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ORIGINAL ARTICLE

Reasons for chemotherapy discontinuation and end-of-life in patients with gastrointestinal cancer: A multicenter prospective AGEO study



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KEYWORDS

Death;
Gastrointestinal
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Terminal Care

Summary

Background: Previous research on chemotherapy discontinuation has mainly focused on predictive factors and outcomes. Few data are available on the reasons for chemotherapy discontinuation. The main objective was to identify the reasons for chemotherapy discontinuation in patients with gastrointestinal cancer. The secondary objectives were to describe the announcement of chemotherapy discontinuation and the time between chemotherapy discontinuation and death.

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Methods: This prospective multicenter French cohort included patients with advanced gastrointestinal cancer, for whom chemotherapy was discontinued between May 2016 and January 2018.

Results: One hundred and fourteen patients were analyzed. The first cause of chemotherapy discontinuation was the impairment of general condition (asthenia, cachexia). Complications such as sepsis, jaundice or occlusion, were the second most frequent cause. Progression was observed at chemotherapy discontinuation in two-thirds of cases. The announcement of the chemotherapy discontinuation was made formally in 74% of cases, with a follow-up by a palliative care team initiated in 50% of cases. Sixty-nine percent of the patients received chemotherapy during the last three months of life and 26% during the last month. The median time between chemotherapy discontinuation and death was 65 days (IQR: 36.5-109); 44% of patients died at the hospital, 39% in a palliative care unit and 16% at home.

Conclusion: Impairment of general condition was the major reason for chemotherapy discontinuation in patients with gastrointestinal cancers. Complications such as jaundice, sepsis or occlusion, were important reasons for discontinuation and could explain our shorter time between chemotherapy discontinuation and death, compared to other oncology sub-specialties.

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Introduction

Discontinuing palliative chemotherapy at an appropriate time is an important issue of end-of-life care. It has been shown that the aggressiveness of care during the final weeks before death can harm the quality of life [1]. Late discontinuation of chemotherapy is also associated with a shorter survival time from first palliative chemotherapy treatment to death, with more hospitalizations and fewer deaths at home but more in intensive care units [2–4]. Therefore, in 2012, the American Association of Clinical Oncology recommended that cancer-directed therapy should be avoided for patients with advanced cancer and an altered performance status [5].

However, the aggressiveness of cancer treatment near the end-of-life has been rapidly increasing over time [6–10]. It may be assessed by the number of admissions in emergency room, medicine, and intensive care unit, but also by the short time between palliative care admission and death [11]. Another way of evaluating the aggressiveness of cancer treatment is to assess the percentage of patients receiving chemotherapy in the last month before death, evaluated around 20%, with variations according to the country and to the cancer type [3,12–15].

Discontinuing palliative chemotherapy remains a very complex decision. Physicians and patients tend to overestimate the probability that anticancer therapies will provide a clinically meaningful benefit [16,17]. This may be due to strong emotional bonding, to an underestimation of the harmful consequences or even to an overestimation of the patient's condition during the doctor visit [14]. Physicians and patients may also be pressured by families to continue therapies of doubtful efficacy [18]. Predictors impacting chemotherapy discontinuation have been studied and seem to be related to the patient's condition (age, comorbidities, ECOG, education level), the disease (localization, chemosensitivity, number of previous lines), the prescribers and to the health care (tertiary hospitals and for-profit facilities have more aggressive cancer care near the end of life) [12,19–21]. Patients having an end-of-life discussion with

their physicians are also less likely to receive aggressive care [6].

Previous research on chemotherapy administration or discontinuation at end-of-life has therefore primarily focused on predictive factors and outcomes. Although these studies have answered important questions, few have analyzed why physicians discontinue chemotherapy in clinical practice. Identifying the main reasons for chemotherapy discontinuation might explain why the chemotherapy is sometimes discontinued a short time before death and could help to predict the clinical deterioration leading to death. Complications such as jaundice, occlusion or sepsis may lead to a rapid death – whereas asthenia or severe comorbidities may lead to an earlier chemotherapy discontinuation. Considering the rate of chemotherapy in the last month of patients' life in an oncology department could have a positive impact on physicians' own point of view, by questioning their personal practice. Digestive oncology is marked by complications, such as occlusion or jaundice that may force the chemotherapy discontinuation, and is therefore particularly interesting to study.

The primary objective of this prospective study was to identify the reasons for chemotherapy discontinuation in patients with gastrointestinal cancer. The secondary objectives were to describe the announcement of chemotherapy discontinuation and the time between chemotherapy discontinuation and death, with potential hospitalizations and the place of death.

Methods

Overview

This prospective multicenter non-interventional study was a questionnaire based on professional practices, between May 2016 and January 2018, by 15 physicians willing to participate, from 6 French care centers (5 university hospitals and 1 general hospital) from the *Association des gastro-entérologues oncologues* (AGEO).

Patients

All consecutive patients with gastrointestinal cancer (pancreatic cancer, colorectal cancer, esophageal cancer, gastric cancer, cholangiocarcinoma, pancreatic and small bowel neuroendocrine carcinoma, anal cancer), for which the prescriber decided to discontinue chemotherapy, were included. Physicians could eventually restart chemotherapy after discontinuation, but patients with planned therapeutic breaks were excluded. Patients with hepatocellular carcinoma or with a well-differentiated neuroendocrine neoplasm were excluded.

Ethics

Ethics committee approval was waived for this study on the evaluation of professional practices. The study was conducted in agreement with the appropriate ethical guidelines and legislation.

Follow-up

Questionnaires were mailed to the physicians participating. First, they responded to an initial questionnaire when they decided to discontinue the chemotherapy. Then, they had to fill intermediate questionnaires every two weeks on the patients' evolution (hospitalizations, palliative care), until the patient's death.

List of reasons for discontinuing chemotherapy

The primary objective was to identify the reasons for chemotherapy discontinuation in patients with gastrointestinal cancer. A list of reasons for discontinuing chemotherapy was proposed to the physicians. This list included the following reasons: no other therapeutic line available, inclusion in a phase I study, chemotherapy's toxicity, life expectancy of less than 3 months, sepsis, jaundice, occlusion, asthenia, patient's will, family's will, intercurrent disease, comorbidities, psycho-social fragilities. Physicians had to select one or several above-mentioned reasons explaining why they discontinued chemotherapy. They also had to rank the reasons from the most important to the least important one, according to them. The list of reasons was first established by the authors that designed the study and then submitted to the AGEO participating members, for further modifications and validation.

Other outcomes

The secondary outcomes were the analysis of the modalities of the announcement of chemotherapy discontinuation and the end-of-life period.

The announcement of the discontinuation was evaluated by the presence or not of a formal announcement, the place of the announcement, the time between the last chemotherapy and the announcement. We also inquired the presence of a palliative care team and of a multidisciplinary meeting on the palliative decision.

The end-of-life period was evaluated by the emergency department visits, the number of hospitalizations in medicine or in an intensive care unit. All consecutive hospitalizations had to be recorded. We also analyzed the number of patients receiving chemotherapy in the three months or in the last month prior to death and the place of death. Physicians' experience was considered as the number of years of practice in digestive oncology.

Statistics

Median and Inter Quartile Range (IQR), mean and standard deviation (SD) were used to describe continuous variables and frequencies and percentages were used to describe categorical variables. The association between the mean time between discontinuation of chemotherapy and death and the prescriber's experience was tested using student test. The cut-off date for the final data analysis was February 15th, 2018. Statistical analyses were computed with R software, with statistical significance set at P -value < 0.05 .

Results

Fifteen prescribers participated in the study, including 114 patients.

Patients and disease's characteristics

Thirty-three point three percent of patients had a colorectal cancer ($n=38/114$), 29.8% a pancreatic cancer ($n=34/114$), 15.8% a gastric cancer ($n=18/114$), 12.3% a cholangiocarcinoma ($n=14/114$), 5.3% an esophageal cancer ($n=6/114$), 1.8% a poorly differentiated neuroendocrine carcinoma ($n=2/114$) and 0.9% an anal cancer ($n=1/114$). They had a mean of 1.9 (± 1.7) metastatic sites. Forty-three percent ($n=40/93$) had a well-differentiated tumor, 35.5% ($n=33/93$) had a moderately-differentiated tumor and 21.5% ($n=20/93$) had a poorly-differentiated tumor. Patients received a mean of 3 lines of chemotherapy (± 2).

The mean age was 67 years (± 10.4), with 53% of men. Forty-three percent of patients received a postgraduate education ($n=49/114$). They were married in 76.3% of cases ($n=87/114$), and 3.5% had a child between 1 and 5 years old ($n=4/114$). For 92.1% ($n=105/114$) of them, their family was present. At inclusion, 76% of patients had an ECOG performance status of 3 or 4.

Physicians

The physicians participating in the study were 5 women and 10 men, from 6 hospitals: 5 university hospitals and 1 general hospital. They were all gastroenterologists. The median age was 36 years old (IQR: 30.5–40.5), with a median number of years of 7-year practice (IQR: 3–11).

Reasons for chemotherapy discontinuation

The first cause of chemotherapy discontinuation was impairment of general condition (asthenia, cachexia) in 38.5% of

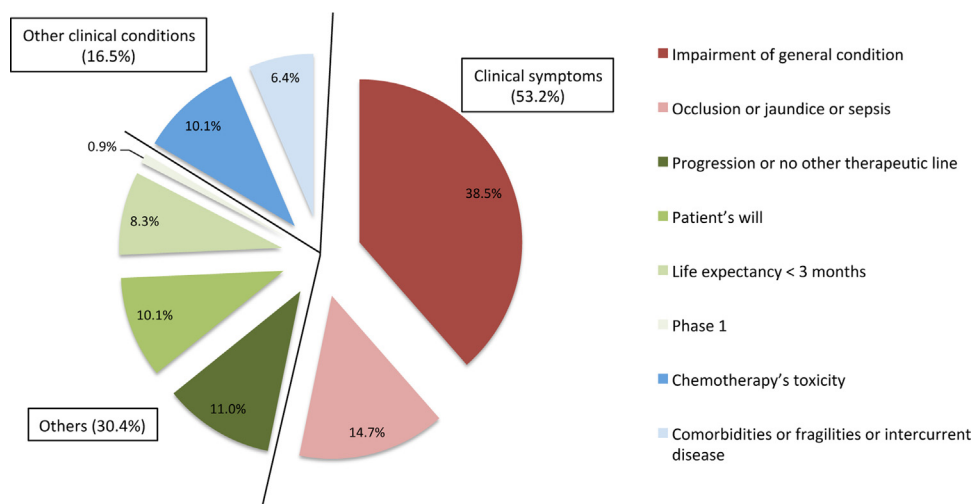


Figure 1 First reasons for chemotherapy discontinuation, according to the physician (on 109 patients).

cases ($n=42/109$). The second cause of chemotherapy discontinuation was complications such as sepsis, jaundice or occlusion (14.7%, $n=16/109$). In 10.1% of cases ($n=11/109$), the first reason for chemotherapy discontinuation was the patient's will. In 10.1% of cases ($n=11/109$), the first reason for chemotherapy discontinuation was chemotherapy toxicity (Fig. 1).

Thirty-six percent ($n=41$) of patients were not considered in progression by the physician at the time of chemotherapy discontinuation. Among those patients, the first reason evoked for chemotherapy discontinuation was still an impairment of general condition in 48.7% of cases ($n=19/41$). The second most important reason for chemotherapy discontinuation was patient's will (20.5%, $n=8/41$) and the third was chemotherapy toxicity (12.8%, $n=5/41$) (Fig. 2).

Announcement of chemotherapy discontinuation

The announcement of the discontinuation of chemotherapy was made formally in 74.1% of cases ($n=83/112$) (Table 1). It was made in consultation in 33.9% ($n=38/112$) of cases, in hospitalization in 60.7% ($n=68/112$) of cases. The mean and the median time between the last chemotherapy and the announcement were respectively 41.6 days (± 63.3) and 19 days (IQR: 11-43).

A palliative care team was present in 68.4% of cases ($n=39/57$), with a follow-up initiated in 50% of cases ($n=28/56$). A multidisciplinary meeting on the palliative decision was made in only 15.8% of cases ($n=9/57$).

Time between chemotherapy discontinuation and death

Four percent of the patients ($n=5/113$) restarted chemotherapy (Table 2).

Twenty-two point three percent of the patients ($n=25/112$) visited at least once the emergency department after chemotherapy discontinuation. Fifty-six point six percent ($n=64/113$) of the patients were hospitalized at

least once in medicine and 4.4% ($n=5/113$) at least three times after chemotherapy discontinuation. Fifty percent ($n=57/114$) of the patients were hospitalized in medicine in the 30 days preceding death. One point eight percent of the patients ($n=2/114$) were hospitalized in an intensive care unit after chemotherapy discontinuation. Thirty-five percent of the patients did not visit the emergency room nor were hospitalized since the chemotherapy discontinuation. Patients who were hospitalized or visited the emergency room had median survivals since chemotherapy discontinuation of 76 days (IQR: 38.8–118) versus 66.5 days (IQR: 38.8–124.6) for patients who were never hospitalized nor visited the emergency room.

Sixty-nine point three percent of the patients received chemotherapy in the three months prior to death ($n=79/114$) and 26.3% in the month prior to death ($n=30/114$). The mean and median time between chemotherapy discontinuation and death were 93 days (± 97) and 65 days (IQR: 36.5-109), respectively. In case of chemotherapy discontinuation in progressing diseases, the median time between chemotherapy discontinuation and death was 70.5 days (IQR: 41.3–111.3) whereas in case of chemotherapy discontinuation without progression, the median time between chemotherapy discontinuation and death was 53 days (IQR: 29–96).

There was no link between the time between discontinuation of chemotherapy and death and the prescriber's experience ($P=0.71$). The time between the discontinuation of chemotherapy and death was quite homogeneous between prescribers (Fig. 3).

One hundred and seven patients died: 44% at the hospital ($n=47/107$), 39% ($n=42/107$) in a palliative care unit and 16% ($n=17/107$) at home. Patients remained in the palliative care unit for a median of 12 days (IQR: 8-24), 7% ($n=3/42$) of patients spending ≤ 3 days in the palliative care unit.

Discussion

To our knowledge, this cohort is the first to study the causes of chemotherapy discontinuation in patients with

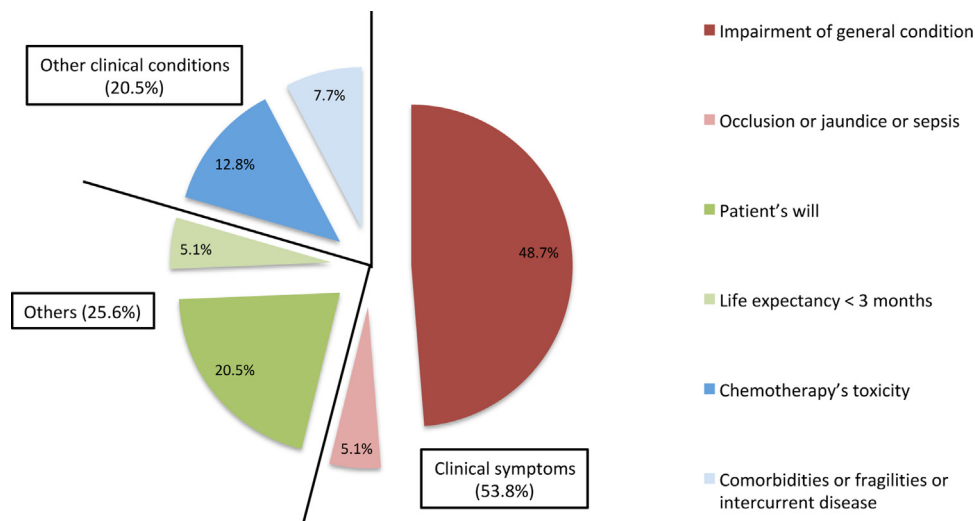


Figure 2 First reasons for chemotherapy discontinuation, according to the physician, when no progression was observed (on 41 patients).

Table 1 Announcement of chemotherapy discontinuation.

Formal announce of chemotherapy discontinuation	74.1% (n = 83/112)
Announce in consultation	33.9% (n = 38/112)
Announce in hospitalization	60.7% (n = 68/112)
Mean time between last chemotherapy and announce (days)	41.6 ± 63.3

Table 2 End-of-life quality.

Restart of the chemotherapy	4.4% (n = 5/113)
≥ 1 visit to the emergency department	22.3% (n = 25/112)
≥ 1 hospitalization in medicine	56.6% (n = 64/113)
≥ 1 hospitalization in reanimation	1.77% (n = 2/113)
Chemotherapy in the last 3 months preceding death	69.3% (n = 79/114)
Chemotherapy in the last month preceding death	26.3% (n = 30/114)
Death at the hospital	43.9% (n = 47/107)
Death in a palliative care unit	39.3% (n = 42/107)
Death at home	15.9% (n = 17/107)

gastrointestinal cancer. The impairment of general condition was the main cause of chemotherapy discontinuation, with or without progression. Complications such as jaundice or occlusion were the second most frequent cause of discontinuation in case of progression. These complications can have an unpredictable and rapid unfavorable outcome. In more than one-third of cases, chemotherapy was discontinued because the physician or patient felt that the patient's general condition was too deteriorated. This underlines that chemotherapy by itself can alter general condition and that disease control is not the ultimate goal for advanced diseases.

A formal announcement of chemotherapy discontinuation was only made in 74.1% of cases, without any particularity in the disease or in the patient's history identified. Half of the patients had no follow-up by the palliative care team initiated when the chemotherapy was discontinued. In a recent

retrospective cohort on patients with lung cancer, almost one-third of the patients had no palliative care reported. [22] Early palliative care leads to less aggressive care near the end of life. [23,24] It could even improve overall survival when associated with standard oncologic care, as shown in lung cancer. [25] Systematic multidisciplinary meetings on chemotherapy discontinuation and palliative care could help limit the aggressiveness near the end-of-life.

Fifty percent of the patients were hospitalized in medicine in the 30 days preceding death. This rate is in the low fork of hospitalization rates in the last 30 days of life in 7 developed countries in 2016, which ranked between 43.2% to 62.6%. [13] Only 1.8% patients were hospitalized in intensive care unit after chemotherapy discontinuation, which is a very low rate compared to other developed countries (average 11%) and testifies of good medical practice [13].

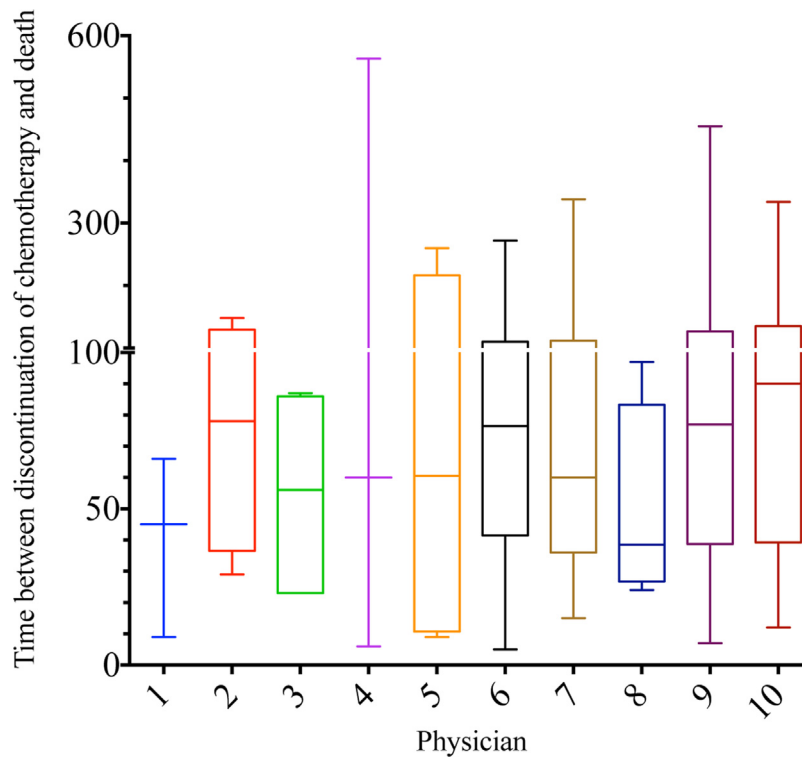


Figure 3 Time between discontinuation of chemotherapy and death for each prescriber (in days).

The time between chemotherapy discontinuation and death in this study is shorter than in the literature on all cancers, demonstrating our inability to anticipate clinical deterioration leading to death. In a French retrospective cohort on patients with cancer between 2010 and 2013, 39.1% of patients received chemotherapy during the last 3 months before death and 19.5% during the last month [12]. Rates of chemotherapy in the last month before death were even lower in other European countries: 16% in Belgium, 13% in Germany, 15% in the Netherlands and 6% in Norway. They also found in the French cohort surprisingly high rates of chemotherapy close to death in patients with metastatic pancreatic cancer or biliary tract cancer. We can hypothesize that it is more difficult to predict the death of these patients, at risk of complications such as jaundice or occlusion, or others complications (pulmonary embolism, gastrointestinal bleeding [26]..). Several prognostic models for patients with advanced cancer exist, such as palliative prognostic score, palliative prognostic index and Glasgow prognostic score [27]. These scores include some clinical data (Karnofsky performance scale, anorexia, dyspnea, oral intake) and some blood results (albumin, C-reactive protein leukocytosis, lymphopenia). However, the performance of these prognostic tools has not been compared. In addition, they may not be as accurate for gastrointestinal oncology, since they do not include data such as bilirubin level, sepsis, portal vein thrombosis or the risk of occlusion or of hemorrhage. One prognostic index was made to predict the clinical outcome for advanced pancreatic cancer, including the ECOG status, the CA 19-9 and CRP levels [28]. In our study, chemotherapy discontinuation practices were mainly based on patient's general condition with a necessity

of stopping chemotherapy rather than on death predictive scores, that might have a lower acceptability for physicians, patients and their family. The few years of practice of our physicians and the predominance of university hospitals in this study may also have had an influence on the short time between chemotherapy discontinuation and death.

Survival since chemotherapy discontinuation was slightly shorter for patients without progression versus patients progressing, even if not significant. We could hypothesize that patients without progression had to stop chemotherapy because of complications that might have accelerated the death.

The rate of death at the hospital of 44% is close to what it is in the developed countries, except from the United States and the Netherlands which have lower rates [13,29]. However, it is much lower than the rate in France in 2008, which was estimated at 72.8% [29]. This diminution of the rate of death at the hospital could be explained by the recent development of home palliative care with local palliative care networks. This study highlighted very short median times at the palliative care unit, compared to other countries. Determining the timing of referral to the palliative care unit is a marker of end-of-life quality care. There are few data on duration of palliative care unit stays, and they vary greatly between countries: the median times range from 12 to 21 days in Korea and US, 53 days in UK [30], to 60-70 days in Canada.

One of the limitations of this study is its number of patients, especially for studying the varying reasons for chemotherapy discontinuation and the differences in prescribers' practice. However, it would not have been possible to analyze chemotherapy discontinuation reasons from

larger patients cohorts such as hospitalizations or insurance data, since the reasons for chemotherapy discontinuation are not available in these data sources. Another limitation may be the lack of diversity among physicians participating in the study: they were mostly young gastroenterologists in university hospitals, probably due to the participation via the AGEO. This makes it difficult to identify a potential impact of the physician practice habits on the decision of chemotherapy discontinuation.

One perspective of this work would be to follow physicians' practices over time, to analyze if they changed their practices after taking notice of the results.

In conclusion, concerning gastrointestinal oncology, impairment of general condition remains a major reason for chemotherapy discontinuation, even in patients with no progression of the disease. Complications such as jaundice, sepsis or occlusion, often observed during the evolution of digestive cancers, are important reasons for discontinuation and could explain our shorter time from chemotherapy discontinuation to death, compared to other oncology subspecialties.

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Disclosure of interest

The authors declare that they have no competing interest.

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