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Decisions about treatment with targeted therapies in a palliative care unit: A case series

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Abstract

Background. Early palliative care integration into the oncologic treatment pattern is recognized and strongly recommended to anticipate end-of-life issues and avoid disproportionate care. Targeted therapies (TTs), with their very rapid onset of action and relatively good tolerance, may have an effect on cancer-related symptoms, which could be beneficial in the context of palliative care.

Methods. Data were extracted from a cohort of all patients hospitalized in an acute palliative care unit between 03.04.2019 and 07.04.2020. Data for all consecutive patients for which a decision on a TT was made during hospitalization were retrospectively analyzed.

Results. Forty-two patients were identified. Thirty-one patients were currently receiving TT on admission. For 19/31 (61.3%) patients, the treatment was discontinued. The remaining 12 patients had TT after discharge from the palliative care unit (continuation of the same TT or modification of the TT during the stay), with an average duration of 208 days and an average of 46 days between the last TT and death. TT was introduced or reintroduced in 7 patients of the 11 patients hospitalized without treatment at admission. In this group, the average duration of treatment was 28 days, with an average of 28 days between the last TT and death. Five of the patients who received re-challenged TT experienced a subjective improvement of their symptom.

Significance of results. TT was discontinued in the majority of our patients. However, in some cases, the treatment was maintained because it was effective on cancer-related symptoms even at the end of life. However, this should not overshadow the palliative process. The continuation or introduction of a specific oncological treatment requires close cooperation between oncologists and palliative care physicians and an honest and clear explanation to patients and their families.

Introduction

Chemotherapy prescribed in the final months of life has been associated with the lower quality of life even in patients with good performance status (Prigerson et al., 2015). Moreover, it interferes with the process of understanding and accepting the incurability of the disease and the coming end of life (Wright et al., 2014). However, about 20% of patients receive chemotherapy in their last month of life (Pacetti et al., 2015; Mathew et al., 2017; Jang et al., 2018; Colombet et al., 2019). With the advent of targeted therapies (TT) over the past decade, the question of the impact of such therapies in the final months of life arises. Some of TT have a particular response profile, with a median time to clinical benefit which can be very short. Clinical benefits on cancer-related symptoms can be maintained even when a tumoral progression is observed. In addition, these treatments sometimes seem effective even in the case of prior progression with the same molecule or family of molecules (Schreuer et al., 2017). The reintroduction of the same type of molecules can be efficient but for a short time. Finally, these treatments have a particular tolerance profile that changes the risk/benefit ratio of using these therapies at the end of life compared to chemotherapy (Gogas et al., 2019). Data on TT at the end of life are still scarce. Rates of patients receiving TT in the last month of life ranged from 3.6% to 49.9% depending on the studies (Soh et al., 2012; Fang et al., 2019). The type of TT and patient characteristics are heterogeneous between studies, and several recent and interesting therapies are not represented. The aim of our study was to report data about the use of TT in an acute palliative care unit located in a comprehensive cancer center and to identify a profile of patients in whom the treatment could be useful.

Methods

Patients

Data from all consecutive patients hospitalized in our acute palliative care unit at the Gustave Roussy Campus Center for which a decision on a TT was made were identified retrospectively from a prospective cohort of patients hospitalized in the unit.

Two types of patients were included:

(1) Patients already treated with TT at admission, and
(2) Patients for whom TT was introduced during hospitalization. Some of these patients had already received TT and the discussion focused on whether or not to repeat treatment with the same molecule or family; and others had never received TT and an initial introduction of TT was discussed. Only oral TTs were selected. Clinical data were collected from medical records using worksheets designed for the current study. The data included information on the history of the disease and management of treatments and symptoms during hospitalization. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistics

Statistical analyses were performed using Excel (Microsoft Excel 2010, Seattle, WA, USA). Continuous and categorical variables are described as means (ranges [minimum to maximum]/interquartile ranges [IQRs]) and frequencies (percentages), respectively.

Ethics

Our database has been approved and registered by our Institutional Review Board according to guidelines for Good Clinical Practice on 4/03/2019.

Results

Population

Between 03.04.2019 and 07.04.2020, 42 patients met the inclusion criteria among the 261 patients hospitalized during the same period. Their characteristics are listed in Table 1. The mean age was 52 years (32–87). Most of the patients had a melanoma (13/42 patients, 31%) or a kidney cancer (11/42, 26%). Most patients had a metastatic disease (39/42, 93%). One third of the patients had a target tumoral mutation (15/42 (36%)), the most represented being BRAF V600E. The others received a TT whose approval was not conditional on a molecular alteration. Patients had received a median of 2 previous treatment lines (0–8). The reason of hospitalization was uncontrolled symptoms in 22 of 42 patients (52%) and altered general condition at home in 13 of the patients (31%). The other seven patients were hospitalized specifically to make a decision on whether or not to continue or introduce TT.

The TTs discussed, for which a decision had to be taken, were VEGFR inhibitors (19/42, 45%) or anti-BRAF + anti-MEK (8/42, 19%). Formal evidence of an onco-palliative meeting (meeting between at least the referring oncologist, a palliative care specialist, and a nurse) was found for 22/42 (52%) of patients.

Decision about the TT

In most cases, the decision was to stop or not to (re)introduce the TT (23/42, 55%). The reason for discontinuing treatment was insufficient efficiency ($N = 11$), altered general state ($N = 6$), or toxicity ($N = 2$). A total of 19 patients received TT upon leaving the unit (45%). The subgroups of patients and the decisions that have been made are illustrated in Figure 1. Considering 31 patients with TT at entrance, 12 patients had TT after discharge

Table 1. Patients' characteristics

Characteristics	No.
Number of patients, *n* (%)	42 (100)
Median age, years (range)	52 (32–87)
Primary site, *n* (%)	
Melanoma	13 (31)
Kidney	11 (26)
Gastric	3 (7)
Breast	2 (5)
Hepatocarcinoma	2 (5)
Others	11 (26)
Median number of prior lines of treatment (range)	2 [0–8]
Targetable mutation, *n* (%)	15 (36)
BRAF V600E	8
Other BRAF	2
HER2	2
Other	3
Metastatic disease, *n* (%)	39 (93)
WHO performance status, *n* (%)	
0–1	0
2	6 (14)
3	21 (50)
4	15 (36)
Renal function (CKD-EPI), *n* (%)	
[0;30]	1 (2)
[31;60]	8 (19)
[61;90]	10 (24)
>90	21 (50)
MD	2 (5)
Liver enzymes, *n* (%)	
Normal	21 (50)
<3N	12 (29)
>3N	9 (21)
Targeted therapy	
Anti-VEGF	19 (45)
Anti-BRAF+/− anti-MEK	8 (19)
Already followed by the palliative care team, *n* (%)	
Yes	19 (45)
No	26 (55)

HER2, Human Epidermal Growth Factor Receptor-2; WHO, World Health Organization; MD, missing data; VEGF, vascular endothelial growth factor; MEK, mitogen-activated protein kinase kinase.

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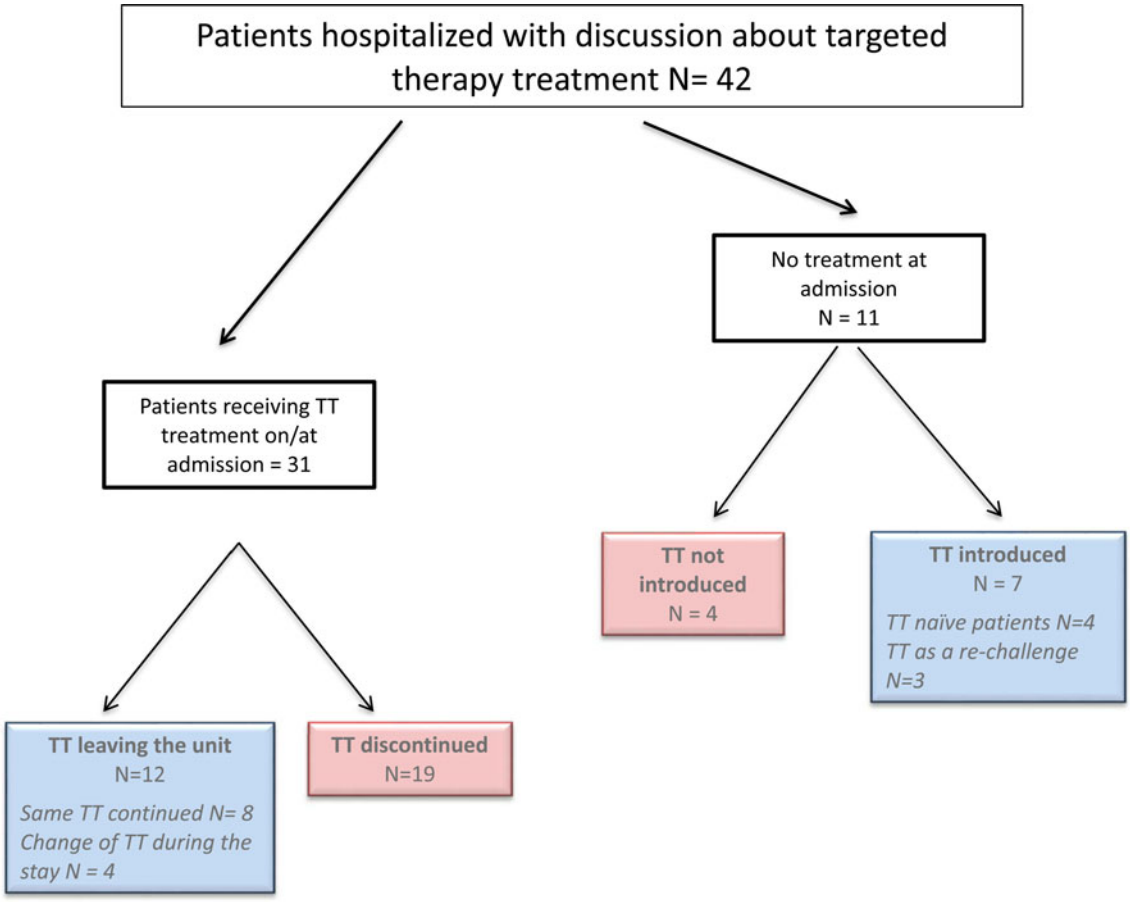

Fig. 1. Distribution of patients included in the study.

from the palliative care unit (continuation of the same TT ($N = 8$) or modification of the TT during the stay ($N = 4$)). On the first reassessment (average time: 35 days), 7 of the 12 patients (58%) had a stable disease or an improvement of cancer-related symptoms. Grade I/II adverse events were observed in 3 out of 12 patients (25%). No grade III/IV adverse event occurred. In this group, the average duration of treatment was 209 days (40–1,170/107 [IQRs]). The average time between the last TT intake and death was 46 days (1–120/48 [IQRs]). Considering 11 patients without a TT at entrance, a TT was introduced in four patients (TT naïve patients), and a previously used TT was reintroduced in three patients. Reasons for starting TT were to control the disease ($N = 4$) or to control a symptom directly related to the cancer ($N = 3$). In these seven patients, at first re-evaluation (average time: 14 days), a stable disease or improvement in cancer symptoms was observed in 3. Grade I/II adverse events were observed in two patients. Grade III/IV adverse event was observed in one patient. In this group, the mean duration of treatment was 28 days (7–60/30 [IQRs]). Median time between the last TT intake/use and death was 28 days (7–69/29.5 [IQRs]). Combining all the patients with a TT who have left the unit, the average duration of the TT after the hospitalization was 31 days. Combining all 42 patients, the median time between the last TT and death was 20 days. This period was less than 3 months for 41 of the 42 patients (95%), less than 1 month for 29 of the 42 patients (67%), and less than 7 days for 10 of 42 patients (23%). After discharge from your palliative care unit, 15/42 (36%) of patients returned home (8/15 in a home hospital setting), 5 (12%) were transferred to a medical unit, and hospitalization was continued in another palliative care unit for 11 patients (26%). Eleven deaths occurred during hospitalization in your unit (26%). All these deaths occurred in patients who had been admitted to the unit for the reason of an altered general condition at home.

Re-challenge of TT

Of the 19 who received TT upon leaving the unit, 11 had already been treated with the same drug, receiving the TT as a new challenge (treatment is used hoping a clinical response again) or to maintain pressure (the therapy is maintained despite a progressive illness in order to avoid a major rebound at the end of the therapy).

For 7 of these 11 patients, the decision to re-challenge a previously used TT (modification of TT in patients with TT at the entry or reintroduction of TT in patients with TT break) was taken during the hospitalization in our unit, after an onco-palliative meeting. Their characteristics are presented in Table 2. Five of these patients experienced a subjective improvement of their symptom.

Discussion

The use of systemic oncologic therapy in patients with very advanced solid tumors near death has been well studied. Chemotherapy was expected to improve the quality of life, particularly in patients with cancer-related symptoms, but it is now clearly demonstrated that its use at the end of life is associated

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Table 2. Characteristics and outcomes of patients in whom a previously used TT was reintroduced

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Cancer	Kidney	Kidney	Kidney	Kidney	Melanoma	Sarcoma	Melanoma
TT	Cabozantinib	Axitinib	Axitinib	Axitinib	Dabrafenib + Trametinib	Regorafenib	Dabrafenib + Trametinib
Progressive disease under the therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Symptoms	Occlusive syndrome	Dyspnea	Pain	Pain	Neurological symptoms	Pain	Neurological symptoms
Antecedent of rebound when therapy stopped	Yes	No	Yes	Yes	Yes	Yes	Yes
Onco-palliative meeting	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subjective improvement of the symptom after reintroduction	Yes	Yes	Yes	No	No	Yes	Yes
Objective measurement	Yes	No	No	Yes	No	No	No
Duration of treatment after reintroduction (days)	110	60	90	7	60	7	14

with lower survival and quality of life (Mathew et al., 2017). The delay between last chemotherapy and the end of life has been proposed as a quality of care criterion. Fewer data are available on the use of TT near the end of life. Compared to the studies published earlier, ours has certain particularities. First, our unit is an acute palliative care unit, which results in an obvious selection bias. Second, many new TTs have recently been developed and are being used in our patients, which was not the case in previous studies, making it difficult to compare. Third, our hospital is a center of inclusion in phase I trials with the possibility of introducing TT in highly pretreated patients who often die quickly if the tested therapy is ineffective. The interest of our study is, therefore, not the comparison with previous studies, but several results are interesting to underline. First, the identification of a group of patients in whom the reintroduction of a TT leads to an improvement of symptoms, even in progressive disease with the same therapy. We know from practice and literature that some patients may experience a rebound of cancer symptoms after discontinuing TT and that the reintroduction of TT may be beneficial despite the lack of objective tumor benefit. In this situation, the drug is not used as oncological treatment, but as symptomatic and palliative treatment. In our study, seven patients were treated with previously used TT to which they had become resistant. Five of these patients were clinically improved on neurological, pulmonary, pain, and effusion symptoms, despite only two objective tumor responses. But this use can also be complicated, which hinders the understanding of the palliative process, as we illustrated in two cases published earlier (Delaye et al., 2020)

However, in our study, it is interesting to note that the introduction or reintroduction of TT interestingly does not seem to avoid the palliative process, as illustrated by the period between the last treatment and death, which lasted about several weeks in this group of patients. Similarly, we noted that the 19 patients we discussed in our unit in which TT was introduced or continued had a higher median time between the cessation of TT and death than the 42 patients in the study (28 compared to 20 days). We cannot conclude in this retrospective and nonrandomized study, but the interaction between oncologists and palliative care physicians is probably at the core of these decisions and could explain this difference. These decisions to pursue specific oncological treatments should be cautious, which are offered to the selected patients, after discussing the risk-benefit report with them. Multidisciplinary oncopalliative meetings are the ideal time to discuss such situations (Goldwasser et al., 2018). A second result to note is the high number of patients admitted to the unit with a deeply impaired general condition who died rapidly in the unit. These patients were still receiving the TT at home. Eight patients lived 7 days or less after the treatment was stopped. This illustrates the upheaval that TTs generate in the managing end-of-life patients. The discontinuation of TT even at an advanced stage of the disease and even in the case of progression can be made difficult by the sometimes observed rebound effect and a death felt as sudden, but also by their effect on the control of symptoms. The continuation of TT at the end of life for these reasons should be explained to the patient and their loved ones, avoiding excessive investment and false hope in treatment. Finally, our study, which has the limitations of a small retrospective study, shows that thinking about TT and palliative care is, in some points, different from thinking about chemotherapy. More data are needed to better select patients who might benefit from ongoing treatment even toward the end of their lives, but also to prevent the misuse of these therapies.

Conclusion

TT represents a growing family of treatments. These treatments have different characteristics than conventional chemotherapy. Our study suggests that TT could be continued at the end of life, in selected patients, to treat cancer-related symptoms despite the progression of the disease, but these decisions need to be discussed and explained to the patient and their loved ones so as not to disrupt the palliative process. The issue of managing TT at the end of life needs to be explored further and interactions between oncologists and palliative care physicians need to be improved.

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Ethics approval. Our database has been approved and registered by our Institutional Review Board, according to guidelines for Good Clinical Practice, on 4/03/2019.

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