Analysis of esophagogastric cancer patients enrolled in the National Cancer Institute Cancer Therapy Evaluation Program sponsored phase 1 trials

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Abstract

Background In phase 1 trials, an important entry criterion is life expectancy predicted to be more than 90 days, which is generally difficult to predict. The Royal Marsden Hospital (RMH) prognostic score that is determined by lactate dehydrogenase level, albumin level, and number of metastatic sites of disease was developed to help project patient outcomes. There have been no systematic analyses to evaluate the utility of the RMH prognostic score for esophagogastric cancer patients.

Methods All nonpediatric phase 1 oncology trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program that began between 2001 and 2013 were considered in this review.

Results Of 4722 patients with solid tumors, 115 patients were eligible for our analysis; 54 (47 %) with cancer of the esophagus, 14 (12 %) with cancer of the esophagogastric junction, and 47 (41 %) with stomach cancer. Eighty-six patients (75 %) had a good RMH prognostic score (0 or 1) and 29 patients (25 %) had a poor RMH prognostic score (2 or 3). Disease control rates were significantly different between patients with good and poor RMH prognostic scores (49 % vs 17 %; two-sided Fisher's exact test $P = 0.004$). The median treatment duration and overall survival for good and poor RMH prognostic score patients were significantly different (median treatment duration 2.1 months vs 1.2 months respectively, $P = 0.016$; median overall survival 10.9 months vs 2.1 months respectively, $P < 0.001$). In the multivariate analysis, age (60 years or older), Eastern Cooperative Oncology Group performance status (2 or greater), and the RMH prognostic score (2 or 3) were significant predictors of poor survival.

Conclusions The RMH prognostic score is a strong tool to predict the prognosis of esophagogastric cancer patients who might participate in a phase 1 trial.

Keywords Phase 1 trials · Esophagogastric cancer · National Cancer Institute · Cancer Therapy Evaluation Program · Royal Marsden Hospital prognostic score

Introduction

Esophageal and gastric cancers are, respectively, the eighth and fifth commonest malignancies in the world [1]. In 2012, an estimated 456,000 new cases of esophageal cancer and 951,000 new cases of esophageal and stomach cancer occurred worldwide. Both diseases often present in advanced stages because of late onset of symptoms and,

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because of the limited availability of effective treatment strategies, are associated with poor survival. There were approximately 400,000 deaths from esophageal cancer and 723,000 deaths from gastric cancer in 2012 [1].

Most esophageal cancers worldwide are squamous cell carcinoma or adenocarcinoma in origin. Although the incidence of squamous cell carcinoma has decreased in the USA, the incidence of adenocarcinoma stemming from Barrett's esophagus has been increasing dramatically [2]. Similarly, the incidences of adenocarcinoma of the esophagogastric junction and proximal part of the stomach have increased, whereas the incidence of distal gastric carcinoma has declined [3].

The incidence of gastric cancer differs with different geographic regions. The rates are highest in eastern Asia, eastern Europe, and South America, and are lowest in North America and parts of Africa [1]. Furthermore, as the worldwide incidence of gastric cancer has declined, especially in North America and western Europe, gastric cancer has become less common in the USA [4].

Patients with unresectable and recurrent esophagogastric cancer (EGC) at time of diagnosis are usually treated with systemic chemotherapy. At present, fluoropyrimidine and platinum-based chemotherapy with or without trastuzumab, a human epidermal growth factor receptor 2 antibody, are globally regarded as standard first-line chemotherapy for esophagogastric adenocarcinoma [5, 6]. Recently, owing to randomized studies, taxanes, irinotecan, and ramucirumab, an antivascular endothelial growth factor receptor 2 antibody, have been regarded as standard second-line therapeutic options [7–11]. However, the prognosis of patients with advanced or recurrent EGC remains poor, with a median overall survival (OS) of only 12 months.

When patients do not respond to conventional systemic chemotherapy but have a good performance status (PS), they are often candidates for clinical trials. Phase 1 trials are designed primarily to evaluate the tolerability and toxicity profile of new therapies and to determine the recommended phase 2 dose. The generally accepted inclusion and exclusion criteria for these trials include adequate organ function and reasonable PS to ensure safety and avoid unnecessary toxicity. Life expectancy predicted to be less than 90 days is also used to exclude patients with poor prognosis although this is notoriously difficult to predict. There have been various analyses to identify the variables to detect poor prognosis. Recently, the Royal Marsden Hospital (RMH) prognosis score was developed to help predict the outcomes of patient in phase 1 trials. From the multivariate analysis of the RMH phase 1 data set, lactate dehydrogenase (LDH) level, albumin level, and number of metastatic sites of disease were selected as significantly poorer prognostic factors [12]. The RMH prognostic score

has also been validated with various prospectively and retrospectively selected cohorts [13, 14].

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) in the USA coordinates and supports the largest publicly funded oncology clinical trials program in the world. NCI-CTEP is currently supporting 180 phase 1 clinical trials. NCI-CTEP also manages and provides about 100 investigational new drugs for NCI-CTEP-sponsored clinical trials.

There have been few analyses of clinical benefits and prognoses for EGC patients who were registered in phase 1 trials [15, 16]. Those analyses assessed the toxicities, treatment-related trial discontinuations, and efficacies. However, the impact of phase 1 treatment on safety and efficacy for patients with EGC has not yet been evaluated in a large population. Although the prognostic variables for OS have been analyzed [15], the usefulness of the RMH prognostic score for EGC patients has not yet been evaluated.

In this analysis, we retrospectively investigated the characteristics and clinical benefits in patients who participated in NCI-CTEP-sponsored phase 1 clinical trials. We also investigated whether the RMH prognostic score is a useful tool to predict the prognosis of EGC patients who might participate in phase 1 trials.

Methods

Patient eligibility

All nonpediatric phase 1 oncology trials sponsored by NCI-CTEP initiated between 2001 and 2013 involving enrolled patients with EGC were analyzed in this study. These trials were conducted at the National Institutes of Health Clinical Center and other academic institutions in the USA. In this analysis, we excluded phase 1/2 trials.

Data were provided from the Clinical Trials Monitoring System (CTMS) database, which is managed by Theradex Systems (Princeton, NJ, USA). The CTMS database is prospectively maintained, with robust data management and auditing practices [17]. We received the anonymized clinical data, containing the types of trials, patients' characteristics, safety profiles, and clinical efficacies as in previous reports [18].

The Royal Marsden Hospital prognostic score

The RMH prognostic score was determined by three variables: LDH level, albumin level, and number of metastatic sites of disease. LDH values greater than the upper limit of normal, albumin level less than 3.5 g/dl, and more than two metastatic sites each received one point. A total score of 0

or 1 indicates a good prognosis, whereas a total score of 2 or 3 denotes a poor prognosis [12].

End points and statistical methods

All statistical evaluations were performed by the primary investigator (H.B.) and the statistician (L.R.). Summary statistics of patient characteristics were provided; Kaplan–Meier product limit estimates were used to generate curves for treatment duration and OS. Treatment duration was defined as the time from the start of phase 1 treatment to the time of discontinuation as judged by the investigator, due to objective or clinical disease progression, intolerable toxicities, or death. OS was defined as the time from the start of phase 1 treatment to death or the last date the patient was known to be alive. For OS, patients were censored at the time of their last follow-up if they were still alive. Responses in phase 1 studies were assessed according to the Response Evaluation Criteria in Solid Tumors version 1.0 or version 1.1.

Fisher's exact test was used to compare the differences in the toxicities, response rates, and disease control rates among the groups with different RMH prognostic scores. A log-rank test was used to assess the differences in treatment duration and OS among the groups with different RMH prognostic scores. Univariate and multivariate Cox proportional hazards models were fit to test the covariate effect on OS. Age, sex, tumor location, Eastern Cooperative Oncology Group (ECOG) PS, hemoglobin value, platelet count, LDH level, albumin level, number of metastatic sites, RMH prognostic score, and number of previous treatments were included in an initial multivariate Cox proportional hazards model. A forward selection method model was also used. Covariates with $P < 0.05$ were retained in the model.

All analyses were done with IBM SPSS Statistics version 21.0 (IBM, Tokyo, Japan). All reported P values were for two-sided tests, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Data from 186 CTEP phase 1 trials conducted between February 2001 and July 2013 were included in this analysis. A total of 4722 patients were enrolled in these trials, and 126 patients (2.7 %) had EGC. Eleven cases were omitted from the analyses because insufficient clinical data were available (type of trial, patient characteristics, safety

profiles, clinical effects, etc.). Thus, we analyzed 115 patients with EGC from 44 CTEP phase 1 studies.

Eighty-four patients (73.0 %) were men and the median patient age was 59 years (range 30–85 years). Most patients were Caucasian (77.4 %; $n = 89$). Fifty-four cancer cases (47 %) were located in the esophagus, 14 (12 %) were in the esophagogastric junction, and 47 (41 %) were in the stomach. The commonest pathologic subtype was adenocarcinoma (89.6 %; $n = 103$). Twenty-six patients (22.6 %) had an ECOG PS of 0, 84 patients (73.0 %) had an ECOG PS of 1, and 5 patients (4.3 %) had an ECOG PS of 2. The median number of prior treatments was 4 (range 0–13). Forty-two patients (36.5 %) had undergone surgery and 31 patients (27.0 %) had received radiation therapy. Of the 115 eligible patients, 86 patients (75 %) had a good RMH prognostic score and 29 patients (25 %) had a poor RMH prognostic score (Table 1).

Treatments

Of 44 CTEP phase 1 studies, 17 were with single agents (3 chemotherapy only and 14 biologic agent only) and 27 were with combination therapy (10 biologic combination and 17 biologic agent plus chemotherapy).

Thirty-two (28 %) of the 115 patients were treated with a single agent and 83 (72 %) were treated with combination therapy. Of the 32 patients treated with a single agent, 8 (7 %) were treated with a cytotoxic agent, and 24 (21 %) were treated with a biologic therapy. Of the 83 patients treated with combination therapy, 18 (16 %) were treated with biologic agent combination therapy, and 65 (56 %) were treated with biologic and cytotoxic agents (Table 2).

Safety

Among the 115 patients, 87 patients (75.7 %) experienced grade 3 or 4 adverse events; these events included 29 cases of neutropenia, 13 cases of thrombocytopenia, 12 cases of diarrhea, 10 cases of nausea, and 8 cases of vomiting. However, only one grade 5 event (0.9 %) was observed in this analysis. When we counted dose-limiting toxicity (DLT) events, 21 cases were observed (ten blood system disorders, five general disorders, five gastrointestinal disorders, and one cardiac disorder) (Table 3).

Although there were trends that adverse events of a higher grade occurred in patients with a poor RMH prognostic score, we did not observe statistical significance either for grade 3 or 4 adverse events (two-sided $P = 0.142$ by Fisher's exact test) or for dose-limiting toxicity events (two-sided $P = 0.406$ by Fisher's exact test) between patients with a good versus a poor RMH prognostic score (Table 3).

Table 1 Patient characteristics ($N = 115$)

Characteristics	Values
Age	
Median (years)	59
Range (years)	30–85
Sex	
Male	84
Female	31
Ethnicity	
Caucasian	89
Asian	5
African	4
Others	3
Unknown	14
Tumor location	
Esophagus	54
EGJ	14
Stomach	47
Histologic type	
Adenocarcinoma	103
Squamous cell carcinoma	10
Not known	2
ECOG PS	
0	26
1	84
2	5
Prior surgery	42
Prior radiation therapy	31
No. of metastatic sites	
Median	2
Range	2–6
≤ 2	85
> 2	30
Hemoglobin level	
Median (g/dl)	11.9
Range (g/dl)	9.0–16.0
LDH level	
Median (U/l)	183
Range (U/l)	91–3156
Platelet count	
Median ($\times 10^3/\mu\text{l}$)	260
Range ($\times 10^3/\mu\text{l}$)	104–797
Albumin level	
Median (g/dl)	3.6
Range (g/dl)	2.1–4.6
RMH prognostic score	
0	40
1	46
2	25
3	4

Table 1 continued

Characteristics	Values
No. of previous treatments	
0–2	44
3 or 4	20
> 4	51

ECJ esophagogastric junction, ECOG PS Eastern Cooperative Oncology Group performance status, LDH lactate dehydrogenase, RMH Royal Marsden Hospital

Table 2 Phase 1 studies ($N = 115$)

Type of phase 1 study	Patients
Monotherapy (17 studies)	32 (28 %)
Chemotherapy only (3 studies)	8 (7 %)
Biologic only (14 studies)	24 (21 %)
Combination therapy (27 studies)	83 (72 %)
Chemotherapy combination (0 study)	0 (0 %)
Biologic combination (10 studies)	18 (16 %)
Biologic and chemotherapy (17 studies)	65 (56 %)
Total (44 studies)	115 (100 %)

Response

Of the 86 patients with a good RMH prognostic score, 7 partial response cases (8 %) and 35 stable disease cases (41 %) were reported (response rate 8 %, disease control rate 49 %). On the other hand, of the 29 patients with a poor RMH prognostic score, only one partial response case (3 %) and four stable disease cases (14 %) were reported (response rate 3 %, disease control rate 17 %). The response rates for patients with good versus poor RMH prognostic scores (8 % vs 3 %) were not significantly different (two-sided $P = 0.68$ by Fisher's exact test), whereas the disease control rates for patients with good versus poor RMH prognostic scores (49 % vs 17 %) were significantly different (two-sided $P = 0.004$ by Fisher's exact test) (Table 4).

Treatment duration and overall survival

The log-rank analysis showed that patients with a good RMH prognostic score had a median treatment duration of 2.1 months (95 % confidence interval 1.7–2.4 months) compared with those with a poor RMH prognostic score, who had a median treatment duration of 1.2 months (95 % confidence interval 1.0–1.4), a statistically significant difference ($P = 0.016$) (Fig. 1a).

The median OS of patients with a good RMH prognostic score was 10.9 months (95 % confidence interval

Table 3 Safety profiles

	Good RMH prognostic score (0 or 1) (<i>n</i> = 86)	Poor RMH prognostic score (2 or 3) (<i>n</i> = 29)	Total (<i>N</i> = 115)
Dose limiting toxicity	14 (16 %)	7 (24 %)	21 (18 %)
General disorder	4 (5 %)	1 (3 %)	5 (4 %)
Gastrointestinal disorder	3 (4 %)	2 (7 %)	5 (4 %)
Blood system disorder	6 (7 %)	4 (14 %)	10 (9 %)
Cardiac disorder	1 (1 %)	0 (0 %)	1 (1 %)
Adverse events of grade 3 or 4	62 (72 %)	25 (86 %)	87 (76 %)
Adverse events of grade 5 (treatment-related death)	0 (0 %)	1 (3 %)	1 (1 %)

RMH Royal Marsden Hospital

Table 4 Treatment responses (*N* = 115)

Best response	Good RMH prognostic score (0 or 1) (<i>n</i> = 86)	Poor RMH prognostic score (2 or 3) (<i>n</i> = 29)	Total (<i>N</i> = 115)
Complete response	0 (0 %)	0 (0 %)	0 (0 %)
Partial response	7 (8 %)	1 (3 %)	8 (7 %)
Stable disease	35 (41 %)	4 (14 %)	39 (34 %)
Progressive disease	30 (35 %)	22 (76 %)	52 (45 %)
Not evaluated	14 (16 %)	2 (7 %)	16 (14 %)
Total	86 (100 %)	29 (100 %)	115 (100 %)
Response rate (complete response + partial response)	8 %	3 %	7 %
Disease control rate (complete response + partial response + stable disease)	49 %	17 %	41 %

RMH Royal Marsden Hospital

8.1–13.7 months), whereas for those with a poor RMH prognostic score it was 2.1 months (95 % confidence interval 1.3–2.8), which was also a statistically significant difference by the log-rank analysis ($P < 0.0001$) (Fig. 1b).

Prognostic value of the Royal Marsden Hospital prognostic score

In the univariate Cox proportional hazards model of OS, ECOG PS (0 or 1 vs 2; $P < 0.0001$), LDH level (upper limit of normal or lower vs above the upper limit of normal; $P < 0.0001$), albumin level (3.5 g/dl or greater vs less than 3.5 g/dl; $P < 0.0001$), and the RMH prognostic score (poor vs good; $P < 0.0001$) were significantly associated

Fig. 1 Kaplan–Meier plots of treatment duration and overall survival for patients with good and poor Royal Marsden Hospital (RMH) prognostic scores. **a** The median treatment durations of patients with a good RMH prognostic score (0 or 1; *n* = 86) and a poor RMH prognostic score (2 or 3; *n* = 29) were respectively 2.1 months [95 % confidence interval (CI) 1.7–2.4] and 1.2 months (95 % CI 1.0–1.4), which was a statistically significant difference by the log-rank analysis ($P = 0.016$). **b** The median overall of patients with a good RMH prognostic score was 10.9 months (95 % CI 8.1–13.7 months), whereas for those with a poor RMH prognostic score it was 2.1 months (95 % CI 1.3–2.8), which was also a statistically significant difference by the log-rank analysis ($P < 0.0001$)

with a poor phase 1 clinical trial OS (Table 5). In the multivariate analysis with the RMH prognostic score, but not including its components (LDH level, albumin level, and number of metastatic sites of disease), the RMH prognostic score (poor vs good; $P < 0.0001$; hazard ratio 0.294), age (younger than 60 years vs 60 years or older; $P = 0.046$; hazard ratio 0.562), and ECOG PS (0 or 1 vs 2;

Table 5 Univariate and multivariate analysis of overall survival by patient characteristics ($N = 115$)

Characteristics	Univariate analysis <i>P</i>	Multivariate analysis ^a		
		Hazard ratio	95% CI	<i>P</i>
Age (years)				
<60 ($n = 58$)	0.064	0.562	0.320–0.990	0.046
≥60 ($n = 57$)				
Sex				
Female ($n = 31$)	0.475			
Male ($n = 84$)				
Tumor location				
Esophagus, EGJ ($n = 68$)	0.198			
Stomach ($n = 47$)				
ECOG PS				
0 or 1 ($n = 110$)	<0.001	0.214	0.059–0.778	0.019
2 ($n = 5$)				
Hemoglobin level (g/dl)				
<10 ($n = 12$)	0.127			
≥10 ($n = 103$)				
Platelet count ($\times 10^3/\mu\text{l}$)				
<150 ($n = 12$)	0.76			
≥150 ($n = 103$)				
LDH level				
≤ULN ($n = 73$)	<0.001			
>ULN ($n = 42$)				
Albumin level (g/dl)				
≥3.5 ($n = 79$)	<0.001			
<3.5 ($n = 36$)				
No. of metastatic sites				
0–2 ($n = 85$)	0.111			
>2 ($n = 30$)				
RMH prognostic score				
0 or 1 ($n = 86$)	<0.001	0.294	0.159–0.545	<0.001
2 or 3 ($n = 29$)				
No. of previous treatments				
≤3 ($n = 56$)	0.128			
>3 ($n = 59$)				

CI confidence interval, EGJ esophagogastric junction, ECOG PS Eastern Cooperative Oncology Group performance status, LDH lactate dehydrogenase, RMH Royal Marsden Hospital, ULN Institutional upper limit of normal

^a Multivariate analysis with RMH prognostic score but not including its components (LDH level, albumin level, and number of metastatic sites of disease)

$P = 0.019$; HR 0.214) were significantly associated with a poor OS (Table 5).

Discussion

We comprehensively reviewed phase 1 oncology trials sponsored by NCI-CTEP between 2001 and 2013 and investigated the characteristics and clinical benefits in

enrolled patients with EGC. Of 4722 patients with a solid tumor, we found only 126 patients (2.7 %) with EGC. This suggests that EGC is a minor component of NCI-CTEP-sponsored phase 1 trials in the USA compared with East Asian countries [16].

Because the main NCI-CTEP-sponsored phase 1 trials use combination therapies with investigational new drugs which completed a dose-finding phase 1 trial as a single agent, the combination therapies with biologic agents

(biologic combination or biologic plus chemotherapy) accounted for the majority (total 72 %) of phase 1 trials for EGC.

In this analysis, 18.3 % of patients with EGC had dose-limiting toxicity events and 75.7 % had grade 3 or 4 adverse events. The 75.7 % of patients with grade 3 or 4 adverse events is considerably higher than reported by previous analyses (19.7–39 %) [15, 16]. A reasonable explanation is that the main NCI-CTEP-sponsored phase 1 trials for EGC were for combinations with biologic and cytotoxic agents. Twenty-seven patients received combinations with cisplatin, irinotecan, and a cyclin-dependent kinase 9 inhibitor and seven received combinations with leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) and a cyclin-dependent kinase 9 inhibitor. Those treatment regimens are expected to yield a high level of hematologic adverse events. On the other hand, grade 5 adverse events were rare (0.9 %).

Despite the finding that expected survival of more than 3 months is frequently one of the eligibility criteria for enrollment in most phase 1 trials, clinicians who screen patients often fail to accurately predict individual survival profiles, and as many as 15–20 % of these patients die within the first 3 months of phase 1 trial entry [19]. In our analysis, the median OS of patients with good RMH prognostic scores and poor RMH prognostic scores were 10.9 and 2.1 months respectively; this was a statistically significant difference in the log-rank analysis ($P < 0.0001$). The median OS of 2.1 months for patients with poor RMH prognostic scores was shorter than the 3 months major entry criterion. In the multivariate analysis, the RMH prognostic score was also significantly associated with a poor OS. The significant difference in OS between patients with good RMH prognostic score and patients with a poor RMH prognostic score was also consistent in the separate age groups (younger than 60 years, median OS 9.9 months vs 1.9 months, $P = 0.001$; 60 years or older, 11.2 months vs 2.7 months, $P = 0.004$).

Our analysis has some limitations. We retrospectively used the CTMS database to analyze patient characteristics, treatment duration, and OS since we could not access the medical records of each patient. Since most NCI-CTEP-sponsored phase 1 clinical trials do not consistently capture the date of death when patients are no longer included in the study, this information was captured for only 52 patients (45 %). Since the patients with good RMH prognostic scores tended to live longer than those with poor RMH prognostic scores, the date of death was captured less frequently for the former (41 %) than for the latter (66 %). Although it is possible that this introduced statistical bias into the calculations of the predictive value of the RMH prognostic score for OS, it is very unlikely that it significantly affected the results.

In conclusion, the RMH prognostic score could be a strong tool to predict the prognosis of EGC patients who will participate in a phase 1 trial. The median OS of 2.1 months for EGC patients with a poor RMH prognostic score also suggests that these patients should not be included in phase 1 clinical trials.

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Compliance with ethical standards

Funding No grant and contract funds were provided.

Conflict of interest The authors have declared no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. We analyzed the delinked anonymous data extracted from the Clinical Trials Monitoring Branch database, which is prospectively managed and closely audited by Theradex Systems (Princeton, NJ, USA) in collaboration with National Cancer Institute. Hideaki Bando received ethical training managed by the National Cancer Institute before accessing the database.

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