Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2217

Cancer Therapy: Clinical

Clinical Cancer Research

Survival of 1,181 Patients in a Phase I Clinic: The MD Anderson Clinical Center for Targeted Therapy Experience

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Abstract

Purpose: To determine whether the Royal Marsden Hospital (RMH; London, UK) prognostic score for phase I patients can be validated in a large group of individuals seen in a different center and whether other prognostic variables are also relevant, we present an analysis of 1,181 patients treated in the MD Anderson Cancer Center (MDACC; Houston, TX) phase I clinic.

Experimental Design: Medical records of 1,181 consecutive patients who were treated on at least one trial in the phase I clinic were reviewed.

Results: The median age was 58 years and 50% were women. The median number of prior therapies was four and median survival 10 months [95% confidence interval (CI), 9.1–10.9 months]. Independent factors that predicted shorter survival in a multivariate Cox model and could be internally validated included RMH score of >1 ($P < 0.0001$; albumin <3.5 g/dL; lactate dehydrogenase >upper limit of normal, and >two sites of metastases), gastrointestinal tumor type ($P < 0.0001$), and Eastern Cooperative Oncology Group performance status ≥ 1 ($P = 0.0004$). The median survival was 24.0, 15.2, 8.4, 6.2, and 4.1 months for patients with 0, 1, 2, 3, and 4 or 5 of the above risk factors, respectively.

Conclusion: The RMH score was validated in a large group of patients at MDACC. Internal validation of the independent prognostic factors for survival led to the development of the MDACC prognostic score, a modification of the RMH score that strengthens it. *Clin Cancer Res; 18(10); 2922–9. ©2012 AACR.*

Introduction

Phase I trials play a key role in the evaluation of novel targeted therapies in patients with advanced cancer. A primary challenge is to select patients who are most likely to benefit from investigational treatments, which is being facilitated by the increasing identification of molecular markers that can select subsets of such patients. Although phase I trials have generally proven safe (1–3), an overall assessment of predicted survival of patients may further help in this decision-making process. However, physicians are not necessarily able to accurately predict the survival of their patients (4). Some groups have therefore proposed models to predict outcome in patients with advanced cancers (4–7).

The objective of this study was to evaluate a large phase I population in our clinic at the MD Anderson Cancer Center (MDACC; Houston, TX) to see whether we could validate one of the best-established prediction models, the Royal Marsden Hospital (RMH; London, UK) score [dichotomized by albumin <3.5 vs. $\geq$3.5 g/dL, lactate dehydrogenase (LDH) > upper limit of normal (ULN) vs. $\leq$ULN, and >2 vs. $\leq$2 sites of metastases; ref. 1], and to identify additional risk factors related to overall survival. Therefore, we studied the clinical characteristics of 1,181 patients who presented to our phase I clinic and correlated these factors to survival outcomes. Our current article validates the RMH score and proposes modifications that strengthens its predictive power.

Materials and Methods

We reviewed the electronic records of 1,181 consecutive patients who were treated on at least one clinical trial in the phase I Clinical Trials Program (Clinical Center for Targeted Therapy) at the MDACC beginning January 1, 2006. Investigational regimens available for patient enrollment varied over time depending upon protocol availability at the time of presentation. All patients' electronic medical records were reviewed to determine clinical characteristics, treatment, and clinical outcomes. This analysis as well as all

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Previous presentation: Poster discussion presentation at 2011 ASCO Annual Meeting, Chicago, IL.

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doi: 10.1158/1078-0432.CCR-11-2217

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Translational Relevance

We found an overall survival of 10 months in our phase I population of 1,181 patients treated at MD Anderson Cancer Center (Houston, TX) in the Department of Investigational Cancer Therapeutics. We analyzed prognostic factors in this patient population and showed that five clinical variables independently predicted survival including low albumin (<3.5 g/dL), lactate dehydrogenase greater than upper limit of normal, more than two sites of metastases, gastrointestinal tumor type, and Eastern Cooperative Oncology Group performance status ≥1. We validated a previously published prognostic model from the Royal Marsden Hospital (London, UK) that included three of these five variables [low albumin (<35 g/L), lactate dehydrogenase greater than upper limit of normal, and more than two sites of metastases], strengthening their model with the addition of two variables. Our data provide a prognostic model for a phase I population that may assist with clinical decision making and selection of targeted therapies.

treatment on clinical trials were conducted in accordance with the guidelines of the MDACC Institutional Review Board.

Endpoints and statistical methods

The purpose of this study was to validate the RMH score and identify additional risk factors related to the overall survival in 1,181 patients with advanced cancers treated in a phase I clinic. The primary endpoint of the current study was overall survival, which was measured from the time of presentation to the phase I program at MDACC, until death from any cause or last follow-up. Patients still alive were censored for survival at the time of their last follow-up. Descriptive statistics were used to summarize the baseline patients' characteristics. Categorical data were described with contingency tables including counts and percentages. Continuously scaled measures were summarized with descriptive statistical measures [i.e., mean (±SD) or median (range)]. Survival curves were estimated by the Kaplan–Meier method. Univariate log-rank test was used to compare survival distributions between groups.

The following covariates were analyzed in univariate analysis (Table 1), including age (>60 vs. ≤60 years), gender, tumor type (breast, gastrointestinal, genitourinary, gynecologic, lung/thoracic/head and neck, and others), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2 or 3; ref. 2), liver metastases (yes vs. no), history of thromboembolism (yes vs. no), platelet levels (<140, 140–440, >440 K/UL), albumin levels (<3.5 vs. ≥3.5 g/dL), number of prior therapies (0, 1, 2, 3, 4, 5+), history of prior radiation (yes vs. no), history of prior surgery (yes vs. no), number of metastatic sites (≤2 vs. >2), LDH levels (≤618 vs. >618 IU/L), and RMH score (0 or 1 vs. 2 or 3). The RMH score includes the following poor prognostic variables: albumin <3.5 g/dL, LDH > ULN (618 IU/L in our institution), and >2 sites of metastases. These variables were measured at the time of presentation to the phase I program. The multivariate Cox proportional hazards regression model was used to validate the RMH score using our complete data set. We examined the predictive ability of prognostic factors for survival with the Harrell *c*-statistic (3); higher *c*-statistic indicates greater predictive ability.

We also wanted to identify additional independent prognostic factors predicting overall survival based on the MDACC data. A randomly selected training set, containing half of the patients, was used to conduct multivariate analysis to identify the independent prognostic factors for survival. We applied this to the validation set, containing the remaining patients and assessed the effectiveness with Harrell *c*-statistics and "bootstrapping" method. Data from the patients who had all the data points (complete demographic and clinical data) at baseline were used to evaluate the 2 prognostic models. All statistical tests were 2-sided and $P < 0.05$ was considered statistically significant. The χ^2 test was used to assess the correlation between the MDACC and RMH prognostic scores. Statistical analyses were conducted with SAS 9.1 (SAS Institute) and S-Plus, version 7.0 (Insightful Corp.) software.

Results

Patients

A total of 1,181 patients who were treated in the phase I clinic on at least one phase I trial were identified. The median age was 58 years (range, 3–89 years) and 44% of patients were older than 60 years. Only 66 patients (5.6%) had not received any therapy for their advanced disease before coming to the phase I clinic and that was generally because of the unavailability of standard-of-care therapy options. Among the 1,115 patients who had received at least one prior treatment, the median number of prior treatments was 4 (range, 1–17). The most common primary tumor site was the gastrointestinal tract (33%). The demographics of patients by primary tumor type are shown in Fig. 1A. Other baseline patient characteristics include 498 patients (42.2%) with liver metastases, 190 patients (16%) with a history of thromboembolism, 136 patients (12%) with elevated platelet levels (>440 K/UL), 419 patients (36%) with elevated LDH levels (>618 IU/L), and 133 patients (11%) with low albumin levels (<3.5 g/dL; Table 1).

Treatments

All the patients received treatment on at least one phase I trial (range, 1–9) and 24% of patients were treated on more than one trial. Eighty-six percent of our patients received a trial that included a targeted agent and 32% of patients were treated on a trial that included a cytotoxic agent. Eighteen percent of patients received treatment that included both a targeted agent and a cytotoxic agent. Of 1,181 patients, 893

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Table 1. Univariate analysis of survival in 1,181 patients by characteristics at first visit to phase I clinic

Variables	*N* (%) 1,181	Number of deaths 795	Median survival, mo (95% CI) 10.0 (9.1–10.9)	Survival rate (1 y), % 44	*P*
Age, y					
≤60	660 (55.9)	434	10.9 (9.7–12.1)	46	0.125
>60	521 (44.1)	361	9.1 (8.1–10.1)	41	
Sex					
Female	594 (50.3)	392	10.1 (8.8–11.2)	44	0.86
Male	587 (49.7)	403	9.8 (8.5–11.4)	44	
Tumor classification					
Breast	112 (9.5)	83	8.3 (6.6–10.8)	35	<0.0001
Gastrointestinal	392 (33.2)	310	7.4 (6.6–8.1)	30	
Genitourinary	110 (9.3)	67	12.8 (9.6–17.5)	54	
Gynecologic	82 (6.9)	55	8.3 (6.8–11.0)	35	
Lung/thoracic/head and neck	149 (12.6)	81	15.5 (12.2–23.1)	59	
Others	336 (28.5)	199	15.5 (12.0–18.3)	55	
ECOG PS[a]					
0	369 (31.2)	234	13.8 (11.6–17.1)	54	<0.0001
1	705 (59.7)	470	9.1 (8.0–10.3)	41	
2	83 (7.0)	68	4.1 (3.5–6.6)	26	
3	7 (0.6)	7	3.1 (2.9, NA)	29	
Liver metastases					
No	683 (57.8)	413	12.8 (11.3–15.2)	52	<0.0001
Yes	498 (42.2)	382	7.6 (6.6–8.4)	33	
History of thromboembolism					
No	991 (83.9)	656	10.8 (9.7–11.7)	46	0.0005
Yes	190 (16.1)	139	7.7 (6.2–9.5)	33	
Platelets,[a] K/UL					
<140	112 (9.5)	84	8.3 (6.8–12.7)	39	<0.0001
140–440	928 (78.6)	603	10.5 (9.6–11.8)	46	
>440	136 (11.5)	106	7.9 (6.3–10.1)	32	
Albumin,[a] g/dL					
≥3.5	1,041 (88.1)	684	10.9 (10.1–12.0)	47	<0.0001
<3.5	133 (11.3)	107	5.4 (3.9–6.8)	20	
Number of prior therapies					
0	66 (5.6)	25	25.3 (22.8 to NA)	81	<0.0001
1	113 (9.6)	65	16.9 (14.6–25.4)	62	
2	192 (16.3)	125	9.2 (7.7–12.0)	42	
3	201 (17.0)	132	9.4 (7.8–11.5)	42	
4	187 (15.8)	137	9.0 (7.5–10.8)	37	
5+	422 (35.7)	311	8.3 (7.5–9.7)	38	
Prior radiation					
No	593 (50.2)	390	10.7 (9.5–12.4)	46	0.028
Yes	588 (49.8)	405	9.2 (8.1–10.7)	42	
Prior surgery					
No	293 (24.8)	202	9.9 (8.1–11.4)	43	0.3253
Yes	888 (75.2)	593	10.1 (8.8–11.3)	44	
Number of metastatic sites					
≤2	734 (62.2)	457	12.4 (10.9–14.6)	51	<0.0001
>2	447 (37.8)	338	7.4 (6.7–8.1)	31	
LDH,[a] IU/L					
≤618	755 (63.9)	449	14.0 (12.4–16.0)	55	<0.0001
>618	419 (35.5)	343	6.8 (6.1–7.4)	24	

(Continued on the following page)

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Table 1. Univariate analysis of survival in 1,181 patients by characteristics at first visit to phase I clinic (Cont'd)

Variables	*N* (%) 1,181	Number of deaths 795	Median survival, mo (95% CI) 10.0 (9.1–10.9)	Survival rate (1 y), % 44	*P*
RMH score[a]					
0 and 1	908 (76.9)	573	12.3 (11.2–13.8)	51	<0.0001
>1	261 (22.1)	216	5.5 (4.8–6.6)	19	

Abbreviation: PS, performance status.

[a]Baseline data at first visit to phase I clinic were not available for all patients for variables including: ECOG PS (17 patients), platelets (5 patients), albumin (7 patients), LDH (7 patients), and RMH score (12 patients).

patients were treated on one protocol, 196 on 2 protocols, 66 on 3 protocols, 16 on 4 protocols, 4 on 5 protocols, 2 on 6 protocols, 3 on 7 protocols, and one patient was treated on 9 protocols. The composition of patients' treatment by study type is illustrated in Fig. 1B.

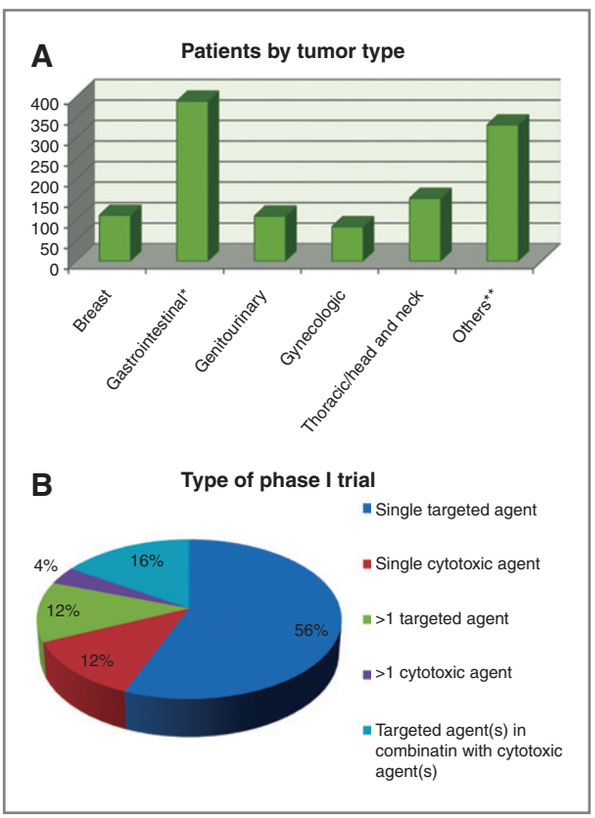

Figure 1. A, patients by tumor type (total $n = 1,181$). *Gastrointestinal tumors ($N = 392$) include colon (185); pancreas (61); rectum (46); esophagus (26); appendix (18); small Intestine (14); gastric (12); hepatocellular (11); cholangiocarcinoma (8); anus (6); cholangiocarcinoma and hepatocellular (2); peritoneum (2); and liver, NOS (1), **Others ($N = 336$) include melanoma (83); thyroid (82); sarcoma (52); lymphoma (19); hematologic other (19); endocrine (16); cancer of unknown primary (16); neuroendocrine (15); non-melanoma skin (15); CNS tumors (12); and mycosis fungoides (7). B, type of phase I trial.

Survival

Among 1,181 patients, there were 795 deaths after a median follow-up of 8.13 months. The overall median survival was 10 months [95% confidence interval (CI), 9.1–10.9 months; Fig. 2A]. The survival rates at 6, 12, and 18 months were 70%, 44%, and 32%, respectively.

Univariate analysis on survival

The factors that were associated with shorter survival in univariate analysis (Table 1) were tumor type ($P < 0.0001$; patients with gastrointestinal tumors had the worst survival), ECOG performance status ≥ 1 ($P < 0.0001$), history of liver metastases ($P < 0.0001$), history of thromboembolism ($P = 0.0005$), elevated platelet levels (>440 K/UL; $P < 0.0001$), low albumin levels (<3.5 g/dL; $P < 0.0001$), increasing number of prior therapies ($P < 0.0001$), prior radiation ($P = 0.028$), >2 metastatic sites ($P < 0.0001$), LDH levels above normal (>618 IU/L; $P < 0.0001$), and RMH score >1 ($P < 0.0001$; RMH variables being albumin <3.5 g/dL, LDH >ULN, and >2 sites of metastases).

Validation of RMH score

In the multivariate analysis using Cox proportional hazards models, a stepwise variable selection procedure was conducted to identify the optimal set of independent variables for overall survival. The final model included low albumin levels (<3.5 g/dL; $P < 0.0001$), number of metastatic sites >2 ($P = 0.0001$), elevated LDH levels (>618 IU/L; $P < 0.0001$), gastrointestinal tumor type ($P < 0.0001$), ECOG performance status ≥ 1 ($P = 0.0004$), elevated platelet levels (>440 K/UL; $P = 0.0047$), and ≥ 3 prior therapies ($P = 0.0007$) that were independently predictive of shorter survival. When the RMH score (which incorporates low albumin, elevated LDH, and >2 metastatic sites) was included in the Cox model, factors independently prognostic for survival were RMH score >1 ($P < 0.0001$), gastrointestinal tumor type ($P < 0.0001$), ECOG performance status ≥ 1 ($P = 0.0004$), elevated platelet levels (>440 K/UL; $P = 0.0008$), and ≥ 3 prior therapies ($P < 0.0001$; Table 2). A subgroup analysis that stratified patients as colorectal carcinoma ($n = 231$) versus those patients with

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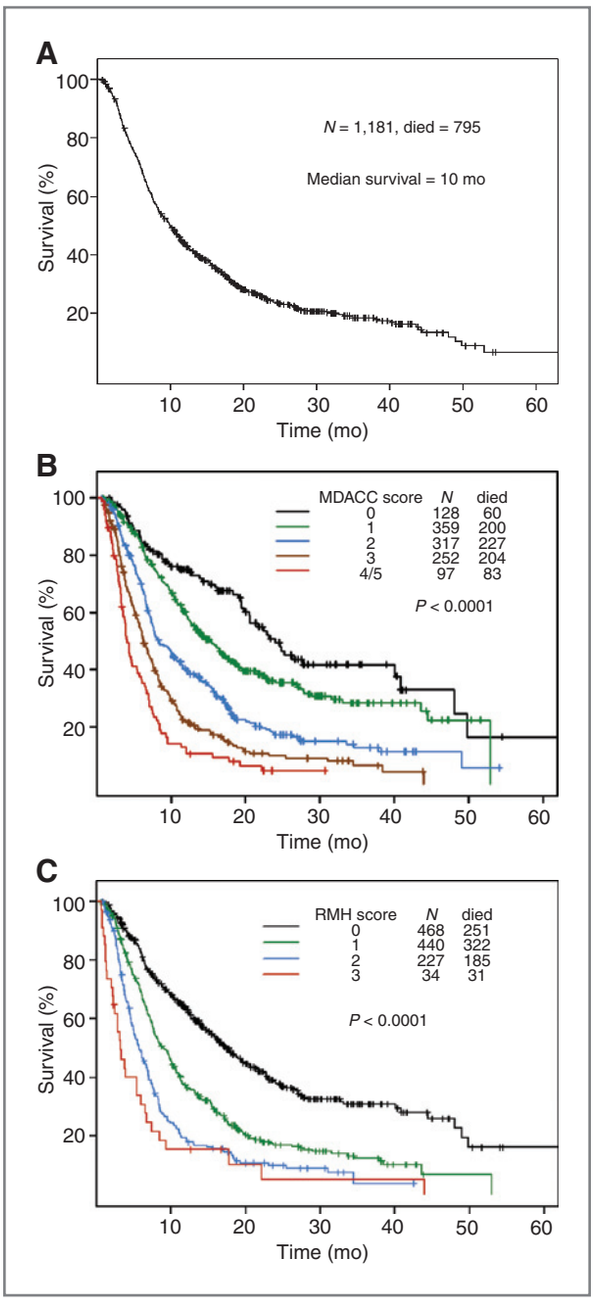

Figure 2. A, Kaplan–Meier survival curve for overall survival in 1,181 patients. Ticks represent patients still alive and hence censored at last follow-up. B, Kaplan–Meier survival curve for the 5 risk groups based on MDACC score ($n = 1,153$ patients for whom all baseline data points were available). Ticks represent patients still alive and hence censored at last follow-up. C, Kaplan–Meier survival curve for the 4 risk groups based on RMH score ($n = 1,169$ patients for whom all baseline data points were available). Ticks represent patients still alive and hence censored at last follow-up.

other gastrointestinal tumors ($n = 161$) failed to show statistically significant survival differences (median survival = 7.5 vs. 6.7 months, respectively; $P = 0.64$). In addition, we assessed effectiveness of the Cox model by the Harrell *c*-statistic. The *c*-statistic was 0.592 for LDH (the best 1-variable model), 0.619 for LDH and the number of metastatic sites of disease (the best 2-variable model), and 0.637 for LDH, number of metastatic sites of disease, and albumin (the best 3-variable model). The *P* value was 0.008 for comparing the 1-variable model versus the 2-variable model and $P = 0.0003$ for comparing the 2-variable model versus the 3-variable model. This means that the RMH score is from the best 3-variable model.

Table 2. Multivariate analysis of survival by independent predictors, including the RMH score variables (LDH, number of metastatic sites >2, and albumin) individually and then by including the RMH score by itself as a single variable

Risk factors	RR for death (95% CI)	*P*
Albumin < 3.5 g/dL[a]	1.66 (1.34–2.05)	<0.0001
Number of metastatic sites > 2[a]	1.34 (1.16–1.55)	0.0001
LDH > 618 IU/L[a,b]	1.78 (1.53–2.06)	<0.0001
Gastrointestinal tumor type	1.55 (1.34–1.80)	<0.0001
ECOG PS ≥ 1	1.32 (1.13–1.55)	0.0004
Platelets > 440 K/UL	1.35 (1.10–1.67)	0.0047
Number of prior therapies ≥ 3	1.33 (1.13–1.57)	0.0007
RMH score as single variable		
RMH score > 1	1.97 (1.67–2.32)	<0.0001
Gastrointestinal tumor type	1.65 (1.43–1.92)	<0.0001
ECOG PS ≥ 1	1.33 (1.13–1.55)	0.0004
Platelet > 440 K/UL	1.43 (1.16–1.76)	0.0008
Number of prior therapies ≥ 3	1.43 (1.21–1.68)	<0.0001

Abbreviations: PS, performance status; RR, relative risk.
[a]Variables included in the RMH score.
[b]618 IU/L is the ULN for LDH at MDACC.

MDACC prognostic score and the prognostic factor model

To identify additional independent prognostic factors predicting overall survival based on the MDACC data, we randomly selected a "training set" with 50% of the patients and a "validation set" containing the remaining patients. A multivariate Cox regression model was used to identify the independent prognostic factors within the training set (Table 3), which was applied to the validation set to get an unbiased estimate of its effectiveness based on Harrell *c*-statistic. In the training data set, the Harrell *c*-statistic is 0.643 for the best 3-variable model (RMH score), 0.659 for the best 4-variable model ($P = 0.008$, in comparison to 3-variable model), 0.673 for the best 5-variable model (MDACC score, $P = 0.009$ in comparison with the 4-variable model), and 0.676 for the best 6-variable model ($P = 0.340$, in comparison with the 5-variable model). Thus, the 5-variable model

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Table 3. Internal validation study of independent predictors of survival

Variables	RR for death (95% CI)	*P*
Training data (randomly selected 50% of patients)		
Albumin < 3.5 g/dL	1.58 (1.16–2.15)	0.0035
Number of metastatic sites > 2	1.42 (1.15–1.75)	0.0012
LDH > 618 IU/L	1.74 (1.40–2.15)	<0.0001
Gastrointestinal tumor type	1.68 (1.36–2.07)	<0.0001
ECOG PS ≥ 1	1.32 (1.05–1.66)	0.0160
Platelet > 440 K/UL	1.40 (1.05–1.88)	0.0230
Prior treatment ≥ 3	1.40 (1.10–1.78)	0.0063
Validation data (the remaining 50% of patients)		
Albumin < 3.5 g/dL	1.69 (1.25–2.29)	0.0006
Number of metastatic sites > 2	1.26 (1.03–1.55)	0.0260
LDH > 618 IU/L	1.83 (1.48–2.27)	<0.0001
Gastrointestinal tumor type	1.42 (1.15–1.76)	0.0010
ECOG PS ≥ 1	1.32 (1.07–1.64)	0.0110
Platelet > 440 K/UL[a]	1.35 (0.99–1.84)	0.0540
Prior treatment ≥ 3[a]	1.23 (0.98–1.55)	0.0730

Abbreviations: PS, performance status; RR, relative risk.
[a]Elevated platelet levels (>440 K/UL) and ≥3 prior therapies are not statistically significant in the validation set and are therefore not included in our prognostic score.

[that includes low albumin levels (<3.5 g/dL), number of metastatic sites >2, elevated LDH levels (>618 IU/L), gastrointestinal tumor type, and ECOG performance status ≥1] with the highest Harrell *c*-statistic that was statistically significant was chosen as a final model.

This result was validated in the validation data set (Table 3) and the Harrell *c*-statistic was 0.661 for the best 5-variable model (i.e., the MDACC score), in comparison with a Harrell *c*-statistic of 0.644 in the best 3-variable model (i.e., RMH score; $P = 0.008$). A similar result was also obtained with the "bootstrapping" method in which elevated LDH levels were independently significant in 100%, tumor type in 99%, low albumin levels in 93%, ECOG performance status ≥1 in 80%, number of metastatic sites >2 in 86% of the 1,000 resampled data sets from 1,181 patients. The respective proportions are only 69% for ≥3 prior therapies and 55% for elevated platelet levels.

Our analyses based on MDACC data suggest that the 3 variables that are included in the RMH score, that is, elevated LDH levels (>618 IU/L), low albumin levels (<3.5 g/dL), number of metastatic sites >2, as well as ECOG performance status ≥1, and gastrointestinal tumor type are independent prognostic variables of survival.

MDACC prognostic score and the prognostic factor model

On the basis of the multivariate analysis and validation studies, the RMH score >1 [elevated LDH levels (>618 IU/L), low albumin levels (<3.5 g/dL), and >2 metastatic sites], as well as ECOG performance status ≥1, and gastrointestinal tumor type were used as the basis of a prognostic score in the phase I program to develop a model for predicting an individual patient's survival (Supplementary Fig. S1). Because the relative risks associated with each of the independently significant risk factors were comparable, the relative risk of death could be characterized by summing the number of risk factors present at the first visit to the phase I clinic. Risk groups were defined by comparing the relative risk of death in patients with each possible number of presenting risk factors (i.e., 0, 1, 2, 3, 4, or 5) and combining categories with similar relative risks (4 with 5). Patients were then assigned to 1 of 5 risk groups on the basis of their number of presenting risk factors: 0, low risk; 1, low-intermediate risk; 2, intermediate risk; 3, high-intermediate risk; and 4 or 5, high risk (Fig. 3). The survival curves for the 5 risk groups are shown in Fig. 2B. The

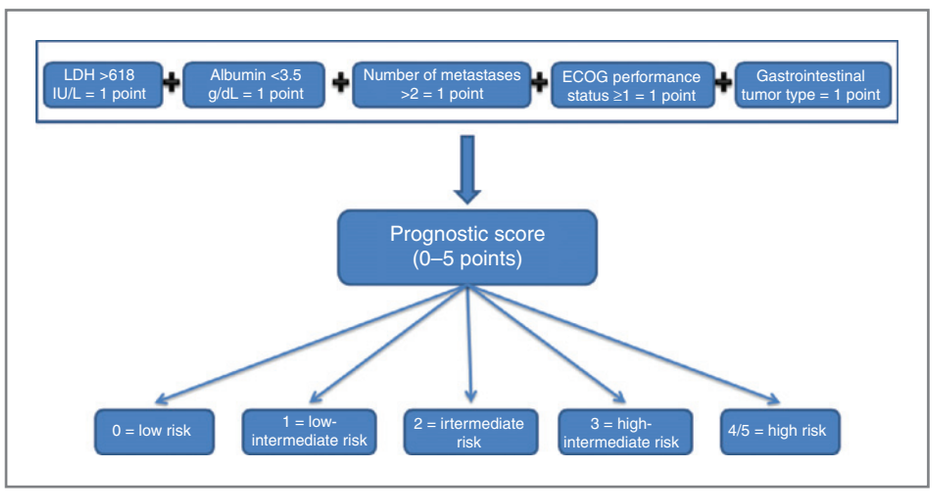

Figure 3. Proposed algorithm to assign patients to 1 of the 5 risk groups that predict survival characterized by summing the number of risk factors present at the time of first visit to the phase I clinic. All risk factors carry equal weight.

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median survival was 24.0 months for patients with low-risk factors, 15.2 months for patients with low-intermediate risk, 8.4 months for patients with intermediate risk, 6.2 months for patients with high-intermediate risk, and 4.1 months for patients with high-risk. At 6 months, 85%, 83%, 70%, 53%, and 36% of patients with low, low-intermediate, intermediate, high-intermediate, and high risk factors, respectively, were expected to remain alive. The respective rates at 12 months were 75%, 59%, 40%, 22%, and 13% ($P < 0.0001$).

When we compared the MDACC score with the RMH score of the 1,153 patients with complete data sets, the 2 scores were very similar (Supplementary Table S1). This is best appreciated in Fig. 2B and C (Supplementary Fig. S2). If the patient had a low MDACC score, they also had a low RMH score. Therefore, there is high correlation between the MDACC score and the RMH score ($P < 0.00001$).

The predictive ability of the 2 models was assessed with Harrell *c*-statistic; the higher the *c*-statistic, the better the predictive ability of the model. The Harrell *c*-statistic is 0.664 (95% CI, 0.618–0.706) for MDACC score and 0.637 (95% CI, 0.591–0.681) for RMH score ($P < 0.0001$). This suggests that the MDACC score strengthens the prediction properties of the RMH score.

Discussion

We report an overall survival of 10 months (95% CI, 9.1–10.9 months) in 1,181 patients seen in our phase I clinic and treated with predominantly targeted agents. Previously, reports of overall survival in phase I patient populations evaluated patients who were primarily treated on cytotoxic versus targeted therapies. Our survival rate is longer than those previously reported (4–7) which ranged from 5 to 9 months (1, 4, 6–8). The survival rates of patients at 6 and 12 months in this study were 70% and 44%. This appears comparable or better than previously shown (43%–70% for 6 months and 18%–44% for 12 months, respectively; ref. 4) and is similar to the survival we reported earlier at 6 (67%) and 12 months (40%) in a group of 200 patients (9). While the increased use of targeted agents may be a significant factor in improved survival rates, other variables such as improved supportive care and different patient population between studies, may also play a role.

The RMH score, a prognostic model for overall survival in patients treated with phase I trials, has been proposed on the basis of a retrospective review of 212 patients treated on phase I studies (1). In this model (1), Arkenau and colleagues found that elevated LDH levels, low albumin levels, and >2 sites of metastases were independently prognostic for poor survival. The RMH prognostic score suggests that patients with 0 to 1 risk factors have a significantly longer overall survival than in patients with 2 to 3 risk factors. This model was prospectively validated in 78 patients (10), 68% of whom were treated on targeted therapies

Our results validated the RMH score. However, we found that the RMH score is strengthened by adding 2 additional independent prognostic variables, ECOG performance status ≥ 1, and gastrointestinal tumor type. In data published by a variety of authors, several of the clinical variables that constitute our current prognostic model have been previously associated with worse outcomes in patients with advanced cancer including serum albumin (1, 4, 11–15), increasing ECOG performance status (4, 8, 16), and the RMH score (1, 5, 10).

Patients in our phase I clinic had an overall survival of 10 months. When our prognostic model was applied, we noted that patients with a low-risk score (0 risk variables) had an overall survival of 24.0 months versus those patients with the highest risk score (4–5 risk variables), whose overall survival was 4.1 months. Our results are relatively consistent with those reported by the RMH score, where low-risk patients (0–1 factors) showed a survival of 74.1 weeks (18.5 months) and high-risk patients (2–3 factors) showed survival 24.9 weeks (6.2 months; ref. 1). Our data provide additional stratification with patients with low-intermediate risk (1 variable; median survival = 15 months), intermediate risk (2 variables; median survival = 8 months), and high-intermediate risk (3 variables; median survival = 6 months).

Gradually, the perception of phase I trials–that they are unduly toxic and fail to provide clinical benefit–is being overcome as data support relatively low toxicity rates (17) and a possibility of clinical benefit that rivals that of standard third-line chemotherapy options (18–20).

The strength of our model is based on a relatively large sample size of patients than in the RMH model. Caution should be taken, however, in generalizing our patient population to those at other institutions, due to the heterogeneity of tumor types and diverse prognoses. While our prognostic model has been internally validated, it will require additional prospective validation. Another potential weakness is the inherent subjectivity of ECOG performance status. Finally, caution needs to be used overall when basing clinical decision making on an "objective" model and should not overcome best clinical judgment and an individualized approach to decision making on a patient-by-patient basis (21).

Emerging data suggest that matching patients with targeted agents based on molecular profile can be highly successful in the phase I setting (22), and it will be important to determine whether such matching independently affects survival. The use of a prognostic score may support clinicians' decision-making process and selection of studies that are best matched to patients' stated goals for treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Received September 1, 2011; revised January 30, 2012; accepted March 11, 2012; published OnlineFirst March 27, 2012.

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Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2217

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Published OnlineFirst March 27, 2012; DOI: 10.1158/1078-0432.CCR-11-2217

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Clin Cancer Res 2012;18:2922-2929. Published OnlineFirst March 27, 2012.

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