Early versus Delayed Therapy of Advanced Gastric Cancer Patients – Does It Make a Difference?

Elena Elimova^a Hironori Shiozaki^a Rebecca S. Slack^b Hsiang-Chun Chen^b
Roopma Wadhwa^a Kazuki Sudo^a Nikolaos Charalampakis^a Adarsh Hiremath^a
Jeannelyn S. Estrella^c Aurelio Matamoros^d Tara Sagebiel^d Prajnan Das^e
Jane E. Rogers^f Jeana L. Garriss^a Mariela A. Blum^a Brian Badgwell^g
Jaffer A. Ajani^a

Departments of ^aGastrointestinal Medical Oncology, ^bBiostatistics, ^cPathology, ^dDiagnostic Radiology, ^eRadiation Oncology, ^fClinical Pharmacy and ^gSurgical Oncology, University of Texas M.D. Anderson Cancer Center, Houston, Tex., USA

Key Words

Gastric cancer · Metastasis · Treatment delay · Palliative therapy

Abstract

Background: Nearly 50% of gastric cancer patients are diagnosed with advanced gastric cancer (AGC). Therapy is palliative but results in ill effects. The median overall survival (OS) of AGC patients is often <12 months. It is unclear if the early initiation of therapy in all AGC patients is beneficial. **Methods:** A retrospective analysis of AGC patients in our database was carried out. The patients were divided into two groups: asymptomatic or symptomatic. We sought to assess whether the delay of systemic therapy was harmful in asymptomatic patients. **Results:** A total of 135 patients were analyzed. Most patients were symptomatic (68%), males (67%), and had low ECOG scores (0–1; 85%). In univariate analyses, ECOG performance status 0 ($p = 0.005$), delayed initiation of therapy ($p = 0.03$), and lack of symptoms ($p = 0.03$) were associated with a longer OS. The multivariate model for OS

identified only ECOG performance status as an independent prognosticator of longer OS ($p = 0.02$). Asymptomatic patients who had delayed (≥ 4 weeks) systemic therapy had an OS rate of 77% at 1 year compared to 58% for patients treated within 4 weeks ($p = 0.47$). **Conclusion:** Symptomatic AGC patients had a poor outcome compared to asymptomatic AGC patients. Treatment delay in asymptomatic patients had no detrimental effect on OS, suggesting that the timing of therapy can be based on patient selection.

© 2015 S. Karger AG, Basel

Introduction

Gastric cancer (GC) represents a serious health problem on a global scale and is the second leading cause of cancer-related death worldwide [1]. In the United States, GC is less common, with 21,600 new cases and 10,990 cancer deaths occurring in 2013 [2]. Between 2002 and 2008, the 5-year relative survival rate was only 27% according to the SEER database [3].

Table 1. Patient characteristics by symptom status

Characteristics	All patients (n = 123)	Asymptomatic patients (n = 39)	Symptomatic patients (n = 84)	p value
<i>At diagnosis</i>				
Median age (min., max.)	58 (33, 83)	60 (33, 83)	58 (33, 79)	0.37
Median BMI (min., max.)	25.7 (17.1, 41.1)	26.8 (18.1, 41.1)	25.5 (17.1, 38.5)	0.71
Gender				0.68
Female	41 (33.3)	14 (35.9)	27 (32.1)	
Male	82 (66.7)	25 (64.1)	57 (67.9)	
Smoking history				0.55
Nonsmoker	62 (50.4)	17 (43.6)	45 (53.6)	
Nonsmoker quit	46 (37.4)	16 (41)	30 (35.7)	
Smoker	15 (12.2)	6 (15.4)	9 (10.7)	
Alcohol history				0.89
Never	41 (33.3)	12 (30.8)	29 (34.5)	
Rarely	39 (31.7)	12 (30.8)	27 (32.1)	
Frequent	29 (23.6)	11 (28.2)	18 (21.4)	
Past	14 (11.4)	4 (10.3)	10 (11.9)	
ECOG PS				<0.001*
0	23 (18.7)	17 (43.6)	6 (7.1)	
1	81 (65.9)	22 (56.4)	59 (70.2)	
2	10 (8.1)	0	10 (11.9)	
Missing	9 (7.3)	0	9 (10.7)	
Site of metastasis				0.49
Visceral metastasis	34 (27.6)	10 (25.6)	24 (28.6)	
Nonvisceral metastasis	76 (61.8)	23 (59)	53 (63.1)	
Both	13 (10.6)	6 (15.4)	7 (8.3)	
Type of nonvisceral metastasis				0.36
Positive peritoneal cytology	21 (27.6)	8 (34.8)	13 (24.5)	
Other	55 (72.4)	15 (65.2)	40 (75.5)	
<i>Treatment</i>				
Treatment delay, weeks				0.77
1–4	38 (28.1)	11 (25.6)	27 (29.3)	
5–8	49 (36.3)	14 (32.6)	35 (38)	
9–12	20 (14.8)	8 (18.6)	12 (13)	
13–16	9 (6.7)	4 (9.3)	5 (5.4)	
≥17	7 (5.2)	2 (4.7)	5 (5.4)	
Type of chemotherapy				0.53
P+A	33 (26.8)	12 (30.8)	21 (25)	
P+A+T	72 (58.5)	20 (51.3)	52 (61.9)	
Other	18 (14.6)	7 (17.9)	11 (13.1)	
Surgery				0.46
Yes**	9 (7.3)	4 (10.3)	5 (6.0)	
No	114 (92.7)	35 (89.7)	79 (94.0)	

Data are presented as n (%), unless otherwise indicated.

P = Platinum analog; A = antimetabolite; T = taxane.

* p value for Fisher's exact test, excluding patients with missing values.

** Among the 9 patients who received surgery, 8 patients had R0 resection (3 were asymptomatic and 5 were symptomatic), and 1 asymptomatic patient had R1 resection.

Table 2. OS estimates among asymptomatic patients

Characteristics	Deaths/ total n	1-year OS (SE), %	p value
Asymptomatic patients	28/39	71.8 (7.6)	0.16*
Age, years			
<60	11/16	72.2 (11.9)	
≥60	17/23	71.6 (9.9)	0.88
BMI			
Underweight (<18.5)	1/1	100 (0)	
Normal (18.5–24.9)	11/15	79 (10.8)	
Overweight (25–29.9)	10/14	63.5 (13.1)	0.25
Obese (≥30)	6/9	68.6 (18.6)	
Gender			
Female	9/14	55.2 (15.4)	0.50
Male	19/25	79.6 (8.1)	
Smoking history			
Nonsmoker	10/17	66.3 (12.4)	0.41
Nonsmoker quit	13/16	74 (11.2)	
Smoker	5/6	80 (17.9)	
Alcohol history			0.38
Frequent/past	11/15	78.6 (11)	
Rarely or never	17/24	67.5 (10.2)	
ECOG PS			0.47
0	12/17	68.8 (11.6)	
≥1	16/22	75.8 (9.5)	
Treatment delayed			0.26
Within 4 weeks	7/11	58.4 (16.3)	
Over 4 weeks	21/28	76.6 (8.4)	
Site of mets			0.22
Visceral mets	5/10	90 (9.5)	
Nonvisceral mets	18/23	67 (10.2)	
Both	5/6	62.5 (21.3)	0.83
Type of nonvisceral mets			
Pos peritoneal cyto	5/8	71.4 (17.1)	
Other	13/15	64.6 (12.8)	0.97
T stage			
T3	20/26	71.2 (9.2)	
T4	3/5	80 (17.9)	
TX	5/8	70 (18.2)	0.17
N stage			
N0	5/6	83.3 (15.2)	
N1	16/20	72.6 (10.5)	
N2	2/4	50 (25)	
N3	0/2	N/A	
NX	5/7	68.6 (18.6)	
Type of chemotherapy			
P+A	8/12	63.5 (14.8)	0.17
P+A+T	15/20	79.2 (9.3)	
Other	5/7	62.5 (21.4)	

mets = Metastasis; Pos peritoneal cyto = positive peritoneal cytology; P = platinum analog; A = antimetabolite; T = taxane.

* p value calculated based on continuous values.

Nearly half of the patients diagnosed with GC have advanced, unresectable, and incurable cancer (AGC). Therapy for these patients is palliative and associated with considerable acute and chronic ill effects. The median overall survival (OS) of patients with AGC is often <12 months. Since their survival is short, the goal of therapy should be to relieve cancer-related symptoms and preserve the quality of life while striving to prolong their OS. Thus, one can consider one of two approaches: (1) once the AGC is documented, start systemic therapy until cancer progression or intolerance, or (2) treat based on tumor burden/symptoms and select the timing for treatment (meaning, delay therapy when AGC is not measurable and symptoms are sparse). Such patients can be counseled, carefully monitored, and treated later. In our institution, multiple oncologists treat AGC patients, and one of the two mentioned approaches is employed. The literature does not provide any guidance on this issue; therefore, we hypothesized that asymptomatic patients with low-volume AGC, will fare well with initial observation and therapy later.

A hypothetical representation of the typical course of AGC with and without therapy is presented. In the early phase, AGC can be nonmeasurable and patients have no or minimal symptoms. In the second phase, the bulk of AGC increases (measurable/evaluable by imaging) and patients have symptoms. This may be the best time to initiate therapy. In the third phase (without standard options), the cancer burden is high, with many symptoms and short OS. In this phase, supportive care is best.

Methods

Patient Selection

A retrospective review from a prospectively maintained database in the Department of Gastrointestinal Medical Oncology at The University of Texas M.D. Anderson Cancer Center (UTMDACC) was carried out. The UTMDACC Institutional Review Board approved this analysis. AGC patients managed between 2000 and 2013 were reviewed and had to meet the following criteria: confirmed histology, stage IV GC, in the first-line therapy setting. Patients for whom no date of treatment initiation existed were excluded. No other selection criteria were implemented. Patients with no symptoms or nonspecific symptoms were designated as ‘asymptomatic’ independent of ECOG status. Two authors determined whether the patients were correctly designated, when it was not clear. The ECOG performance status (PS) was extracted directly from the dictated medical oncology note.

Study Design

The primary objective of this analysis was to assess whether the delay of therapy was harmful to asymptomatic AGC patients.

Fig. 1. a OS by symptom status. **b** OS by treatment delay among asymptomatic patients. ‘No delay’ refers to treatment within 4 weeks of diagnosis while ‘delay’ refers to treatment more than 4 weeks after diagnosis. The selection of 4 weeks was determined by univariate RPA.

Follow-Up and Survival

Patients on observation were seen with imaging studies carried out every 2–3 months. Patients on therapy were seen frequently.

Statistical Methods

Differences in age and BMI were compared by the Kruskal-Wallis test. Differences between other characteristics were tested using χ^2 tests or Fisher’s exact tests as needed. OS was calculated from therapy initiation until the last follow-up or death by Kaplan-Meier [4] methods. Univariate and multivariate Cox proportional hazards regression models [5] were used to assess the association between patient characteristics and OS. Characteristics significant in the univariate model at the 0.10 level were included in a multivariate model (full model), followed by backward elimination (reduced model). Recursive partitioning analysis (RPA) [6] was performed to identify combinations of characteristics that classify patients into OS risk groups, with at least 20 patients required in any terminal subgroup. Terminal subgroups with a pairwise log-rank p value >0.05 were combined. The time of delay in therapy was defined as the weeks between diagnosis and initial systemic therapy. RPA was performed in R (The R Foundation for Statistical Computing, Vienna, Austria), remaining analyses used SAS 9.3 (The SAS Institute, Cary, N.C., USA), and figures were created in Stata 13.1 (StataCorp, College Station, Tex., USA).

Results

A total of 123 patients with AGC were analyzed. Table 1 shows the patient characteristics. Patients were similar across symptom status except for ECOG score ($p < 0.001$). Asymptomatic patients were more likely to have an ECOG score of 0 (44 vs. 7%).

Treatment

Of the 123 patients studied, only 9 patients had surgery, 8 patients had R0 resection (3 asymptomatic and 5 symptomatic), and 1 asymptomatic patient had R1 resection. The majority of patients were treated with a platinum analog and fluoropyrimidine $\pm$ taxane (85%), while the remaining patients were treated in clinical trials. There was no difference in terms of therapy received by symptomatic versus asymptomatic patients ($p = 0.53$). There was also no significant difference in terms of the type of therapy received by asymptomatic patients with therapy delayed by more than 4 weeks versus those treated within 4 weeks ($p = 0.07$; table 2).

Overall Survival

Ninety-nine (80%) patients had died at the last follow-up. The median follow-up time was 10.8 months (range 0.5–130.6). The median OS (95% confidence interval) was 12.9 months (10.4–15.2). The 1-year OS rate was 53% (SE = 5%).

Table 3 shows OS by patient categories. RPA for therapy delay partitioned the patients into two groups at 4 weeks, and this grouping was used for further analyses. More asymptomatic versus symptomatic patients were alive at 1 year (72 vs. 45%; $p = 0.03$; fig. 1a). ECOG PS 0 ($p = 0.005$) and delayed therapy (>4 weeks; $p = 0.03$) were also associated with a prolonged OS. The site of metastases (visceral vs. nonvisceral vs. both) did not significantly affect OS. Patients with positive peritoneal cytology as

Table 3. OS estimates among all patients**a** Univariate

Characteristics	Deaths/ total n	1-year OS (SE), %	p value
All patients	99/123	53.3 (4.7)	
Age, years			0.82*
<60	56/67	50.6 (6.3)	
≥60	43/56	56.7 (7)	
BMI			0.92*
Underweight (<18.5)	3/3	66.7 (27.2)	
Normal (18.5–24.9)	40/50	58.5 (7.1)	
Overweight (25–29.9)	33/40	42.7 (8.3)	
Obese (≥30)	23/30	56.9 (9.5)	
Gender			0.53
Female	33/41	55.1 (8.2)	
Male	66/82	52.4 (5.7)	
Smoking history			0.90
Nonsmoker	48/62	52.1 (6.6)	
Nonsmoker quit	38/46	53.3 (7.7)	
Smoker	13/15	58.2 (13.1)	
Alcohol history			0.20
Frequent/past	33/43	59.5 (7.9)	
Rarely or never	66/80	50.1 (5.8)	
ECOG PS			0.005
0	15/23	72.7 (9.5)	
≥1	76/91	48 (5.5)	
Treatment delayed			0.03
Within 4 weeks	31/38	34.8 (8.2)	
Over 4 weeks	68/85	61.3 (5.5)	
Site of mets			0.82
Visceral mets	26/34	45.1 (8.8)	
Nonvisceral mets	62/76	56.6 (5.9)	
Both	11/13	57.1 (14.6)	
Type of nonvisceral mets			0.06
Pos peritoneal cyto	15/21	63.8 (11.0)	
Other	47/55	53.8 (7.0)	
T stage			0.78
T2	2/2	50 (35.4)	
T3	66/77	54.8 (5.9)	
T4	13/17	50.7 (12.5)	
TX	16/24	53 (11.1)	
N stage			0.76
N0	19/22	61.4 (10.8)	
N1	50/58	55.9 (6.8)	
N2	12/16	33.3 (12.2)	
N3	0/3	100 (0)	
NX	16/21	50.8 (11.2)	
Symptoms			0.03
No	28/39	71.8 (7.6)	
Yes	71/84	44.6 (5.6)	
Type of chemotherapy			0.41
P+A	23/33	45.3 (9.4)	
P+A+T	62/72	56 (5.9)	
Other	14/18	54.5 (13.1)	

b Multivariate

Characteristics	HR	95% CI	p value
ECOG PS			0.04
≥1 versus 0	1.86	(1.03–3.38)	
Treatment delayed			0.08
Over 4 weeks versus within 4 weeks	0.67	(0.43–1.05)	
Symptoms			0.20
Yes versus no	1.37	(0.85–2.21)	

mets = Metastasis; Pos peritoneal cyto = positive peritoneal cytology; P = platinum analog; A = antimetabolite; T = taxane; HR = hazard ratio; CI = confidence interval.

* p value calculated based on continuous values.

their only metastatic site tended to have a longer OS ($p = 0.06$). In the multivariate model, ECOG PS was an independent prognosticator of longer OS ($p = 0.04$). After backward elimination, only ECOG PS remained.

Patients with a >4-week delay in treatment were more likely to be alive at 1 year (61%) compared to those who started treatment at <4 weeks of diagnosis (35%; $p = 0.03$). Asymptomatic patients who received delayed therapy had a 1-year OS rate of 77% compared to 58% for patients treated in <4 weeks ($p = 0.47$; fig. 1b). Among asymptomatic patients, the median time to therapy was 7 weeks (95% confidence interval 5–10).

Discussion

In our practices, asymptomatic patients with low tumor burden are often observed until the onset of modest symptoms (interfering with patients' routine) and especially when AGC is progressing on imaging studies. The issue is partially addressed in colorectal cancer patients [7]. In one study, 183 patients were randomized to chemotherapy or best supportive care until symptoms. There was a 5-month OS advantage for patients who were treated early. This was offset by two major factors. Firstly, patients with 'delayed' therapy received suboptimal therapy, 40% received no therapy, and less than 20% received the same chemotherapy as those in the comparison group. Secondly, this study contradicts published literature [8, 9]. We find that one can select patients to delay therapy based on three variables: symptom status, PS, and tumor volume. Symptom status and tumor volume are easy to

discern; however, PS is a soft call [10, 11]. We find that patients with low tumor volume and good PS do well even if their treatment is delayed. We did not include the treatment delay period in OS calculations to be stringent. This time frame between diagnosis and treatment is an opportunity to avoid treatment-related toxicity. We may have preserved the quality of life in some patients; however, this needs to be investigated further.

In other diseases, ECOG PS is an important OS prognosticator [12, 13]. Our report is consistent as patients with an ECOG score of 0 had a 1-year survival rate of 73% compared to those with an ECOG score of ≥ 1 (48%; $p = 0.005$).

Our study being retrospective has shortcomings. We acknowledge that some patients naturally had a favorable clinical course. This is a single high-volume center experience and not necessarily generalizable. An ideal study would be a multicenter and prospective comparison of two approaches. Our data have strengths that can contribute to the management of patients with AGC: (1) we studied a large cohort of patients, and (2) we studied a uniform group of untreated patients.

In conclusion, AGC patients with low tumor volume and good PS do at least as well with treatment delay. Patient selection may be important to provide patients with a treatment-free interval. Therapy is best given when AGC is progressive (especially associated with worsening symptoms) rather than given when it will only produce side effects and no other material benefit. Although our patients are often anxious to start therapy immediately after diagnosis, our data in all patients suggest that a treatment delay of ≥ 4 weeks is safe.

Acknowledgements

Supported by generous grants from the Caporella, Dallas, Sultan, Park, Smith, Frazier, Oaks, Vanstekelenberg, Planjery, and Cantu Families, from the Schecter Private Foundation, Rivercreek Foundation, Kevin Fund, Myer Fund, Dio Fund, Milrod Fund, and Multidisciplinary Grants from the University of Texas M.D. Anderson Cancer Center, Houston, Tex., USA. Supported in part by the National Cancer Institute awards CA138671, CA172741, CA129926 (J.A.A.) and P30CA016672 and the Biostatistics Resource Group (R.S., H.-C.C.).

References

- 1 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- 2 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
- 3 Howlader N, Ries LA, Stinchcomb DG, Edwards BK: The impact of underreported Veterans Affairs data on national cancer statistics: analysis using population-based SEER registries. *J Natl Cancer Inst* 2009;101:533–536.
- 4 Kaplan EL, Meier P: Nonparametric estimator from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
- 5 Cox DR: Regression models and life-tables. *J R Stat Soc B* 1972;34:187–220.
- 6 Breiman L, Friedman JH, Olshen RA, Stone CJ: Classification and Regression Trees. Belmont, Wadsworth International Group, 1984.
- 7 Nordic Gastrointestinal Tumor Adjuvant Therapy Group: Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992;10:904–911.
- 8 Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P: Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413–1418.
- 9 Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D: Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993;306:752–755.
- 10 Zimmermann C, Burman D, Bandukwala S, Seccareccia D, Kaya E, Bryson J, Rodin G, Lo C: Nurse and physician inter-rater agreement of three performance status measures in palliative care outpatients. *Support Care Cancer* 2010;18:609–616.
- 11 Sorensen JB, Klee M, Palshof T, Hansen HH: Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer* 1993;67:773–775.
- 12 Martinez-Salamanca JI, Shariat SF, Rodriguez JC, Chromecki TF, Ficarra V, Fritsche HM, Kassouf W, Matsumoto K, Cabello LO, Seitz C, Tritschler S, Walton TJ, Zattoni F, Novara G: Prognostic role of ECOG performance status in patients with urothelial carcinoma of the upper urinary tract: an international study. *BJU Int* 2012;109:1155–1161.
- 13 Tarhan MO, Demir L, Somali I, Yigit S, Erten C, Alacacioglu A, Ellidokuz H, Seseogullari O, Kucukzeybek Y, Can A, Dirican A, Bayoglu V, Akyol M: The clinicopathological evaluation of the breast cancer patients with brain metastases: predictors of survival. *Clin Exp Metastasis* 2013;30:201–213.