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New Drugs

# ErbB small molecule tyrosine kinase inhibitor (TKI) induced diarrhoea: Chloride secretion as a mechanistic hypothesis

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ABSTRACT

Diarrhoea is a common, debilitating and potentially life threatening toxicity of many cancer therapies. While the mechanisms of diarrhoea induced by traditional chemotherapy have been the focus of much research, the mechanism(s) of diarrhoea induced by small molecule ErbB TKI, have received relatively little attention. Given the increasing use of small molecule ErbB TKIs, identifying this mechanism is key to optimal cancer care. This paper critically reviews the literature and forms a hypothesis that diarrhoea induced by small molecule ErbB TKIs is driven by intestinal chloride secretion based on the negative regulation of chloride secretion by ErbB receptors being disrupted by tyrosine kinase inhibition.


## Introduction

In clinical oncology practice diarrhoea is a very common and severe side effect of cancer treatments including radiotherapy, chemotherapy, and targeted therapies [1]. Diarrhoea occurs in between 50% and 100% of patients depending on their treatment regimen [2,3]. It is a debilitating and potentially life threatening toxicity as fluid and electrolyte loss associated with persistent and/or severe diarrhoea can result in electrolyte imbalances, renal insufficiency, malnutrition, and extreme dehydration, all of which can lead to cardiovascular compromise and death [4]. Furthermore, these often necessitate dose reductions and treatment breaks, compromising clinical outcomes [5,6]. The need for prevention of cancer therapy-induced diarrhoea is critical. Identification of the pathogenesis may lead to a more accurate management to help reduce severe complications that may be irreversible [7,8].

Cancer therapy-induced diarrhoea is also associated with considerable economic costs with recent reports suggesting that additional costs of up to $25,000 (USD) per chemotherapy cycle are incurred [9]. These costs are attributed to patients with cancer therapy-induced diarrhoea having an increased risk of infection, increased hospital stays and increased resource utilisation for supportive care measures [10,11]. Consequently, prevention, minimisation, and/or prediction of cancer therapy-induced diarrhoea may significantly reduce health system costs over the total course of cancer treatment.

Small molecule ErbB receptor tyrosine kinase inhibitors (TKIs) are used for the treatment of a variety of cancers that overexpress ErbB receptors. These cancers include but are not limited to breast, non-small cell lung cancer (NSCLC) and head and neck cancers. Small molecule ErbB TKIs act by competitively binding to the intracellular ATP domain of the tyrosine kinase, effectively inhibiting phosphorylation of the receptor and therefore downstream signalling [12,13]. To date, the mechanism(s) of action of ErbB TKI-induced diarrhoea has yet to be elucidated. This is in contrast to diarrhoea induced by traditional chemotherapy agents including fluropyrimidines, topotecans, platinum analogues, folate inhibitors and taxanes [2]. Recent research has suggested that chemotherapy-induced diarrhoea is a result of severe intestinal damage caused by mucositis. Mucositis is a multi-factorial process whereby acute damage to the intestinal mucosa (including, increased apoptosis, villus atrophy, crypt hypoplasia and dilation, loss of epithelium, excessive mucous secretion, necrosis and inflammation) causes an imbalance between absorption and secretion, ultimately resulting in an anatomic derangement diarrhoea phenotype [2,14,15]. Numerous preclinical and clinical studies have documented the pathobiology of chemotherapy-induced diarrhoea and have reported that it is largely based on indirect biological signalling, rather than direct tissue damage [16–21]. The mechanisms of chemotherapy-induced diarrhoea are becoming

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better characterised, this is not the case for TKI-induced diarrhoea; this critical review will outline potential mechanisms of ErbB receptor TKI-induced diarrhoea.

## ErbB receptors

Many tumours including but not limited to breast, NSCLC, squamous cell cancers of the head and neck, have been identified as overexpressing ErbB receptors. This has meant that many targeted therapies have been developed to act on the ErbB family of receptors [22]. The ErbB family (interchangeably known as HER/EGFR), is comprised of four membrane receptor tyrosine kinases: ErbB1 (HER1 or EGFR), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4) [23]. The activity of the ErbB receptors is dictated by the expression of their ligands [24], which can be classified into three groups: Group (1) those binding specifically to ErbB1; Group (2) ligands which exhibit dual specificity binding to both ErbB1 and ErbB4; and Group (3) neuregulins, which can be further sub-classified based upon their ability to bind only ErbB4 or both ErbB3 and ErbB4 (Table 1) [25]. To date, no ligand has been identified as being specific for ErbB2, although this receptor does form heterodimers with the other ErbB receptors.

When ligands bind to the extracellular domain of the ErbB receptors, receptor dimerisation and phosphorylation of intracellular tyrosine kinase domains occur. This leads to activation of a cascade of signalling pathways including the mitogen activated protein kinases/extracellular signal regulated kinases (MAPK/ERK), and phosphatidylinositol-3′-kinase (PI3K/Akt) pathways [26]. Once activated, these pathways lead to changes in both protein functions and activation of gene transcription [26–28], leading to interactions with apoptotic signalling, cell proliferation, differentiation, migration and survival. These can all promote tumourigenesis [27,29].

In addition to being expressed on cancer cells, ErbB receptors are also found on healthy cells throughout the body, of specific interest to this review are the receptors expressed in the gastrointestinal tract. Specifically, they are abundantly expressed on the basolateral membranes of healthy intestinal epithelial cells and are crucial for essential normal functions and development in the gut [30,31]. For example, ErbB receptors activated on intestinal epithelial cells cause a cascade of complex signalling pathways resulting in maintenance of mucosal integrity via induction of mucus and prostaglandin synthesis, promotion of enterocyte migration, prevention of intestinal epithelial cell apoptosis, decreasing bacterial translocation and preservation of gut barrier function after injury [32,33].

The first anti-cancer agents targeting ErbB receptors were developed in the 1980s. This led to the development of the first generation of two overarching subtypes of ErbB receptor inhibitors: monoclonal antibodies, and small molecule tyrosine kinase inhibitors [34–37]. Monoclonal antibodies are directed against the extracellular domain of ErbB receptors, whereas small molecule TKIs act directly on cytoplasmic domains of ErbB TKI activity. The overexpression of ErbB receptors in many solid tumours is correlated with advanced stages and often a worse prognosis of the cancer [38]. In many different cancer cell types, the ErbB pathway becomes hyper-activated by a range of mechanisms, including overproduction of ligands, overproduction of receptors, or constitutive activation of receptors [31]. This hyper-activity and hence key role of the ErbB network has made it an attractive target for therapies. After an initial response however, patients being treated with first generation ErbB TKIs often develop secondary mutations such as T790M, MET or HER2 amplifications, resulting in acquired resistance [39]. Ultimately, this limits the effectiveness of these first generation agents over time. Pan-ErbB TKIs are now considered second-generation and are resistant to acquired mutations. As a result, these TKIs are now commonly used. However, they are associated with clinical toxicities and which are important to recognise and manage.

**Table 1**
ErbB receptors and their ligands.

| Receptor | Ligands |
|---|---|
| ErbB1 | EGF, Areg, TGFα |
| ErbB1 and ErbB4 | Btc, HBEGF and Ereg |
| ErbB3 and ErbB4 | Nrg1 and Nrg2 |
| ErbB4 | Nrg3 and Nrg4 |

EGF: Epidermal Growth Factor; Areg: Amphiregulin; TGF: transforming growth factor; Btc: Betacellulin; HBEGF: Heparin-binding EGF-like growth factor; Ereg: Epiregulin; Nrg: Neuregulins.

## ErbB TKIs and diarrhoea

Toxicities are common in patients receiving first generation ErbB TKIs, including but not limited to erlotinib, gefitinib, and lapatinib. In particular, up to 69% of patients experience diarrhoea [12]. Large randomised trials have shown that erlotinib and lapatinib induce diarrhoea in 40–60% of patients, with approximately 10% of these presenting with grade 3–4 symptoms (National Cancer Institute Common Toxicity Criteria) [40,41]. One of the most frequent toxicity associated with second-generation pan-ErbB TKIs is also diarrhoea. Recent clinical data suggests that all grades of diarrhoea are more frequently seen with pan-ErbB TKIs than first generation ErbB TKIs (e.g. dacomitinib vs. erolitinib). Up to 96% of patients receiving second generation pan-ErbB TKI's develop diarrhoea, and perhaps more importantly, the incidence of grade 3 (severe) diarrhoea is significantly higher [42]. Further exacerbating this diarrhoea is that many TKIs are given daily for months at a time, and side effects are therefore often chronic, unlike the acute manifestations typically seen following traditional chemotherapy regimens.

## Do ErbB TKIs induce diarrhoea via a distinctly different mechanism than chemotherapy-induced diarrhoea?

One common hypothesis for the mechanism of action of diarrhoea following TKI treatment is thought to be due to inhibition of ErbB signalling within intestinal epithelia, leading to direct mucosal atrophy and damage [43–45]. Research suggested that this diarrhoea was associated with reduced growth, characterised by reduced growth and healing of the intestinal epithelium leading to mucosal atrophy due to the stimulatory effect of ErbB pathway on enterocyte proliferation [46], nutrient and electrolyte transport [47], brush border enzyme expression [48] and epithelial restitution being impeded [49]. Increased frequency of diarrhoea in patients using oral compounds (e.g. small molecule TKI's) compared to monoclonal antibodies supports this theory. This direct mucosal damage hypothesis mimics chemotherapy-induced diarrhoea, bought about by the manifestation of mucositis (Fig. 1).

A more recent hypothesis suggests that despite a similar clinical manifestation as is seen in traditional chemotherapy induced diarrhoea, ErbB TKI-induced diarrhoea is due to a distinctly different pathological mechanism [22,50]. This followed the recent development of a preclinical model to study the gastrointestinal toxicity associated with ErbB inhibitors [51]. Using lapatinib, an oral small molecule ErbB1 and ErbB2 TKI for 7–28 days, this large ($n = 128$) study showed no significant pathology in the intestines of rats, despite rats displaying a dose-dependent diarrhoea profile consistent with that observed clinically [51]. No significant changes were noted in intestinal weights and no significant histopathology was