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# Targeted therapy-induced diarrhea: A review of the literature

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**Abstract**

*Purpose of research:* Revision of the literature on targeted therapy-induced diarrhea (TT-ID).
*Principal results:* TT-ID is frequent; the mechanisms are mainly secretive, followed by ischemic or autoimmune ones. The duration of TT-ID is protracted over time. Its intensity is of grade G1–G3 but may be fatal in patients with diffuse colitis or on ipilimumab. However, no specific guidelines are available on management of different grades of TT-ID. Preventive measures with antibiotics, probiotics or activated charcoal should be further investigated. Loperamide is the first choice drug followed by octreotide. The role of corticosteroids is controversial.
*Conclusion:* Early assessment and management of TT-ID is essential to prevent the worsening of this side-effect, patients' hospitalization and dose reduction or oncological treatment discontinuation. Future research is needed to better understand the pathophysiological mechanisms of TT-ID and it should also be investigated whether a specific pharmacological and/or non pharmachological approach is indicated.


*Keywords:* Targeted therapy; Diarrhea; Incidence; Assessment; Treatment

## 1. Introduction

Diarrhea is a common and serious side-effect associated with radiation therapy to the abdomen and with a variety of chemotherapy (CT) agents, in particular fluoropyrimidines and irinotecan. It may have a negative impact on the patients' health as well as on their quality of life (QoL), causing dehydration, renal insufficiency, electrolyte imbalance, metabolic acidosis, malnutrition, fatigue, sleep disturbance; in some rare cases it can even be life-threatening. Furthermore diarrhea can alter treatment schedules, leading to dose reduction and treatment discontinuation [1–3]. Despite the availability of recommendations and guidelines for the treatment of CT-induced diarrhea, there are still few data reported by patients on targeted-therapy. Results of toxicity profiles obtained from clinical trials show that diarrhea is frequent, of mild-moderate grade and protracted over time in a large number of patients.

This paper aims to review the available evidence on: (1) the incidence and intensity of diarrhea induced by targeted agents, (2) the possible pathophysiological mechanisms and (3) the prophylactic and therapeutic measures to prevent and reduce its severity and its duration.

### 1.1. Type of research

PubMed, Cancer-Lit, Embase databases and Cochrane Library were searched for Randomized Controlled Trials in March 2013. Search terms were "Diarrhea" [Substance Name] and "Target Therapy" [Substance Name]. The proceedings from 2008 to 2013 conferences of the American Society of Clinical Oncology, European Society of Medical Oncology and International Society for the Study of Lung Cancer World Conference were also searched for relevant abstracts through EMBASE. Authors of primary studies were not contacted to identify additional studies. No language or date limits were applied.

## 2. Diarrhea: definition, pathophysiology, assessment

Diarrhea is generally defined as the frequent passage of loose stools with urgency, commonly more than three unformed stools in 24 h [4]. Although a practical definition is lacking, diarrhea is commonly diagnosed when an abnormal increase in daily stool weight [5], water content more than 75%, and frequency, whether or not accompanied by urgency, perianal discomfort, or incontinence, is present as a consequence of incomplete absorption of electrolytes and water from luminal content [6,7]. Normally an average solid stool of 50–200 g/day passes through the colon; it is formed by bacteria, non-absorbed carbohydrates, water, electrolytes and short chain fatty acids. Diarrhea is classified according to the duration: acute if <2 weeks, persistent if 2–4 weeks, and chronic if >4 weeks. Stool consistency probably best defines diarrhea, but it cannot be easily measured [8].

The specific different pathophysiological mechanisms of diarrhea induced by targeted therapy have not been adequately investigated up to now. The different classes of biological agents, but also a single agent in a specific class may cause diarrhea through different mechanisms which are distinguished in:

(1). Secretive (i.e. most of the Anti EGFR agents) [9,10],
(2). Direct Ischemic mucosal damage (i.e. sorafenib) [11] and
(3). Immuno-related (i.e. ipilimumab) [12,13].

Table 1 shows the assessment of the patient: physical examination, subjective report, pain related to frequent evacuation, vital signs, grading, laboratory tests and imaging studies.

The most commonly used method for assessing the severity of diarrhea is the National Cancer Institute Common Toxicity Criteria (NCI CTC). The last version includes 5 grades where 5 corresponds to death [14]. Even though the NCI CTC is a helpful tool, clinicians need to be rigorous in the assessment of every sign and symptom presented by the patient: they have to assess the frequency of stools evacuation, the stool composition and the presence of coexisting systemic signs and symptoms, such as fever, neutropenia, abdominal pain/cramping, nausea and vomiting, weakness, dizziness, hydration status, malnutrition and Performance Status deterioration. Complicated patients are described as having grade 3–4 diarrhea or lower grade diarrhea with multiple other symptoms, while uncomplicated patients are those

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