since the goal was to achieve a simple and objective test able to advise whether or not a patient should be advised to participate.

The 21 potential prognostic factors, mentioned previously, were identified from the literature. Only those that were significant in the univariate analysis in our dataset and had clear clinical relevance were considered for our prognostic score. Those 13 factors were: Hb, albumin, LDH, age, performance status, number of metastatic sites, sodium, potassium, AF, ALAT, calcium and leucocytes. To prevent over-fitting i.e. non-generalizability of the fitted model to other datasets, we reduced the number of factors in such a way that the maximum number of factors was one tenth of the number of events[7] Those factors were selected on the basis of clinical relevance and statistical significance in the univariate Cox regression. The degree of clinical relevance was determined by professionals with extensive experience.

To arrive at a clinically interpretable prognostic score, we categorised these factors to low risk (0 point) and high risk (1 point) based on the upper and lower limits of normal. We then used forwards and backwards Cox multivariate regression for overall survival, to identify the factors for our prognostic score i.e. factors non-significant in the multivariate regression were excluded. The resulting forward and backward selection models were compared in terms of the strength of the hazard ratio for overall survival. To arrive at a simple model to calculate score, we defined our prognostic score as the sum of the identified factors i.e. our prognostic score was the number of risk factors. We determined its cut-off value as the value that gave the greatest separation in overall survival, PFS, participation duration, and 90-d mortality, based on highest hazard/odds ratio and statistical significance. This means that the score was based on its results for overall survival, but was also evaluated for PFS, 90-d mortality rate and participation duration. The Kaplan–Meier method was used to estimate the survival curves for OS, PFS and participation duration.

We investigated whether other prognostic scores had an additional value in predicting OS, while using our prognostic score as follows. We performed a multivariate Cox regression including our prognostic score and the additional score as the only two predictors. Therefore, we modified the outcome of the existing scores into: high and low risk. If the additional score was statistically significant, it had additional value.

Analyses were performed using the SPSS program (version 16.0). A p-value below 0.05 was considered to be significant.

3. Results

3.1. Patients characteristics

The baseline patient characteristics of the 122 identified patients are presented in Table 1. The median age

Table 1 – Baseline patient characteristics (*n* = 122)

Characteristics	Median (range)	Number	(%)
Sex		83	68
Male		39	32
Female			
Age	57 years	111	91
<70 years	(30–82)	11	9
⩾70 years			
Performance status	1 (0–2)	10	8
ECOG 0		108	89
ECOG 1		4	3
ECOG 2			
Type of malignancy		49	40
Gastro-intestinal cancer		18	15
Melanoma		15	12
Urological cancer		12	10
Non small cell lung cancer		9	7
Head and Neck cancer		8	6
Breast and gynaecological cancer		7	6
Sarcomas		4	3
Other			
Metastatic sites	2 (0–5)	3	3
0		28	23
1		60	48
2		27	22
3		4	4
4 or higher			
Previous systemic treatments	3 (0–11)	1	1
0		12	10
1		28	23
2		44	36
3		15	13
4		14	11
5		7	6
⩾6			
Serious Adverse Events (SAE)	0 (0–4)	85	70
0		29	24
1		8	6
⩾2			
Overall Survival (OS)	31 weeks (4–241)		
Progression free survival (PFS)	10 weeks (3–119)		
Participation duration	11 weeks (1–119)		
90-d Mortality rate		13	11
LDH	483	69	57
>450 U/L		51	42
⩽450 U/L			
Hb	7.95	55	45
<LLN		67	55
⩾LLN			
Sodium	140	8	7
<135 mmol/L		114	93
⩾135 mmol/L			
Potassium	4.0	14	12
<3.5 mmol/L		108	88
>3.5 mmol/L			
CRP	19.0	31	25
>10 mg/L		22	18
<10 mg/L			

LLN = lower limit of normal, for Hb < 8.1 in male and <7.3 in female.
CRP = C-reactive protein.

was 57 years (range 30–82 years). Eleven patients (9%) were aged older than 70 years, 10 patients (8%) were younger than 40 years. The male/female ratio was 2.1:1 (83 males, 39 females). The five most common tumours were gastro-

Table 2 – Overview of studies focused on phase I trial clinical outcome.

	N	OS (weeks)	PFS (weeks)	90 DM (%)	Age (years)	ECOG 0–1 (%)	Most frequent reported types of malignancy	No. Tr.
Arkenau et al. (2009)[1]	78	27	ND	21.8	56	95	39% GI 24% Breast and gynaecological 10% Sarcoma 9% Thoracic and head and neck 8% Urological	2
Postel-Vinay et al. (2009)[17]	135	38	10	ND	57	90	18% Breast and gynaecological 16% Prostate 16% Sarcoma 15% Thoracic 11% GI	2
Wheler et al. (2009)[5]	200	35	ND	ND	58	95	33% GI 13% Lung 13% Urological 12% Melanoma 6.5% Head and Neck	4
Arkenau et al. (2008)[6]	148	43	11	ND	58	94	34% Urological 16% Breast and gynaecological 14% Lung, esothelioma and head and neck 12% Sarcoma 12% GI	2
Bachelot et al. (2000)[2]	154	22	15	ND	54	73	36% GI 17% Head and Neck 15% Breast 9% Gynaecological 6% Urological	ND
Han et al. (2003)[15]	420	27-37[a]	ND	16–21	56	86	19% GI 15% Melanoma 11% Breast 9% Renal 9% Ovarian	ND
Penel et al. (2008)[14]	156	25	ND	27	54	92	23% Breast 17% Head and Neck 11% GI 11% Lung 5% Ovary	3
Penel *et al.* (2009)[3]	257	34	ND	17.5-13	56	97	13% Lung 12% Breast 11% GI 9% Sarcomas 7% Unknown primary	3
Janisch et al. (1994)[4]	349	28	ND	± 25[b]	58	78	30% GI 17% Renal 9% Breast 9% Lung 4% Sarcomas	ND
This Study	122	31	10	11	57	97	40% GI 15% Skin 10% Lung 12% Urologic 7% Head and Neck	3

N = number of patients, OS = median overall survival in weeks, PFS = progression free survival in weeks, No. Tr. = median number of previous treatments, 90 DM = 90-d mortality rate, ND = not done GI = gastro intestinal.

[a] Median OS 27 weeks in non-chemotherapy phase I populations, OS 37 weeks in chemotherapy phase I trials.

[b] As shown in figure.

intestinal cancer (40.2%), melanoma (14.8%), urological cancer (12.3%), non small cell lung cancer (9.8%), and squamous cell carcinoma of the head and neck (7.8%). The median number of metastatic sites was 2 (range 0–5). The median number of previous systemic treatments was 3 (range 0–12). Most of the participants had a good performance status (96.7%, ECOG 0 or 1). The population was comparable to previously described phase I populations. (Table 2)

Table 3 – Scores proposed in literature.

Score	Penel[3]	Bachelot[2]	Wheler[5]	Janisch[4]	Arkenau[1]	Arkenau[6]	Nijmegen
Risk factors	Albumin $\leqslant$ 38 g/L Lymphocyte count < 700	LDH > 600 UI/L PS > ECOG 1	History of thromboembolism Platelets $\geqslant 440 \times 10^9$/L Hepatic metastasis	PS Platelet count > 321,000 μL Albumin < 39 g/L No genitourinary/ gynecological tumour Cisplatin exposure	LDH > ULN Albumin < 35 g/L Site of metastatic sites > 2	LDH > ULN Albumin < 35 g/l Site of metastases > 2	LDH > 450 U/L (ULN) Hb < LLN Sodium < 135 mmol/L
Risk-groups	alb $\geqslant$ 38 g/L	0	0	PS 100% + 0–2 risk factors	0–1	0–1	0–1
Low	Albumin < 38 g/L	1	1	PS 60–70 + 0–1 risk factors	-	–	–
Intermediate	Lymphocyte count $\geqslant$ 700	2	2–3	PS 80–90 + 0–2 risk factors	2–3	2–3	2–3
High	Albumin < 38 g/L lymphocyte count < 700			PS 60-70 + 2-4 risk factors PS 80 – 100 + 3-4 risk factors			
OS	–	37 versus 19 versus 6 ($p < 0.001$)	53 versus 35 versus 23 ($p < 0.001$)	55 versus 32 versus 15 ($p < 0.0001$)	33 versus 16 ($p = 0.036$)	74 versus 25 ($p < 0.001$)	38 versus 19 ($p = 0.003$)
PFS (weeks)	–	–	–	–	–	–	11 versus 8 ($p = 0.038$)
90-d Mortality (%)	90-d: 19% versus 35% versus 100%	12% versus 32% versus 85%	–	–	–	–	5.8% versus 20.6% ($p = 0.022$)
Participation duration (weeks)	–	–	–	–	–	–	12 versus 7 ($p = 0.004$)

Prognostic scores proposed in literature. OS = overall survival in weeks. PFS = progression free survival in weeks, PS = performance status, LDH = lactate dehydrogenase, ULN = upper limit of normal, LLN = lower limit of normal.

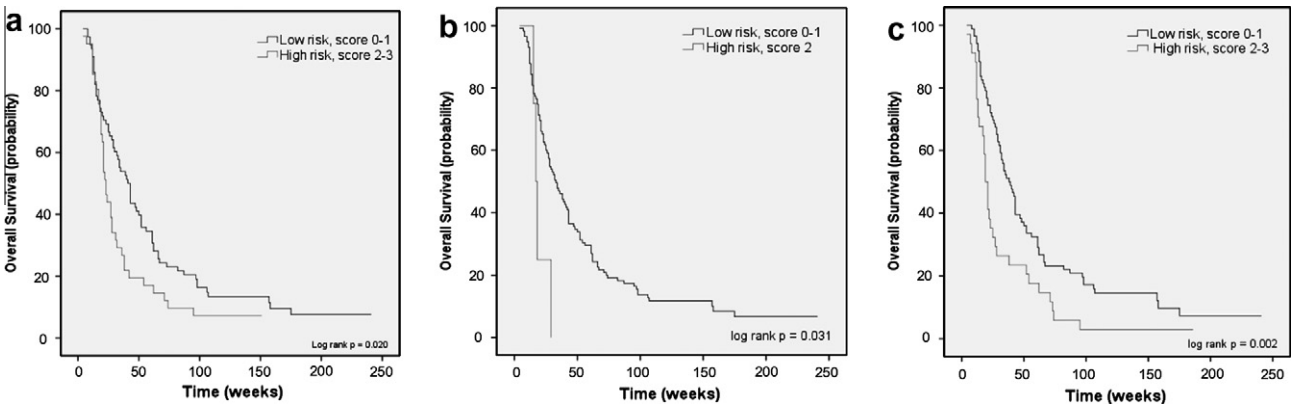

Fig. 1 – Overall survival based on prognostic scores in literature. Panel A: Overall survival according to the Arkenau prognostic risk score as applied in the current study population of patients enrolled into eight phase I trials in one clinical centre between 2004 and 2008. Risk factors are LDH > ULN, Albumin < 35 g/L and more than to sites of metastases. The prognostic score ranges from 0 to 3. Median overall survival of the low risk group is 41 weeks versus median overall survival of the high risk group is 23 weeks. ($p = 0.020$). Panel B: Overall survival according to the Penel prognostic risk score as applied in the current study population of patients enrolled into eight phase I trials in one clinical centre between 2004 and 2008. Risk factors are lymphocyte count <700 and albumin ⩽38 g/L. The prognostic score ranges from 0 to 2. Median overall survival of the low risk group is 33 weeks versus median overall survival of the high risk group is 17 weeks. ($p = 0.031$). Panel C: Overall survival according to the Nijmegen prognostic risk score for patients enrolled onto phase I clinical trials. Risk factors are, LDH > 450 U/L, Hb ⩽ lower limit of normal, sodium ⩽ 135 mmol/L. Prognostic score ranges from 0 to 3. The low risk group comprises patients with a score of 0–1 and the high risk group comprises patients with a score of 2–3. Median overall survival of low risk group is 38 weeks. Medial overall survival of high risk group is 19 weeks.($p = 0.002$).

3.2. *Clinical outcome*

The median OS and PFS were 31 weeks (range 4–241 weeks, 10 patients are still alive) and 10 weeks (range 3–119 weeks), respectively. The median duration of phase I study participation was 11 weeks (range 1–119 weeks). Thirteen patients (11%) died within 90-d. SAEs were reported in 30.3% of the participants with a median number of occurrence of 1 per patient and 1 treatment related death was identified. (Table 2)

3.3. *Reproducibility of the prognostic scores published in the literature*

Five prognostic scores were identified (Table 3). We were not able to test the reproducibility of the scores proposed by Wheler et al. and by Janish et al. because data on 'history of thromboembolism' and 'cisplatin exposure' were not available in our dataset.[4,5] Applying the prognostic score of Arkenau et al., we were able to distinguish patients with a favourable (median OS 41 weeks) or non-favourable prognosis (median OS 23 weeks, $p = 0.020$).[1] (Fig. 1) In our population the score of Arkenau et al. also predicted the duration of study participation (HR 1.577, $p = 0.023$). We could also validate the Penel score in our study population for OS (HR 2.889, $p = 0.042$). In the high risk group the median OS was 17 weeks compared to 33 weeks in the low risk group.(Fig. 1) The modified Bachelot criteria did not predict OS, PFS or 90-d mortality in our dataset. Tested scores and modifications are provided in Table 4.

Table 4 – Prognostic scores validated in our dataset.

Score	Factors	Risk-groups	Modification	OS (weeks)	PFS (weeks)	90 DM (%)	Participation duration (wks)
Penel[61]	Alb < 38 g/L Lymphocyte count < ULN	Low: 0 Int: 1 High: 2	Low:0–1 High: 2	HR 2.9 $p = 0.042$	HR 0.95 $p = 0.922$	OR 0 $p = 0.99$	HR 1.3 $p = 0.646$
Bachelot[62]	LDH > 600 ECOG > 1	Low:0 Int:1 High:2	Low:0–1 High:2	HR 1.3 $p = 0.262$	HR 1.3 $p = 0.195$	OR 1.09 $p = 0.869$	HR 1.5 $p = 0.056$
Arkenau[63]	LDH > ULN Alb < ULN metastatic sites > 2	Low:0–1 High: 2–3	-	HR 1.6 $p = 0.023$	HR 1.4 $p = 0.116$	OR 1.4 $p = 0.581$	HR 1.6 $p = 0.023$

OS = overall survival in weeks, PFS = progression free survival in weeks, 90 DM = 90-d mortality rate in%, low = low risk group, int = intermediate risk group, high = high risk group, alb = albumin, LDH = lactate dehydrogenase, ECOG = performance status, PS = Karnofsky performance status, thrombo = thrombocytes count, Cisplatin = cisplatin exposure.
Scores proposed in literature are validated in our dataset.

Table 5 – Univariate analysis of 13 clinical relevant prognostic factors.

	OS			PFS			90-d mortality			Participation duration		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	Odds	95% CI	*p*-value	HR	95% CI	*p*-value
Albumin[a]	0.943	0.910–0.977	0.001	0.959	0.920–1.000	NS	0.871	0.775–0.980	0.021	0.946	0.913–0.981	0.003
Hb[a]	0.774	0.668–0.898	0.001	0.771	0.651–0.913	0.003	0.668	0.416–1.073	NS	0.738	0.629–0.866	<0.001
LDH[a]	1.000	1.000–1.000	NS	1.001	1.000–1.001	0.008	1.001	1.000–1.001	NS	1.001	1.000–1.001	<0.001
Sodium[a]	0.868	0.860–0.935	<0.001	0.931	0.872–0.955	0.036	0.718	0.585–0.882	0.002	0.945	0.881–1.012	NS
Potassium[a]	0.602	0.343–1.057	NS	0.793	0.439–1.433	NS	0.094	0.016–0.559	0.009	0.715	0.409–1.250	NS
Calcium	2.459	0.887–6.821	NS	3.787	0.967–14.835	NS	4.376	0.196–97.843	NS	3.503	1.156–10.618	0.027
PS[a]	0.958	0.931–0.968	0.003	0.970	0.940–1.001	NS	0.958	0.885–1.038	NS	0.954	0.925–0.984	0.003
AF	1.002	1.001–1.004	0.003	1.003	1.001–1.004	0.001	1.001	0.996–1.006	NS	1.003	1.001–1.004	<0.001
ALAT[a]	1.005	0.999–1.011	NS	1.010	1.002–1.018	0.017	1.000	0.978–1.022	NS	1.008	1.000–1.012	0.043
CRP[a]	1.006	1.002–1.011	0.006	1.005	1.000–1.010	0.039	1.024	1.005–1.043	0.011	1.007	1.002–1.012	0.003
Leucocytes[a]	1.047	0.983–1.115	NS	0.985	0.929–1.045	NS	1.143	0.966–1.352	NS	1.005	0.947–1.066	NS
⩾ 70 years[a]	0.808	0.443–1.508	NS	0.438	0.219–0.877	0.020	0.000	0.000–0.000	NS	0.530	0.283–0.993	0.047
Number of metastatic sites[a]	0.966	0.766–1.217	NS	0.973	0.785–1.208	NS	0.975	0.494–1.922	NS	0.993	0.802–1.230	NS

Independent prognostic factors for OS, PFS, 90-d mortality and participation duration. Results for OS, PFS and participation duration are based on univariate Cox regression analysis. Results for 90-d mortality rate are based on univariate log regression analysis.
HR = hazard ratio, OS = overall survival, PFS = progression free survival, CI = confidence interval, PS = performance status, LDH = lactate dehydrogenase, AF = Alkaline phosphatase, ALAT = Alanine aminotranseferase, CRP = C-reactive protein.
Univariate analysis was performed on factors with continuous scale i.e. without cut-off values.
[a] Factors used for multivariate Cox regression analysis.

3.4. *Prognostic factors for OS, PFS, 90-d mortality and participation duration*

In Table 5 the 13 univariate prognostic variables for OS, PFS and participation duration are presented. The most important variables identified for OS were: sodium ($p < 0.0001$, HR 0.868), CRP ($p = 0.006$, HR 1.006), albumin ($p = 0.001$, HR 0.943), Hb ($p = 0.001$, HR 0.774) and performance ($p = 0.003$, HR 0.958). The lower these values are, the poorer the prognosis is. For 90-d mortality rate a lower potassium ($p = 0.009$, OR 0.094) and albumin ($p = 0.021$, OR 0.871) and a higher ($p = 0.021$, OR 0.871) gave a higher chance of mortality within 90-d.

Table 6 – Nijmegen prognostic score.

Variable	Score	Hazard Ratio	*p*-value
LDH	0	2.255	0.013
<450 U/L (ULN)	1		
⩾450 U/L (ULN)			
Hb	0	2.377	0.006
Male:	1		
>8.1 mmol/L	0		
⩽8.1 mmol/L	1		
Female:			
>7.3 mmol/L			
⩽7.3 mmol/L			
Sodium	0	11.474	<0.001
⩾135 mmol/L	1		
<135 mmol/L			
Prognostic score	0–1 factors	1.878	0.003
Low risk	2–3 factors		
High risk			

p-Value for multivariate analysis, Hazard Ratio for overall survival.

3.5. *Nijmegen prognostic score*

In the multivariate Cox regression we tested 11 variables, based on 111 deaths. From the 13 factors proposed, calcium and AF were excluded from the multivariate Cox regression selection. The 11 variables were: Hb, albumin, LDH, sodium, potassium, age, performance status, number of metastatic sites, ALAT, CRP, leucocytes. According to the HR for OS backwards selection model was chosen. Significant outcome results were found in the following factors: LDH > 450 U/L (HR 2.255, $p = 0.013$), Hb < 7.3 mmol/L in female and <8.1 mmol/L in male (HR 2.377, $p = 0.006$) and sodium < 135 mmol/L (HR 11.474, $p < 0.001$). Each factor accounts for one point. (Table 6) A score of 0–1 (low risk) versus 2–3 (high risk) resulted in the best cut-off point compared to other cut-off possibilities within this set (HR 1.878, $p = 0.003$, 95% CI 1.241–2.839). Using this score, OS was significantly lower for patients in the high risk group (median 19 weeks, range 4–186 weeks) compared with patients in the low risk group (median 38 weeks, range 8–241 weeks).(Fig. 1) The score was also able to predict PFS (median 8 versus 11 weeks, $p = 0.038$, HR 1.156), 90-d mortality (20.6% versus 5.8% $p = 0.022$, OR 4.200) and participation duration (median 7 versus 12 weeks, $p = 0.004$, HR 1.858). (Table 3)

Prognostic scores proposed by Arkenau and Bachelot did not have additional values compared to the Nijmegen criteria. Penel prognostic score, which includes the lymphocyte count, showed added values to the Nijmegen criteria ($p = 0.036$). This suggests that besides the factors considered in our score, lymphocyte count also has a predictive value in our dataset.

4. Discussion

In order to carefully select those patients who may benefit from participation in phase I trials, several prognostic scores

for OS have been published. A prognostic score should be accurate and easy to incorporate in daily clinical practice. We here propose an objective and simple prognostic score, able to predict OS, PFS, participation duration and 90-d mortality.

In a review of the literature we identified eight studies on phase I population outcomes, with five different prognostic scores. (Table 2) In our population we observed a mean OS of 31 weeks, which is comparable to the eight earlier studies. Remarkably, in our population the observed 90-d mortality rate (11%) was less than in other study populations which cannot be explained by the published population characteristics.

The median age of participating patients was 57 years and comparable to the other studies. This is a relatively young age for advanced cancer patients. In this study, only 9% of the patients was older than 70 years, which is an underrepresentation compared with a normal cancer patient population. Contrary to common beliefs, we did not find a relationship between age and OS or severe toxicity ($p > 0.1$). Older patients participated even longer (median 26 versus 11 weeks in >70 compared to $\leqslant$70 years, $p = 0.047$, HR 0.530), which probably reflects patient selection. Of course, due to the strict study eligibility criteria in general only the very fit older patients will enter the studies. However, when older patients fulfil the inclusion and exclusion criteria, age alone is no reason to exclude them from phase I trial participation. Since the rising incidence of cancer and the highest prevalence of cancer in the elderly, establishing age-based standards for cancer care is important.[8]

We were able to validate the scores of Arkenau et al. and Penel in our population for OS, but not for 90-d mortality. Generally, OS is a more sensitive outcome, therefore, differences in OS can be detected with a smaller sample size. The expectation is that if the sample size is large enough and a true difference in 90-d mortality rate does exist, then a significant difference in 90-d mortality rate would be detected.

We proposed a new prognostic score, based on three simple, cheap and objective laboratory measurements which were able to differentiate between low and high risk patients not only for OS, but also for PFS, duration of participation and 90-d mortality. Further validation of our score, in another phase I population is warranted. In a multivariate analysis, only the Penel score had additional value. Comparing the predictors used by Penel and in the Nijmegen score, we see that Penel used lymphocyte count and albumin. We did consider albumin in the 11 clinical meaningful factors used, but it was not statistically significant and because of this, it was not included in our score. Therefore, our hypothesis is that only the contribution of lymphocyte count in the Penel score accounts for the additional value of the Penel score beyond our score. The lymphocyte count was included in our set of 11 predictors because lymphocyte count is not always determined in our clinic. Instead of the lymphocyte count, we used leucocytes.

The goal of this study was to develop a rapid, objective, clinically applicable and simple prognostic score. We, therefore, decided to incorporate a maximum of three prognostic factors in our prognostic score, using hyponaetremia, anaemia and elevated LDH. Hyponaetremia is a well known complication of cancer, caused by several mechanisms including the paraneoplastic production of anti-diuretic hormone (ADH, therefore called syndrome of inappropriate ADH; SiADH), pituitary dysfunction, treatment-related hyponaetremia, sodium depletion and decreases in effective circulating blood volume.[9,10] Hyponaetremia is associated with poor prognosis in cancer populations and this has been shown not to be attributable to the hyponaetremia itself.[9,11,12] Its role in phase I populations is unclear. Hyponaetremia was not part of the previously proposed prognostic scores. Anaemia has an impact on prognosis, survival and response to therapy in cancer patients. This is caused by several factors including tumour grade and severity, response to therapy, patient compliance and secondary organ function.[13] However, there is a consensus on the central role of tumour hypoxia. There is still no clarity about the role of anaemia in phase I patients. Anaemia was not incorporated in the previously developed prognostic scores for phase I populations. In fact, other studies did not discriminate between levels of haemoglobin in female and male patients by determining the presence of anaemia.[1,4,5,14] A level of 7.45 mmol/l was used to determine whether or not a patient had anaemia.[1,3] In our population we used different levels by gender to accurately demonstrate the existence of anaemia.

An elevated LDH is a well known poor prognosis factor in metastatic cancer patients, partly reflecting a tumour load. An elevated LDH was used in the scores of Arkenau and Bachelot.[1,2,6]

As well as the three selected factors, other factors were also correlated with treatment outcome (Table 5). CRP appeared to be of prognostic value to OS, PFS, participation duration and 90-d mortality as well. As an acute phase protein, this seems to be understandable. This factor was not included in our prognostic score since the amount of missing values was high and because CRP is not always a routine measurement within phase I studies. As reported in earlier studies of prognostic factors in phase I patients, hypo-albumin was a prognostic factor for OS, 90-d mortality and participation duration.[1,3,4,6,14,15]

A study population of 122 patients is relatively small compared to other studies which contain between 148 and 349 patients.[1,3–5] Our score needs to be validated in another study population. Recently, Olmos et al. collected the outcome of 2232 patients enrolled in phase I oncology trials, treated in 14 leading European Units. A seven variables score was not superior to the Arkenau prognostic score. Our score, based on only laboratory values and, therefore, simple, should be validated in this database.[16]

In conclusion, we propose an objective and simple prognostic model based on Hb, sodium and LDH convincingly selecting patients likely to benefit from participation in phase I studies. Further studies are needed to validate this Nijmegen prognostic score.

5. Disclosures

None

Conflict of interest statement

None declared.

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