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SHORT REPORT

Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients

Noor Al-Dasooqi · Joanne M. Bowen · Rachel J. Gibson · Thomas Sullivan · Jude Lees · Dorothy M. Keefe

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Summary *Purpose*: To characterise the gastrointestinal toxicities associated with Trastuzumab administration in HER2-overexpressing breast cancer patients. *Methods*: All patients (n=46) who received Trastuzumab as a single agent or in conjunction with conventional anti-cancer treatment within the Royal Adelaide Hospital Cancer Centre from 2002–2007 were included in this study. A retrospective analysis of case-notes was conducted to investigate the toxicities associated with Trastuzumab. *Results*: Trastuzumab as a single agent induced toxicities following 22% of administrations. Gastrointestinal toxicities were observed following 12% of administrations and included nausea and vomiting, diarrhoea, abdominal pain and bloating. However, other prominent toxicities that were not related to the gastrointestinal tract were also observed including fatigue and lung symptoms (10.4%). Elderly patients (≥60 years) and those with metastatic disease experienced the highest frequency of toxicity. *Conclusion*: Trastuzumab induces a range of gastrointestinal toxicities in HER2-overexpressing breast cancer patients. These toxicities are separate to those caused by concurrent chemotherapy and/or radiotherapy.

Keywords HER2-overexpressing breast cancer · Targeted therapy · Trastuzumab · Gastrointestinal tract · Toxicity

N. Al-Dasooqi
Department of Physiology, University of Adelaide,
North Terrace, Adelaide, SA, Australia

N. Al-Dasooqi (✉) · J. M. Bowen · R. J. Gibson · D. M. Keefe
Department of Medical Oncology, Royal Adelaide Hospital,
North Terrace, Adelaide 5000 SA, Australia
e-mail: noor.abdulghafour@student.adelaide.edu.au

J. M. Bowen · D. M. Keefe
Department of Medicine, University of Adelaide,
North Terrace, Adelaide, SA, Australia

R. J. Gibson
Discipline of Anatomical Sciences,
University of Adelaide,
North Terrace, Adelaide, SA, Australia

T. Sullivan
Discipline of Public Health, University of Adelaide,
North Terrace, Adelaide, SA, Australia

J. Lees
RAH Cancer Centre, Royal Adelaide Hospital,
North Terrace, Adelaide, SA, Australia

D. M. Keefe
Cancer Council South Australia,
Eastwood, SA, Australia

Introduction

Targeted therapies are a relatively new class of anti-cancer treatment, and their use as single agents or in combination with cytotoxic chemotherapy and/or radiotherapy are becoming increasingly significant for the treatment of specific cancers, including breast cancer [1–3]. The term targeted therapies refers to compounds that inhibit a particular target molecule involved in tumour progression. Therefore, in contrast to conventional anti-cancer treatment which target cellular machinery common to both malignant as well as normal dividing cells, targeted therapy drugs are directed at a more specific target.

Trastuzumab is a monoclonal antibody directed at the extracellular portion of the HER2 receptor [4–7], and is used in the treatment of HER2-overexpressing breast cancer [8–11]. The HER2 receptor controls multiple pathways

associated with epidermal growth factor (EGFR) and HER receptor activation [12]. Furthermore, these pathways regulate proliferation, cell death, angiogenesis and migration [5]. Therefore, aberrant expression of HER2 receptors contributes significantly to the progression of cancer [5, 6, 10]. A study by Xu and colleagues [13] demonstrated that the inhibition of this receptor reduced the proliferative capacity and increased apoptosis of HER2-overexpressing malignant cells. Moreover, clinical studies investigating the efficacy of Trastuzumab in treating HER2-overexpressing cancers have clearly shown that Trastuzumab decreases the rate of recurrence and increases disease free survival amongst patients [4, 10, 14].

Previous research has established that traditional anti-cancer agents, including chemotherapy and radiation therapy, induce alimentary tract (AT) mucositis in a wide range of patients [15, 16]. This condition is manifest by pain and ulceration, vomiting, bloating and diarrhoea, depending on the area of the gastrointestinal tract (GIT) affected [16, 17]. Many of these gastrointestinal symptoms have been described in patients receiving Trastuzumab as part of their treatment [18]. However, as yet it is uncertain whether these symptoms arise as a result of Trastuzumab alone or as a result of other cytotoxic treatment. Moreover, the specific toxicities associated with Trastuzumab treatment have not been well characterised and the underlying mechanisms remain poorly understood. Therefore, better characterisation of the toxicities associated with Trastuzumab is required to give an insight into their source and allow for appropriate intervention strategies.

It has been recently proposed that toxicities arise following Trastuzumab administration due to its ability to cross-react with HER2 receptors present on normal cells [2]. The HER2 receptor is a member of the EGFR family [5] and appears to play an important role in numerous biological phenomena, including regulation of cell differentiation, death and proliferation [19, 20]. Previous studies have demonstrated the expression of the HER2 receptor by normal epithelial cells throughout the body, including mammary gland, lungs and GIT [12, 20, 21]. In the GIT, the main function of the HER2 receptor is to aid in the maintenance of mucosal layer integrity [19, 22]. Although Trastuzumab is aimed at malignant cells, it cannot be avoided that there will be a certain level of interaction with healthy cells, subsequently leading to toxicity.

The aim of this study was to characterise the specific toxicities associated with Trastuzumab administration and to identify whether these toxicities are separate to those produced by concurrent conventional anti-cancer therapy. It is hypothesised that Trastuzumab administration is associated with subsequent gastrointestinal toxicities.

Methods

Ethics

This study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and was carried out in accordance with the Declaration of Helsinki.

Patients

All patients (n=46) who received Trastuzumab as a second-line regimen, with or without conventional anti-cancer treatment, within the Royal Adelaide Hospital between 2002 and 2007 were identified via pharmacy records and included in this study. All data were de-identified.

Analysis of medical records

To identify the toxicities associated with Trastuzumab treatment, a retrospective case-note review of consecutive patients was performed. The toxicities to record were as identified by the National Cancer Institute common GIT toxicity criteria following anti-cancer treatment. These included oral symptoms, stomatitis, nausea and vomiting, diarrhoea, constipation, abdominal pain and bloating. Toxicities not related to GIT manifestations were also recorded.

Data collation and statistics

The frequency of each toxicity was calculated as a percentage of the total administrations of Trastuzumab (percent of administrations). A Poisson regression model was used to predict risk factors which enhanced the vulnerability of patients to toxicity. Predictor variables included were age, disease status and Trastuzumab treatment regimen. The interaction between these variables was also assessed.

Results

Patient characteristics

All 46 patients who received Trastuzumab had breast cancer tumours that over-expressed the HER2 receptor. Patients had a mean age of 53 years (33–84 years). Trastuzumab was given to patients with both early (67%) and metastatic disease (33%; Table 1). In the majority of administrations, Trastuzumab was administered as a single agent following completion of first-line chemotherapy and/or radiotherapy (85%) while in the remaining administrations it was given concurrently with conventional anti-cancer therapy (15%; Table 1).

Overall toxicity of Trastuzumab

Trastuzumab, with or without chemotherapy, induced toxicities following 27% of administrations. The most prevalent gastrointestinal toxicities were nausea and vomiting (9.7%) and diarrhoea (2.4%). However, a significant proportion of toxicities that patients experienced were non-GIT related (12.9%) and these included lung symptoms, fatigue and headaches (Fig. 1).

Toxicity of Trastuzumab as a single agent

Trastuzumab as a single agent induced toxicities following 20% of administrations. The most prominent gastrointestinal side effects induced following administration were nausea and vomiting (7.1%; Fig. 2). Diarrhoea, abdominal pain and constipation were also recorded following a small subset of Trastuzumab administrations (Fig. 2).

Table 1 Demographics of patients who received Trastuzumab within the Royal Adelaide Hospital Cancer Centre

Characteristics	Number (%)
Age	
Mean	53
Range	33–84
HER2-overexpressing breast cancer	
Early	31 (67)
Metastatic	15 (33)
Trastuzumab treatment regimen	
weekly	18 (39)
3 weekly	28 (61)
Number of Trastuzumab administrations	
Mean	11
Range	1–78
Number of toxicities experiences	
Mean	3
Range	0–21
Prophylactic treatment	
Analgesics (paracetamol)	46 (100)
anti-histamines (loratadine)	46 (100)
anti-emetics (tropisteron/dexamethasone)	5 (11)/only if concurrent CT/RT is given
Concurrent anti-cancer treatment	
None	39 (85)
Chemotherapy	5 (11)
Radiotherapy	1 (2)
Chemoradiotherapy	1 (2)
Previous anti-cancer treatment	
None	5 (10)
Chemotherapy	24 (52)
Radiotherapy	1 (2)
Chemoradiotherapy	16 (36)

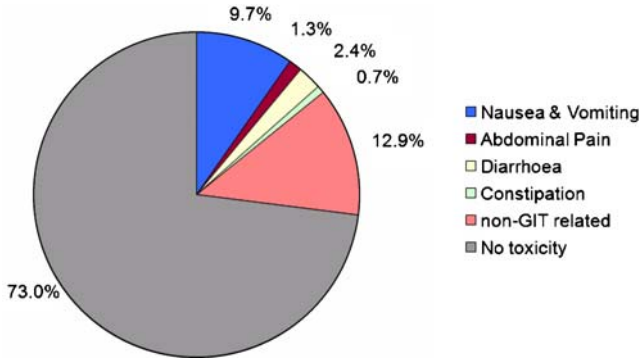

Fig. 1 The frequency of toxicities associated with Trastuzumab administration as a percent of total administrations. Data shown indicate occurrence of gastrointestinal toxicities following administration of Trastuzumab as a single agent or in combination with chemotherapy in HER2-overexpressing breast cancer patients

Non-GIT related toxicities were also evident (10.4%; Fig. 2). The most common non-GIT related toxicities observed following single agent Trastuzumab included lung symptoms (2.3%) and fatigue (2%; Table 2). Headaches, muscular and joint pain, skin toxicities and visual disturbances were also recorded following a small subset of administrations (Table 2).

Toxicity of Trastuzumab in combination with cytotoxics

In the present study, Trastuzumab was given concurrently with conventional anti-cancer treatment in only 15% of

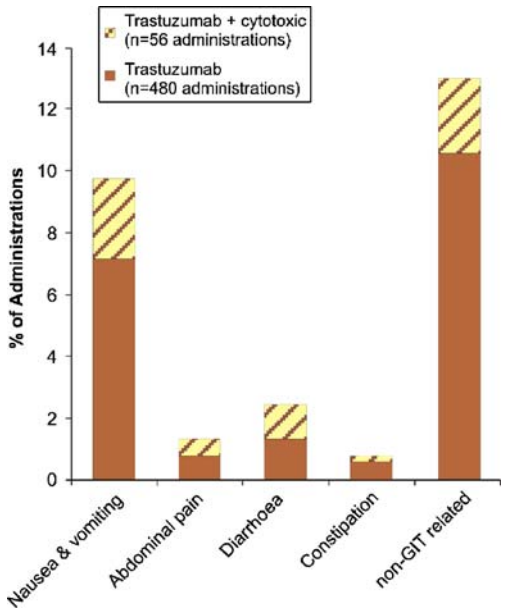

Fig. 2 The contribution of single agent Trastuzumab to the overall toxicities observed in patients. Data indicate that the toxicities manifest are not solely due to concurrent chemotherapy. Toxicities were also evident following Trastuzumab only administrations

Table 2 The prevalence of non-GIT related toxicities following single agent Trastuzumab administration

Non-GIT toxicity	Number (%)
Lung symptoms	11 (2.3)
Fatigue	10 (2)
Headaches	2 (1)
Muscular aches	2 (1)
Fever	2 (1)
Joint pain	4 (0.8)
Skin	4 (0.8)
Visual	2 (0.8)

administrations. Toxicity was observed following 52% of these administrations (data not shown). The GIT toxicities following combination treatments were similar to those induced by single agent Trastuzumab, with the additional toxicity of stomatitis. Furthermore, febrile neutropaenia, genitourinary symptoms and neurological complications were also recorded in patients receiving chemotherapy concurrently with Trastuzumab.

Characteristics predisposing patients to Trastuzumab-induced toxicity

Our study identified two patient characteristics that increased the vulnerability of patients to single agent Trastuzumab-induced toxicity. Patients under 60 years experienced toxicities following a significantly lower percentage of Trastuzumab administrations in comparison to those above 60 years (18.46% vs. 34.58%, p=0.031; Fig. 3a). Moreover, patients with metastatic disease experienced toxicity following a significantly larger percentage of administrations in comparison to early stage cancer patients (38.18% vs. 15.68%, p=0.016; Fig. 3b). There was no evidence of an interaction effect (p=0.854).

Discussion

The current study investigated the toxicities associated with Trastuzumab administration, either as a single agent or in combination with conventional anti-cancer therapy. Key findings from this study indicated that a substantial portion of single agent Trastuzumab administrations resulted in gastrointestinal toxicities including nausea and vomiting, abdominal pain and diarrhoea. Furthermore, Trastuzumab induced non-GIT related toxicities including lung symptoms and fatigue. We have also shown that age and disease status are significant predictive risk factors for adverse events during Trastuzumab treatment.

Targeted therapies are an evolving class of anti-cancer drugs. Considerable research efforts have gone into exploring their mechanism of action while little research has focused on their side effects, even though these can significantly reduce patient quality of life (QoL) and may also be dose limiting [2, 17]. Past studies have reported that diarrhoea is the most common gastrointestinal toxicity associated with HER2 receptor blockade by targeted therapy drugs including Trastuzumab and Lapatinib [18, 23]. This is contradictory to the findings of the current study which indicated that nausea and vomiting are the most prevalent. These conflicting findings may be due to differences in patient characteristics of the current study including age and disease status. Moreover, it is believed that toxicities associated with Trastuzumab treatment were under reported in patient case notes.

In the current study, the incidence of nausea and vomiting following single agent trastuzumab was 7.1% of administrations. According to the Multinational Association for Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) antiemetic guidelines, which divide cancer drugs into four classes according to likely incidence of vomiting, Trastuzumab is categorised as low

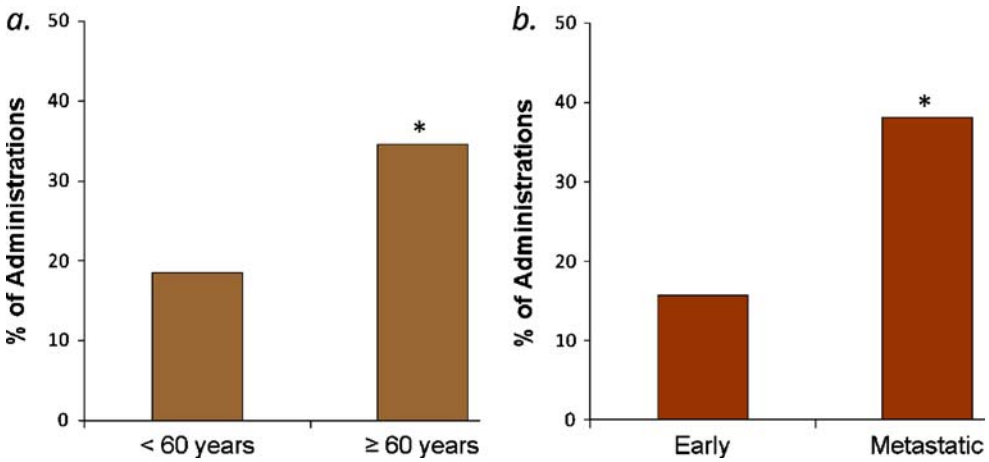

Fig. 3 Variables that tended to increase susceptibility of patients to Trastuzumab-induced toxicity. The frequency of toxicity as a function of **a** age or **b** degree of disease progression. There is statistically significant increase (*asterisk*) in the percentage of administrations that resulted in toxicity in elderly patients and those with metastatic disease

risk of emesis [24, 25]. Although there is little clinical trial evidence for recommendations of low or minimal risk classes, both guidelines suggest a prophylactic single agent antiemetic such as low dose dexamethasone. In contrast, and more consistent with the findings of the current study, the National Comprehensive Cancer Network (NCCN) guidelines classify trastuzumab as minimal risk (<10%) which does not require antiemetic prophylaxis [26]. In the case vomiting does occur on subsequent cycles of trastuzumab, antiemetics are advised.

Although Trastuzumab has been shown to cause gastrointestinal toxicities in patients, the mechanisms underlying these toxicities require further investigation. Interaction of Trastuzumab with HER2 receptors on normal cells has been proposed as a potential mechanism [2]. Furthermore, previous studies have demonstrated the expression of HER2 receptors in many structures which are vital for the proper function of the GIT [27]. Epithelial cells as well as enteric nervous system (ENS) neurons have been shown to express HER2 receptors [28]. Furthermore, a study by Crone and colleagues [28] has demonstrated that HER2 activation is vital for the production of survival factors required for the postnatal maintenance of the ENS. Therefore, future research should focus on characterising changes in gastrointestinal histology and functionality following Trastuzumab in order to gain a broader understanding of the mechanism underlying these toxicities.

This study was primarily concerned with the toxicities that arise following Trastuzumab when used as a single agent. However, the use of Trastuzumab in combination with cytotoxic chemotherapy is becoming progressively more popular in treating HER2-overexpressing cancers [8, 9, 14]. The rationale behind combining targeted therapy drugs and chemotherapy stems from research which suggests Trastuzumab, when used in combination with chemotherapy, predisposes tumour cells to damage thus enhancing the cytotoxic effect of the treatment [29]. It is therefore expected that the unwanted toxicities arising from such treatment regimen are much more frequent and severe. This study provides strong evidence that targeted therapies induce toxicity independently and may therefore enhance chemotherapy-induced toxicity. Hence, it is imperative to thoroughly assess the level of toxicity that patients would experience if Trastuzumab and cytotoxic chemotherapy are given concurrently.

Two patient characteristics were identified as being predisposing risk factors to Trastuzumab-induced toxicity. These included older age and advanced disease progression. It is well known that many physiological changes occur with aging, including decreased renal and liver function and the development of a range of comorbid conditions. Age related changes could influence drug absorption, distribution, metabolism and excretion and may therefore increase the incidence and severity of cancer therapy-induced toxicity [30]. Furthermore, it has been suggested that elderly patients and those with advanced cancers are particularly vulnerable to cancer therapy-induced toxicity as a consequence of decreased immune system activity [31–33]. It has been well documented that there is an age- and cancer-related diminishing of bone marrow reserves and bone density which can make elderly patients and those with advanced disease the most susceptible to Trastuzumab-induced toxicity [31–33].

Trastuzumab as a single agent has the potential to induce a range of gastrointestinal toxicities in patients with HER2-overexpressing breast cancer. Furthermore, these toxicities are specific and separate to those caused by concurrent conventional anti-cancer treatment. Age and disease status of patients were identified as risk factors that increase vulnerability of patients to Trastuzumab-induced toxicity.

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