RESEARCH ARTICLE

Profile of HER2 +ve Gastric Cancers in Brunei Darussalam

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Abstract

Background: Gastric cancer is the second most common gastrointestinal cancer and is still associated with significant morbidity and mortality due to late presentation and diagnosis at advanced stages. Studies have reported that a variable proportion of gastric cancer is positive for the human epidermal growth factor receptor 2 (HER2) and patients with HER2 positive (HER2 +ve) lesions can benefit from targeted therapy. This study was conducted to assess the prevalence of HER2 +ve gastric cancers in Brunei Darussalam, a developing Southeast Asian nation. Materials and Methods: Patients were identified from the Department of Pathology registry and retrospectively reviewed. HER2 expression was assessed by immunohistochemistry and only those staining 3+ were considered positive. Results: Our study included 103 cases (66 males and 37 females) with a mean age of 65.1 ± 14.8 years old. There were 14 cases positive for HER2 (10 males and 4 females) giving a prevalence of 13.6%. The HER2 +ve cases were significantly older (70.6 ± 19.3 years old) than the negative cases (64.2 ± 13.8, p=0.041) and had significantly more advanced disease (stages 3 and 4, p=0.026). There were no significant differences in gender distribution, presence of intestinal metaplasia, EBV status, *Helicobacter pylori* status, tumor location (proximal vs. distal) and degree of tumor differentiation (all p values >0.05). Conclusions: Our study showed that 13.6% of our gastric cancers are positive for HER2, the affected patients being older and having more advanced disease at diagnosis.

Keywords: Gastric carcinoma - prevalence - HER2 - characteristics - Brunei Darussalam

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Introduction

Gastric cancer is the second most common gastrointestinal cancers after colorectal cancers, and is the second most common cause of cancer related death (Jemal et al., 2011). The incidence of gastric cancer has been declining correlating infection and improvement in the standard of living (Chong et al., 2009; IARC GLOBOCAN 2012) with the decline of Helicobacter pylori (*H pylori*) infection (Chong et al., 2009; Watanabe et al., 2015). However, the mortality rate remains significant as most are still diagnosed at the advanced stages as results of late presentation or delayed investigations.

Since the discovery of expression of the human epidermal growth factor receptor 2 (HER2) in gastric cancer cells, targeted therapy with trastuzumab, an anti-HER2 blocker, in addition to standard regime (platinum and fluorouracil) has been shown to be is associated with better response and prolonged survival (Bang et al., 2010). Trastuzumab targeted combination therapy is now the recommended regime for patient with advanced gastric adenocarcinoma or gastroesophageal junction tumors that are positive for HER2. Therefore, testing for HER2 is now widely recommended for the gastric cancers (Rüschoff et al., 2012; Wada et al., 2016).

The prevalence of HER2 overexpression in gastric cancer has been reported to vary widely from as low as 4.4% to as high as 53.4% (Allgayer et al., 2000; Grabsch et al., 2010; Jørgensen and Hersom. 2012). Generally, the rate is reported to be over 20% and higher in the gastroesophageal junction tumor (~33%) (Albarello et al., 2011). The largest study (ToGA study), a multicenter study that assessed the role of anti-HER2 in addition to standard chemotherapy reported a rate of 76% positivity based on IHC 3+ or IHC 2+ and positive for FISH; more in those with proximal tumor location and advanced disease (Bang et al., 2010). The likely explanation postulated for the variable prevalence rates reported in the literature are mainly related to techniques used to stain for HER2 and definition of positivity. However, population differences may also be important. It is now recommended based on the ToGA study that patients should only be considered for additional targeted therapy if they are positive for HER2; 3+ immunohistochemistry (IHC) or IHC 2+ positive with FISH or SISH (Bang et al., 2010; Rüschoff et al., 2012; Wada et al., 2016).

Gastric cancer is the second most common gastrointestinal cancer in Brunei Darussalam (Chong

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et al., 2012) and is a significant cause of morbidity and mortality. Given that most cases are in the advanced stages of disease at diagnosis due to delayed presentations, it is important to identify factors, in this case HER2 which can provide treatment advantage. This study assesses the prevalence and characteristic of HER2 positive gastric cancers Brunei Darussalam.

Materials and Methods

Patient Population: This study is a prospective based cross-sectional study. Patients diagnosed with gastric cancers who had staining for HER done were identified from the registry maintained by the Department of Pathology, the only state laboratory that handles all histological specimens, located in RIPAS Hospital, the major tertiary referral centre in Brunei Darussalam. This cancer registry captures all histology proven gastric cancers for the country. Cancers other than adenocarcinoma such as gastrointestinal stroma tumor (GIST), neuroendocrine tumor or lymphoma were excluded. Patients with significant missing data or did not have their tumour stained for HER2 were also excluded.

Clinicopathologic data collected included age, gender, locations and staging of the tumors based on the TNM classification. Histopathologic data collected included differentiation of carcinoma, intestinal metaplasia, H. pylori and EBV status.

Immunohistochemical analysis: In our institutions, all gastric adenocarcinomas are routinely stained for HER2 following recommendations after the publication of the ToGA trial (Bang et al., 2010; Rüschoff et al., 2012). All patients diagnosed with gastric cancers during the study period were studied for HER2 through immunohistochemical (IHC) staining. Following the recommendation of the ToGA trail, any case which were IHC 3+ positive were taken as positive (Figure 1). We did not include IHC 2+ cases as we did not have facility to do FISH analyses (Bang et al., 2010; Rüschoff et al., 2012).

Histological Classification, Pathology and Staging; tumors location was classified anatomically as cardia, fundus, body and antrum based on the predominant location of the tumours. The locations were subcategorized into proximal (body, cardia and fundus) and distal (antral and pylorus). Histological diagnosis and grade of differentiation were determined in accordance with World Health Organization criteria for gastric cancer (WHO, 2000). The TNM classification was applied for staging.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS), version 20.0. Collected sociodemographic, clinicopathological and histopathological data were presented in percentages and frequency. Pearson's Chi-square and Fisher's exact test were used for categorical variables where appropriate. Level if significance was taken with a p value of <0.05.

Results

Our study included 103 patients; mean age 65.1 ± 14.8 years old with a gender breakdown of more male than female. The demographic and tumor type and stage of disease at diagnosis is shown in Table 1. Overall, majority of the cases were at the advanced stages of disease at diagnosis.

Overall, there were 14 cases that was positive for HER2, giving a prevalence of HER2 +ve gastric cancer of 13.6%.

Comparing HER2 +ve with HER2 –ve gastric cancers showed that HER2 +ve gastric cancer patients were significantly older (70.6 ± 19.3 vs. 64.2 ± 13.8, p=0.041) and with more advanced disease (stages 3 and 4; 85.7% vs. 54.0%, p=0.026). For the other parameters compared, there were no difference in gender breakdown, location of tumor, stage of disease, level of tumor differentiations, *H pylori* and EBV positivity. These are shown in Table 2.

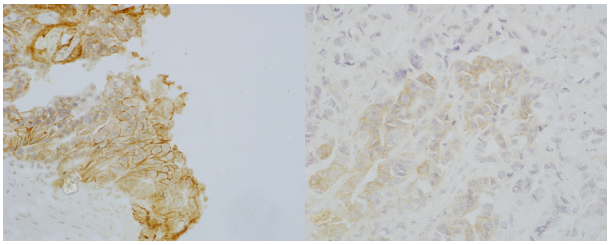

Figure 1. a) Positive strong (IHC 3+) and b) weak staining for HER2 (IHC 1+)

Table 1. Demographic and Tumor Characteristics

Variables	n (%)
Gender	
Male	66 (64.1)
Female	37 (25.9)
Ethnicity	
Malays	81 (78.6)
Chinese	16 (15.5)
Indigenous	5 (4.9)
Others	1 (1.0)
Tumour location *	
Cardia/Fundus	39 (39)
Body	17 (17)
Antrum	39 (39)
Extensive	6 (6)
Intestinal metaplasia	
Present	40 (38.8)
Absent	63 (61.2)
H pylori	
Present	29 (28.2)
Absent	74 (71.8)
EBV staining	
Positive	27 (26.2)
Negative	73 (70.9)
Not stained	3 (2.9)
Differentiation **	
Well	14 (14.1)
Moderately	30 (30.3)
Poorly	55 (55.6)
Stage of disease ***	
Stage 1	20 (19.8)
Stage 2	22 (21.8)
Stage 3	25 (24.8)
Stage 4	34 (33.7)

* based on 2 missing data; ** based on missing 4 data; *** based on 2 missing data

Table 2. Comparison Between HER2+ve and HER2-ve Gastric Cancer Cases

Variables	HER2+ve	Her2-ve	p value
Mean age (years)	70.6 ± 19.3	64.2 ± 13.8	0.041
Gender			0.537
Male	10 (71.4)	56 (62.9)	
Female	4 (28.6)	33 (37.1)	
Ethnic			0.849 for trend
Malays	10 (71.4)	71 (79.8)	
Chinese	3 (21.4)	13 (14.6)	
Indigenous	1 (7.1)	4 (4.5)	
Others	0 (0)	1 (1.1)	
Intestinal metaplasia			0.131
Present	8 (57.1)	32 (36.0)	
Absent	6 (42.9)	57 (64.0)	
Tumour location			
Proximal	10 (71.4)	52 (59.8)	0.406
Distal	4 (28.6)	35 (40.2)	
EBV status			0.733
Positive	3 (23.1)	24 (27.6)	
Negative	10 (76.9)	63 (72.4)	
H pylori			0.547
Positive	3 (21.4)	26 (29.2)	
Negative	11 (78.6)	63 (70.8)	
Differentiation **			0.703 for trend
Well	1 (7.1)	13 (15.3)	
Moderately	5 (35.8)	25 (29.4)	
Poorly	8 (57.1)	47 (55.3)	
Tumor stage			
Advanced (Stage 3/4)	12 (85.7)	47 (54.0)	0.026
Early (Stage 1/2)	2 (14.3)	40 (46.0)	

Discussion

Our study showed that 13.6% of gastric cancer in Brunei Darussalam is positive for HER2. This is consistent with what have been reported in the literature. Our rate would likely to have been slightly higher as we excluded IHC 2+ cases as we did not have the facility to do FISH or SISH for further confirmation. The rates reported in the literature range between 4.4% and 53.4% (Allgayer et al., 2000; Grabsch et al., 2010; Jørgensen and Hersom. 2012; Boku, 2014). However, earlier studies have been based on non-standardized assessment of HER2. Assessment for HER2 is well established in breast cancer but for gastric cancer, there are differences, mainly due to tumor heterogeneity (focal staining) and incomplete staining of the basolateral or lateral basement membrane (Rüschoff et al., 2012). Therefore application of the standardized methods used for breast cancer has been reported to underestimate the actual prevalence of HER2 in gastric cancer. Consensus has now been standardized for reporting HER2 in gastric cancer (Rüschoff et al., 2012; Wada et al., 2016).

The difference in the rates of HER2 gastric cancer is unlikely to be just due to staining and assessment methodology, but also the tumor and demographic differences. HER2 is more common in the intestinal type compared to the diffuse tumor type (Bang et al., 2012; Rüschoff et al., 2012; Rakhshani et al., 2014; Madani et al., 2015; Wada et al., 2016). It is therefore more common in the well differentiated type compared to the poorly differentiated tumor. Underlying genetic difference also play a role.

HER2 positive gastric cancer has been traditionally been associated with more advanced disease and poor prognosis. Based on newer studies, these believes have been questioned. Recent studies have reported no difference in the prognosis. However one important aspect of HER2 gastric cancer is that for a subset, it has been shown to respond favorable with addition of anti-HER2 to standard therapy of platinum and fluorouracil. The landmark ToGA multi-center trial showed that patient positive of HER2 (IHC 3+ or IHC2+/FISH confirmed) had longer overall survival with better self-reported functional status, without difference in adverse effects compared to standard therapy (Bang et al., 2012). The ToGA trial has led to the recommendation of routine testing for HER2 in gastric cancer and targeted therapy for positive HER2 cases (Bang et al., 2012; Rüschoff et al., 2012; Wada et al., 2016).

In our study, we showed that HER2 gastric cancer were generally older than HER2 negative cases and had significantly more advanced diseases in HER2 positive cases. These are also consistent with what have been reported in the literature. However, there was no difference in the tumor locations. Possible explanations for the negative findings in our study include; a) small sample size, b) most of our cases were advanced at presentation therefore, affecting the results and c) possible differences in the tumor or population characteristics.

There were also no difference in the other parameters assesses; gender, ethnicity, level of differentiations, *H pylori* and EBV status. Gastric cancer is a predominant male disease and no association have been reported in the literature. Given that HER2 is more common in the intestinal type tumor, it is surprising that there was no association with *H pylori*. However, we only assessed for active *H pylori* infection and it is possible that many cases had *H pylori* as the underlying etiology of their gastric cancer but had eradication therapy or non-detection of *H pylori* based on rapid urease test or histology. EBV is also a recognised etiology for a subset of gastric cancer (Yen et al., 2014), reported to account for 10% of gastric cancers. Given that the pathogenesis of *H pylori* related and EBV related gastric cancer and that HER2 positive is more common in the intestinal type of gastric cancer, it is not surprising that there was no association found in our study.

Even though the incidence of gastric cancer is decreasing (Jemal et al., 2011; IARC GLOBOCAN 2012; Chong et al., 2014), the outcomes are still poor due to advanced diseases at diagnosis. Therefore, it is very important to find ways to overcome this problem. In countries where screening program is available like Japan and Korea (Sugano, 2015), cases are detected early and hence screening for HER2 may not be so important. In the Asia Pacific region where *H pylori* infection remain common compared to the rest of the world, gastric cancer will continue to be an important cancer related mortality and early diagnosis remains an issue. Improving treatment

outcomes, even though not curative is important. As our understanding improve and newer targeted therapies become available, future treatment options will provide better outcomes. In the meantime, it is important to be vigilant and evaluate patient early, continue the practice of *H pylori* eradication, education of public and perhaps in limited resource nations, devise a system for identifying high risk patients so that selective screening can be done.

There are several limitation in our study. First the sample size is small and it is a single centre study. Second, we had only used IHC to identify positive case and this meant that there is a possibility of underestimation. However, underestimation is likely to be small. The strength of our study was that the method used was standardized and experienced senior pathologist assessed or reassessed all the slides.

In conclusion, we showed that HER2 positive gastric cancer accounted for one in eight cases. HER2 positive gastric cancers patients were older and had more advanced disease at diagnosis. Generally most of our patients still present late accounting for the advanced diseases at diagnosis for majority of the patients.

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