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Original Article

Ramucirumab and paclitaxel in second or greater lines of therapy in patients with HER2-positive gastroesophageal cancer: a single center study

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Abstract

Background: Human epidermal growth factor receptor 2 (HER2) overexpression is present in approximately 20-25 of patients with advanced gastroesophageal adenocarcinoma (GEA). Upon progression on 1st line therapy, ramucirumab and paclitaxel (rampac) is given in ≥2 line setting regardless of HER2 status. We aim to assess whether ramucirumab is associated with better survival in HER2 positive(+) pts compared to those with HER2(−) disease.

Methods: We reviewed all consecutive adult patients with metastatic/unresectable GEA who were treated with rampac for ≥2nd line therapy at Princess Margaret Cancer Centre from 2010 to 2021. Progression free survival (PFS) and overall survival (OS) were defined as time from starting rampac to progression or death and estimated using the Kaplan-Meier method.

Results: There were 126 patients who received rampac following progression of 1st line chemotherapy, 96(76%) were male. The age at time of presentation and starting rampac was 59.0 ± 10.3 years and 59.9 ± 10.3 years, respectively. At the time of diagnosis, 32(25%) patients were HER2+. The majority of patients (n = 99;78%) received rampac in the 2L line setting compared to 28(22%) patients who received it in the 3rd/4th line setting. The median PFS and OS for HER2 + pts were 3.6 months and 9.4 months, respectively, which were similar to HER2- patients (median PFS = 3.6 months; median OS = 8.2 months). There was no statistically significant association between HER2 positivity and PFS (adjusted hazards ratio (HR) = 0.76, 95% confidence interval (CI) 0.48-1.22, P = .26), nor OS (adjusted HR = 0.88, 95% CI, 0.55-1.41, P = .59).

Conclusion: Rampac remains a valid treatment option for patients who are unable to participate in trials or do not have access to further HER2-directed therapy beyond first line.

Key words: esophageal cancer; gastric cancer; clinical oncology; genes; HER2.

Implications for practice

As novel anti-HER2 agents, such as zanidatamab and trastuzumab-deruxtecan, are being tested in≥2L trials and in combination with immunotherapy, it is crucial to establish the appropriate comparator arms during trial design. In the current study, ≥2L rampac was not associated with better survival outcomes in metastatic HER2+ patients who have developed resistance to trastuzumab when compared to HER2- patients. We conclude that although rampac remains a valid treatment option for patients who are unable to participate in trials or do not have access to further HER2-directed therapy beyond first line, it is reasonable to choose a regimen (such as FOLFIRI) based on patient's toxicity from 1L therapy and presence of gastrointestinal stent, rather than HER2 status.

Introduction

Human epidermal growth factor receptor 2 (HER2) protein overexpression is present in approximately 20%-25% of patients with esophageal, gastroesophageal junction (GEJ), or gastric adenocarcinoma.[1-5] The current standard of care therapy in the first line setting for advanced or unresectable gastroesophageal adenocarcinoma (GEA) is a combination of a fluoropyrimidine (5-FU or capecitabine) and a platinum-based agent (oxaliplatin or cisplatin). The addition of trastuzumab, an anti-HER2 monoclonal antibody, in patients with HER2 overexpression was established as standard-of-care practice when the ToGA trial demonstrated a median overall survival (OS) increase from 11.8 to 16.0 months in HER2 positive GEA patients treated with chemotherapy and trastuzumab.[4] Most recently, the addition of pembrolizumab, an immune checkpoint inhibitor, to trastuzumab was approved for HER2+ tumors with a PD-L1 combined positive score≥1 as per KEYNOTE-811.[6] Although the prognostic

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value of HER2 overexpression remains equivocal,[1-3,7-14] HER2 positivity has been associated with better prognosis since the introduction of HER2-targeted treatment in breast and gastroesophageal cancer patients.[4,15,16]

Upon disease progression on first line treatment, other regimens such as FOLFIRI (5-fluorouracil and irinotecan) or ramucirumab and paclitaxel (rampac) are prescribed regardless of HER2 positivity in GEA.[17,18] In the phase III double-blind randomized control RAINBOW trial, addition of ramucirumab to paclitaxel showed a significant increase in overall survival compared to patients treated with placebo and paclitaxel (median OS 9.6 months vs 7.4 months, respectively; hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.68-0.96, $P = 0.017$).[17] Similarly, a study from the AGAMENON-SEOM registry compared rampac to chemotherapy in the second line setting, which showed superiority of rampac in progression free survival (PFS), OS, and response rate, independent of HER2 status.[19] However, it should be noted that the chemotherapy arm was a heterogeneous group of patients treated with different 2L regimens.

Whether HER2 positive (+) patients have a better response to rampac is unclear. Preclinical models in breast cancer have shown a positive relationship between HER2 overexpression and angiogenesis,[20-25] suggesting that vascular endothelial growth factor receptor inhibitors may induce a greater response in patients with HER2+ disease. In a recent multi-center study in South Korea,[26] Kim et al found that although objective response rate (ORR) was significantly higher in HER2+ gastric/GEJ adenocarcinoma patients compared to those with HER2 negative (−) disease (23.0% vs 15.1%; $P = .025$), median PFS (4.3 months vs 3.7 months, $P = .054$) and OS (9.8 months vs 10.1 months, $P = .564$) were not statistically significant. There has been little else published on this subgroup of patients with GEA, especially in the North American setting.

In this single-center study, we aimed to compare response rate, PFS, and OS between patients with HER2+ and HER2− GEA who received rampac following progression on first line therapy. Furthermore, we conducted an exploratory subgroup analysis to compare survival outcomes between patients who received 2L rampac and 2L FOLFIRI.

Methods

Study design

This was a single-center retrospective cohort study including all consecutive adult patients (≥18 years old) diagnosed with de novo metastatic or recurrent GEA presenting to Princess Margaret Cancer Centre (PMCC), Toronto, Canada, between January 2010 and December 2021. Patients were excluded if: (1) they did not receive rampac following progression on first-line systemic therapy and/or (2) have an unknown HER2 status. Patients were stratified into 2 cohorts based on their pretreatment HER2 status as stated on their pathology reports and/or consultation notes (internal or external to PMCC). HER2+ disease was defined as tumors with immunohistochemistry (IHC) 3+ *or* IHC 2+ and fluorescence in situ hybridization positive. Patient outcomes such as response rate, PFS, and OS were compared across subgroups. For the purpose of the current study, response rate was defined by the report of the first CT following the start of rampac/FOLFIRI. If the reference radiologist described the disease to be stable or have a partial response, this was defined as having a response to treatment. Survival time was defined as the duration between start of rampac/FOLFIRI to time of event. Patients without a documented event were censored at the date of last follow-up.

Data collection

We reviewed clinicopathological data from patients' electronic medical records at the PMCC. Study data were de-identified, collected, and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at PMCC.[27] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Accuracy of data abstraction was independently verified by two trained research coordinators. The study was approved by our institutional research ethics board.

Statistical analysis

Data were reported as means and standard deviations for continuous variables and as counts and percentages for categorical variables. Normality was assessed using Shapiro-Wilk test. To compare between groups, rank-sum or ANOVA tests and chi-square or Fisher-exact tests were used for continuous and categorical variables, respectively. The association between HER2 status and response to rampac was performed with a univariable logistic regression model and reported as an odds ratio (OR). To examine the effect of HER2 positivity on survival, we performed uni- and multivariable analyses of baseline characteristics and adjusted for significant prognostic factors (age of starting rampac, sex, Charlson comorbiditiy index (CCI), Eastern Cooperative Oncology Group, tumor location, tumor grade). HR and 95% CI were reported to describe the magnitude and direction of associations. Statistically significant results were defined with P-values ≤.05 using a 2-sided test. Statistical analyses were performed using R v4.1.2.

Results

Study population

From January 2010 to December 2021, there were 126 patients treated with rampac beyond first line therapy and had a known HER2 status. The mean age at time of starting rampac was 59.9 ± 10.3 years with 96 (76%) patients being male (Table 1). At initial diagnosis, majority of patients had metastatic or unresectable disease ($n = 92$; 72%) with the primary tumor located at the gastroesophageal junction (GEJ) or stomach ($n = 116$; 91%). Of the total cohort, 32 (25%) patients had HER2+ disease. All HER2+ patients received a combination of chemotherapy and trastuzumab in the first line setting. Tumor grade was the only characteristic found to be statistically different between the 2 cohorts ($P < .001$). More specifically, there was a higher proportion of poorly-differentiated subtype in HER2− patients compared to HER2+ patients (55% vs 16%). Median follow-up duration of the total cohort, excluding patients who were lost to follow-up, was 8.1 months from the time of starting rampac.

Table 1. Patient characteristics.

Variable	Total $n = 126$	HER2 negative ($n = 94$)	HER2 positive ($n = 32$)	*P*-value
Age[1], years (mean ± SD)	59.8 ± 10.3	59.6 ± 10.6	60.3 ± 9.6	.93
Sex, male, *n* (%)	95 (75)	67 (71)	28 (88)	.10
CCI (mean ± SD)	0.5 ± 0.8	0.5 ± 0.8	0.4 ± 0.8	.29
0, *n* (%)	87 (69)	62 (65)	25 (78)	
1-2, *n* (%)	36 (29)	30 (32)	6 (19)	
3-4, *n* (%)	3 (2)	2 (2)	1 (3)	
≥ 5, *n* (%)	0	0	0	
ECOG[1]				1.00
0-1	41 (33)	34 (36)	7 (22)	
2-3	17 (13)	15 (16)	2 (6)	
Unknown	68 (54)	45 (48)	23 (72)	
De novo metastatic disease, *n* (%)	91 (72)	64 (68)	27 (84)	.21
Tumour grade, *n* (%)				<.001
G1: Well-differentiated	8 (6)	2 (2)	6 (19)	
G2: Moderately differentiated	30 (24)	17 (18)	13 (41)	
G3: Poorly differentiated	57 (45)	52 (55)	5 (16)	
GX: Unknown	31 (25)	23 (25)	8 (24)	
Location of primary tumour, *n* (%)				.26
Esophagus	11 (9)	7 (7)	4 (12)	
GEJ (Siewart I-III)	64 (52)	46 (49)	18 (56)	
Gastric	51 (40)	41 (44)	10 (31)	
1st line systemic treatment, *n* (%)				<.001
Chemotherapy	91 (72)	90 (96)	1 (3)	
Chemotherapy + HER2 agent	31 (25)	0 (0)	31 (97)	
Chemotherapy + IO	4 (3)	4 (4)	0 (0)	
Ramucirumab/paclitaxel treatment line, *n* (%)				.40
2nd line	99 (79)	71 (76)	28 (88)	
3rd line	25 (20)	21 (22)	4 (12)	
4th line	2 (2)	2 (2)	0 (0)	
Response rate[2], *n* (%)	55 (50)	40 (51)	15 (48)	.83

[1]At the time of starting rampac;
[2]based on original radiologist's reporting of first CT scan after starting rampac ($n = 110$; $n = 79$ HER2–; $n = 31$ HER2+).

Response rate of rampac in HER2+ versus HER2– patients

Patients with an unknown date of progression/discontinuation from rampac prior to the first computed tomography (CT) scan following the start of rampac were excluded ($n = 17$). Of the 110 patients, 55 (50%) patients had either stable disease or partial response from rampac as described from their original CT report (Table 1). There was no statistically significant association between HER2 status and response to rampac (unadjusted odds ratio (OR) = 0.96, 95% CI, 0.63-1.44, $P = .83$).

Survival of rampac treatment in HER2+ versus HER2– patients

Kaplan-Meier curves for PFS and OS are shown in Figures 1 and 2, respectively. The median PFS for the entire cohort was 3.6 months with no observed difference between HER2– and HER2+ patients (3.6 vs 3.6 months, respectively, unadjusted HR 0.78, 95% CI, 0.49-1.23, $P = .29$) (Table 2). Median OS was 8.3 months for the total cohort and was comparable between HER2– and HER2+ cohorts (8.2 vs 9.4 months, respectively, unadjusted HR 0.88, 95% CI, 0.57-1.38, $P = .59$) (Table 3). After adjusting for age at time of starting rampac, sex, CCI, and primary tumor location, HER2 positivity was not independently associated with PFS (adjusted HR 0.69, 95% CI, 0.43-1.11, $P = .13$) nor OS (adjusted HR 0.88, 95% CI, 0.56-1.38, $P = .57$).

Exploratory analysis 2L rampac versus 2L FOLFIRI

In our preplanned exploratory analysis, we compared patients who received 2L rampac ($n = 99$) and those who received 2L FOLFIRI ($n = 48$). Age of starting 2L therapy (59.4 ± 10.4 years vs 57.4 ± 11.3, respectively, $P = .25$) and HER2 positivity (28% vs 21%, respectively, $P = .44$) were similar across both groups. The decision to treat patients with 2L rampac or 2L FOLFIRI did not show any statistically significant differences in median PFS (3.5 vs 2.8 months, $P = .79$) nor OS (8.1 vs 9.9 months, $P = .33$). Similarly, of those with HER2+ disease ($n = 38$), patients who were treated with 2L rampac ($n = 28$) had similar median PFS and OS when compared

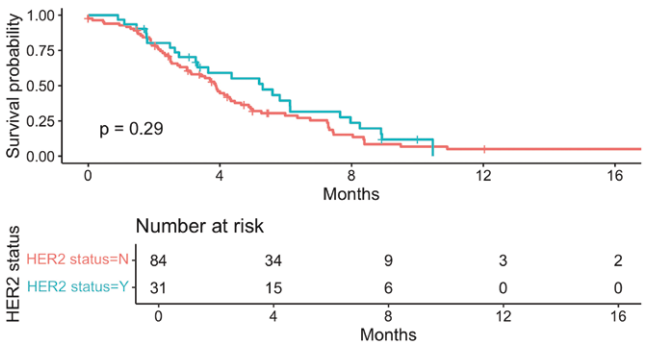

Figure 1. PFS in HER2 negative vs HER2 positive patients.

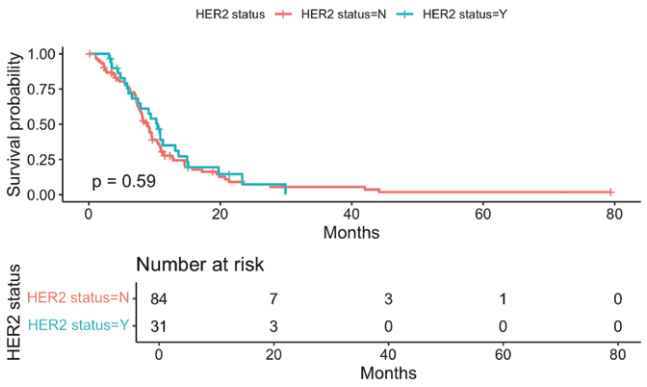

Figure 2. OS in HER2 negative vs HER2 positive patients.

to those treated with 2L FOLFIRI ($n = 10$) (Supplementary Figure S1).

Discussion

There has been debate on whether anti-VEGFR agents in the 2L setting may help overcome the resistance developed in HER2+ patients.[19,26] Although the RAINBOW trial has confirmed superiority of rampac to single-agent paclitaxel,[17] HER2 positivity was not reported and included in their subgroup analyses. In this single-centre study, HER2 positivity was not significantly associated with treatment response nor survival following ≥2L rampac. Similar to prior literature, we conclude that physician's choice of using rampac following 1L progression can be made regardless of HER2 status.

Survival following ≥2L rampac

In contrast to a cohort study conducted in South Korea which found HER2+ patients to have a higher ORR compared to HER2– patients (23.0% vs 15.1%, $P = .025$) when given 2L rampac,[26] we did not observe any statistically significant association between HER2 positivity and ORR (unadjusted OR = 0.96, 95% CI, 0.63-1.44, $P = 0.83$). This may be due to the differences in how treatment response was defined in each study. Although HER2+ patients from the South Korean study had a better ORR, it did not translate to a survival benefit in PFS nor OS.[26]

In a subgroup analysis of the AGAMENOM-SEOM Registry, 2L rampac was superior to chemotherapy in PFS (HR = 0.64, 95% CI, 0.53-0.78, $P < .0001$) and OS (HR = 0.68, 95% CI 0.55-0.83, $P = .0002$), *regardless* of HER2 status.[19] In the comparison between HER2+ vs HER2– cohorts, median 2L PFS were 4.7 and 3.5 months, respectively, and median 2L OS were 7.4 and 6.6 months. This was also similar to the current study which did not find statistically significant differences in PFS and OS between HER2+ and HER2– patients. It is important to note that in these studies, including the current one, survival was stratified by HER2 status at *baseline* (ie, time of diagnosis) rather than time of starting rampac.

Clinical significance

As novel anti-HER2 agents, such as zanidatamab and trastuzumab-deruxtecan, are being tested in ≥2L trials and in combination with immunotherapy, it is crucial to establish the appropriate comparator arms during trial design. In the current study, ≥2L rampac was not associated with better survival outcomes in metastatic HER2+ patients who have developed resistance to trastuzumab when compared to HER2- patients. We conclude that although rampac remains a valid treatment option for patients who are unable to participate in trials or do not have access to further HER2-directed therapy beyond first line, it is reasonable to choose a regimen (such as FOLFIRI) based on patient's toxicity from 1L therapy and presence of gastrointestinal stent, rather than HER2 status.

Limitations

First, this study was retrospective. The stratification of patients into HER2+ and HER2– cohorts was based on pathology and clinical reports, introducing misclassification bias due to the changes in cutoff values of the IHC scoring system over time. There has also been emerging evidence that HER2 "low" gastric cancer characterized by IHC 1+ or 2+/ISH negative, should be considered its own distinct cohort.[28] Temporal changes in HER2 status following progression on 1L therapy could not be assessed in the current study, which may be a more revealing analysis. Second, this was a single-center study and as such, our sample size limits our ability to observe subtle differences in outcomes.

Future directions

To address the issue of HER2 heterogeneity in GEA tumor samples,[1,5,29-32] pathology review of archival materials to define HER2 positivity as a continuous variable may create a better stratification system of HER2+ vs HER2- patients. Furthermore, as there is an increase in patients receiving post-1L biopsies/endoscopies for clinical trials screening, perhaps HER2 biomarker testing can be reassessed and used to address temporal heterogeneity of HER2 expression. A meta-analysis of the current and previous studies[19,26] analyzing the role of anti-VEGFR agents in the 2L setting in GEA may address the relatively small sample sizes of each study.

Conclusion

In this single-center study, we did not find a survival benefit in PFS nor OS in HER2+patients receiving rampac when compared to HER2– patients in GEA. Rampac remains a valid treatment option for patients who are unable to participate in trials or do not have access to further HER2-directed therapy beyond first line.

Table 2. Uni- and multivariable analysis for progression-free survival (PFS).

Covariate	Univariable analysis			Multivariable analysis	
	HR (95%CI)	*P*-value	*n*	HR (95%CI)	*P*-value
Age[1]	0.98 (0.96-1.00)	.016	115	0.98 (0.96-1.00)	.098
Male sex	0.62 (0.39-0.99)	.044	115	0.65 (0.37-1.15)	.14
CCI	0.84 (0.63-1.10)	.20	115	0.87 (0.66-1.16)	.34
ECOG[1]			50		
0-1	Reference	—	35	—	—
2-3	1.98 (1.05-3.74)	.035	15	—	—
Location of primary tumour		.31	115		
GEJ (Siewart I-III)	Reference	—	55	Reference	—
Esophagus	0.81 (0.41-1.6)	.54	11	0.83 (0.41-1.67)	.60
Gastric	1.30 (0.84-2.03)	.24	49	1.16 (0.69-1.97)	.59
Tumour grade		.034	115	—	—
G1	Reference	—	8	—	—
G2	1.73 (0.62-4.28)	.32	28	—	—
G3	2.91 (1.14-7.47)	.03	49	—	—
HER2 status	0.78 (0.49-1.23)	.29	115	0.69 (0.43-1.11)	.13

PFS is defined as start of ram/pac to time of disease progression or last dose of ram/pac.
[1]At the time of starting rampac.

Table 3. Uni- and multivariable analysis for overall survival (OS).

Covariate	Univariable analysis			Multivariable analysis	
	HR (95%CI)	*P*-value	*n*	HR (95%CI)	*P*-value
Age[1]	0.99 (0.97-1.01)	.41	126	1.00 (0.98-1.02)	.84
Male sex	0.73 (0.47-1.13)	.16	126	0.63 (0.35-1.13)	.12
CCI	0.82 (0.62-1.09)	.17	126	0.81 (0.60-1.10)	.17
ECOG 2-3	2.76 (1.47-5.20)	.002	58	—	—
Location of primary tumour		.98	126		
GEJ (Siewart I-III)	Reference	—	64	Reference	—
Esophagus	0.98 (0.49-1.93)	.94	11	0.94 (0.47-1.88)	.86
Gastric	1.04 (0.68-1.58)	.87	51	0.76 (0.43-1.33)	.34
Tumour grade		.12	95	—	—
G1	Reference	—	8	—	—
G2	1.78 (0.68-4.71)	.24	30	—	—
G3	2.55 (1.01-6.47)	.05	57	—	—
HER2 status	0.88 (0.57-1.38)	.59	126	0.88 (0.56-1.38)	.57

OS is defined as start of ram/pac to time of death or lost to follow-up.
[1]At the time of starting rampac.

Author contributions

Yvonne Bach (Conceptualization, Data curation, Investigation, Methodology, Writing—original draft). Divya Sharma (Formal analysis, Writing-review and editing). Hiroko Aoyama (Data curation, Validation, Writing-review & editing). Lucy X Ma (Supervision, Writing—review & editing). Xin Wang (Writing-review & editing). Carly C Barron (Writing-review & editing). Sokaina Akhtar (Validation, Data curation). Yahan Yang (Validation, Data curation). Alana St Bernard (Validation, Data curation). Ronan McLaughlin (Writing-review & editing). Thais BC Megid (Writing-review & editing). Abdul R Farooq (Writing-review & editing). Eric X Chen (Writing—review & editing). Raymond W.J. Jang (Supervision, Writing-review & editing). Elena Elimova (Conceptualization, Supervision, Resources, writing—review & editing)

Conflicts of interest

LXM: Consulting—Eisai, Bristol Myers Squibb; RWJJ: Research Funding: AstraZeneca, Merck, Camurus Honoraria: BMS; EE: Consultant for: BMS, Zymeworks, Adaptimmune, Beigene, Jazz, Astellas, Virecta Tx, Natera, Abbvie, Daiichi –Sankyo, Roche Grant/Research support from: BMS, Zymeworks, Astra Zeneca, Jazz, Amgen, Bold Therapeutics,

Arcus Biosciences Steering Committee Member: Jazz, Astra Zeneca. Additional financial relationship disclosures: Employment for: Merck (family member).

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical approval

The study received ethics approval from the University Health Network Review Ethics Board (CAPCR ID: 23-5888).

Supplementary material

Supplementary material is available at *The Oncologist* online.

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