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REVIEW

Molecular targeted therapy-related life-threatening toxicity in patients with malignancies. A systematic review of published cases

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Abstract

Background: Molecular targeted therapy increased overall and disease-free survival in a wide range of malignancies. Although generally well tolerated compared to chemotherapy, molecular targeted therapy may be associated with adverse events requiring ICU admission. Informing clinicians about clinical features of these toxic events might maintain awareness and favor early recognition, prompt diagnosis and treatment.

Methods: We performed a systematic review of published case reports of molecular targeted therapy-related life-threatening toxicity that led to ICU admission. The search used the Pubmed database using medical subject heading (Mesh) terms, including all FDA-approved molecular targeted therapy (TT), up to March 2019. No language restriction was applied. All cases reports of patients admitted to the ICU for molecular targeted therapy-related toxicity were included. Non-FDA-approved combinations of treatments or hormonal therapy were not included.

Results: Two hundred and fifty-three cases were identified. Nearly half of them ($n = 102$; 40.3%) were related to anti-angiogenic agents, mostly for gastrointestinal and cardiovascular complications. Other molecules responsible for adverse events were chiefly immune checkpoint inhibitors ($n = 85$, 33.6%), EGFR inhibitors ($n = 33$; 13.0%), and anti-HER2 ($n = 10$; 4.0%). They were associated with adverse events such as respiratory or hypersensitivity events. Management and outcomes associated with these life-threatening complications are reported.

Conclusions: Based on the vast number of treated patients, only 253 cases of molecular therapy-related severe toxicity are reported in cancer patients. Symptoms and biomarkers that depict these events need to be better identified as to allow appropriate reporting and improving dose and schedule of the treatment adapted to each patient.

Keywords: Molecular targeted therapy, Malignancies, Critical care, Pneumonitis, Digestive perforation

Introduction

Survival of patients with solid tumors has markedly improved over the last decade with the advent of molecular targeted therapies [1]. Compared with conventional cytotoxic chemotherapy, these targeted agents offer a more tolerable toxicity profile, thereby promising both optimized dose intensity and better quality of life. Given the rise of an effective cancer screening throughout the world, the ageing population, the improvement of overall survival of patients with solid tumors, and the better understanding of molecular and cellular pathways involved in tumor progression, an ever-increasing number of patients will be receiving single or combined molecular treatments [2, 3]. These new therapeutic drugs significantly improve progression-free survival in several

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types of cancer, but also generate adverse events (AEs), which vary widely in nature and severity.

The majority of these AEs are of low to moderate severity, classified as grade 1 to 2 toxicities according to the Common Terminology Criteria of Adverse Events defined by the National Cancer Institute. Broadly reported in the literature, including in pivotal phase II and III clinical trials, they involve multiple organ systems, including the skin, gastrointestinal tract, peripheral nervous system, liver and endocrine system. These AEs are typically foreseeable and expected, as they correspond to a so-called on-target toxicity, as a result of inhibition of the targeted cellular pathway [4]. Although most AEs are well-managed in an outpatient setting, some AEs occasionally lead to severe morbidity or can even be fatal. Life-threatening, drug-related toxicities remain rarely described in clinical trials, which involve only carefully selected patients with middle-term clinical follow-up. Thus, few data are available regarding serious drug-related AEs in real-world patients who would not have been eligible for clinical trials. Recently, the development of immune checkpoint inhibitors in different settings and for different types of cancer has led to the rise of a new spectrum of immunotherapy-related adverse events (irAEs) [5–7], as a consequence of self-tolerance impairment through reduced cytotoxic T cell inhibition; however, the risk of life-threatening or fatal autoimmune-like AEs is unclear at this point, given the novelty of this class [8]. Therefore, data are needed on type, clinical presentation, management and outcomes of potential life-threatening AEs related to molecular targeted therapies, particularly those requiring an admission to an intensive care unit (ICU). In the years to come, intensivists will be managing an increasing number of patients treated with new single or combined targeted therapies. Consequently, clinicians should not overlook potential harmful effects of these new drugs, to allow for prompt diagnosis and initiation of specific treatments. Furthermore, identifying reliable predictive biomarkers of efficacy and toxicity is an urgent need to improve patient selection and help oncologists in treatment decision-making.

In this systematic review, we aimed to identify published cases of life-threatening AEs leading to an ICU admission following a targeted anticancer therapy in patients with solid tumors.

Search strategy

A systematic research on PubMed was performed, using the medical subject headings (MeSH) terms "drug-related adverse event" and "erlotinib, gefitinib, afatinib, cetuximab, panitumumab, osimertinib, rociletinib, trastuzumab, pertuzumab, TDM-1, lapatinib, neratinib, bevacizumab, sunitinib, sorafenib, pazopanib, axitinib, lenvatinib, regorafenib, aflibercept, ramucirumab, cabozantinib, olaparib, niraparib, rucaparib, talazoparib, palbociclib, ribociclib, abemaciclib, crizotinib, ceritinib, alectinib, lorlatinib, brigatinib, vemurafenib, dabrafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, everolimus, temsirolimus, vismodegib, vandetanib, nintedanib". We added a manual bibliography search of selected articles.

Take-home message

In cancer patients, molecular therapy-related severe toxicity can be life-threatening and require ICU management. Half the cases were reported to angiogenic agents, mostly for severe gastrointestinal and cardiovascular complications. Immune checkpoint inhibitors, EGFR inhibitors, and anti-HER2 were associated to respiratory or hypersensitivity events.

All case reports and case series of drug-related AEs resulting in an ICU admission in patients with solid cancer following treatment with an US Food and Drug Administration (FDA)-approved molecular targeted therapy (Table 1S) published up to March 2019 were included, with no language restrictions. Patients admitted to a high-dependency unit (HDU) or coronary care unit (CCU) were included. We excluded pediatric cases, cases in pregnancy and those referring to non-oncological indications of molecular therapies. All above-mentioned targeted therapies were considered, whether the patient received the treatment in a clinical trial, off label or as usual care. We excluded case reports on non-FDA-approved combinations of targeted agents or hormonal therapies. For each type of targeted therapy, we also collected grade III–IV sides effects described in the randomized controlled trial (Table 1).

We collected clinical features of reported patients (age, gender, cancer localization, prior or concomitant anticancer treatments by chemotherapy, radiotherapy or corticosteroids). Characteristics of drug-related AEs by molecular therapy family (clinical presentation at ICU admission, time since treatment initiation, and diagnosis of complication), management of toxicity in ICU (required organ support, surgery, anti-infectious or immunosuppressive treatment, corticosteroids use) and outcomes were also collected.

Results

All cases

As shown in Fig. 1, 7344 case reports and series were identified, including 253 cases that were included in the present study. We identified 96 (37.9%) women and 157 (62.1%) men. Median age was 62 (23–88) years. Targeted treatments of interest were predominantly

Table 1 Incidence of grade III or IV toxicities in phase III pivotal clinical trials by molecular targeted therapy

%	Bevacizumab[a] [1, 18–26]	Sunitinib [49]	Sorafenib [50]	Gefitinib [51–53]	Erlotinib [54, 55]	Cetuximab [56–60]	Trastuzumab[b] [61–64]	Everolimus [65–67]	Vemurafenib [68, 69]	Ipilimumab [29–32]	Nivolumab [30, 31, 33–35]	Ipilimumab + nivolumab [30, 31]
Colitis/ileitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	5–14	< 1	8–18
Digestive perforation or fistula	< 1–6	NR	NR	NR	NR	NR	NR	NR	NR	< 1	NR	NR
Haemorrhagic events	0–9.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pneumonitis/ILD**	NR	NR	NR	1–5.3	< 1	NR	NR	2–3	NR	0–2	< 1	1–2
PRES	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Neurological events	NR	NR	NR	< 1	NR	NR	NR	NR	NR	1	< 1	NR
Heart failure	< 1	NR	NR	NR	NR	NR	<1–4.1	NR	1	NR	NR	NR
Ischemic events	< 1–3	NR	3	< 1	NR	NR	NR	NR	NR	NR	NR	NR
Thromboembolic events	0–12.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pericarditis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	< 1	NR
Renal injury	NR	1	NR	NR	NR	NR	1	NR	NR	< 1	< 1	NR
Hypersensitivity	NR	NR	NR	NR	NR	1.2–4.5	6	NR	NR	NR	NR	NR
Hepatitis	NR	1–2	NR	26.3	NR	NR	NR	3	8–11	0–2	0.5–3	6–8
Drug-related death	0.5–2.3	NR	NR	1–3.8	< 1	1.4	2–3	< 1	1–2	0–3	< 1	0–3

Adverse events reported above were attributed by the investigators only to mentioned molecular targeted therapy in case of combination with other treatment(s)

**Interstitial lung disease

[a] Bevacizumab-related adverse events reported here were collected from pivotal clinical trials assessing bevacizumab at doses of either 7.5 mg/kg or 15 mg/kg every 3 weeks, 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks

[b] Without combined anthracycline treatment. *NR* not reported

antiangiogenic agents ($n = 102$, 40.3%), immune checkpoint inhibitors ($n = 85$, 33.6%), EGFR inhibitors ($n = 33$, 13%), or monoclonal anti-HER2 antibodies ($n = 10$, 4.0%) (Table 2). Reported patients presented with various types of cancer, mainly melanoma ($n = 64$, 25.3%), kidney ($n = 46$, 18.2%), lung ($n = 44$, 17.4%), colorectal ($n = 40$, 15.8%), and breast ($n = 18$, 7.1%) cancer. All but 17 patients presented with unresectable or metastatic tumors at ICU admission ($n = 236$, 93.3%), and 129 patients received targeted therapy of interest as first-line treatment (51.0%). One hundred and seventy-one (67.6%) patients received molecular therapy as monotherapy, whereas chemotherapy and radiotherapy were associated with targeted therapy in 65 (25.7%) and five (1.9%) patients, respectively. Combinations of targeted molecular agents were reported in 12 (4.7%) patients.

Median time from treatment initiation to ICU admission was 1.4 (0.03–54) months. We collected cases of 50 (19.8%) digestive perforations or fistulas, three (1.2%) non-perforated colitis and/or ileitis, 58 (22.9%) cardiovascular events, 29 (11.5%) pulmonary events, 39 (15.4%) neurological events, 13 (5.1%) infectious complications, 10 (4.0%) hepatic failures, 10 (4.0%) acute renal failures, 9 (3.6%) hypersensitivity or infusion-related reactions, 4 (1.6%) dermatological events, 3 (1.2%) muscular events, 3 (1.2%) severe hypothyroidism events, and 12 (4.7%) other complications (Table 2). ICU mortality was 31.6% (80 deaths). Time since treatment onset, ICU admission, and number of cases are detailed in Fig. 2.

Antiangiogenic agent: bevacizumab, sunitinib, sorafenib (Table 2S)

In the 102 patients who had received an antiangiogenic agent, gastrointestinal AEs were reported in 42.2% of the cases, mainly as digestive perforations (25.5%), which represent almost one-third of life-threatening bevacizumab-related events admitted into an ICU. Eight patients (30.8%) suffering from digestive perforations died in the ICU, mostly from post-operative septic shock. Additionally, 22.5% patients experienced a cardiovascular complication, mainly toxic cardiomyopathy, including 51.7% (4/7) who died during ICU stay. Moreover, ten (9.8%) cases of posterior reversible encephalopathy syndrome (PRES) were reported, eight cases of which occurred after bevacizumab treatment and led to three ICU deaths (30.0%). Other less frequent but relevant AEs included three (2.9%) cases of sunitinib-related severe hypothyroidism and three (2.9%) cases of sunitinib-related thrombotic microangiopathy syndrome. Median time from antiangiogenic agent initiation to ICU admission was 1.8 (0.03–54) months with a median number of received courses of three (1–34).

Mechanical ventilation and vasopressors were required in 55 (53.9%) and 23 (22.5%) patients, respectively. Death in the ICU was reported as a result of AEs in 30 (29.4%) patients, from which 12, 7, and 8 patients were treated with bevacizumab, sunitinib, and sorafenib, respectively. Of note, one case of sorafenib-related fulminant hepatitis was successfully treated with emergency hepatic transplantation [9].

Immune checkpoint inhibitors: nivolumab, pembrolizumab, ipilimumab (Table 3S)

Eighty-five cases of irAEs requiring admission into an ICU were collected. The most common reported irAEs were perforated colitis or enterocolitis ($n=15$, 17.6%), fulminant myocarditis ($n=13$, 15.3%), polyradiculoneuritis ($n=11$, 12.9%), pericarditis ($n=9$, 10.6%), and myasthenia gravis ($n=9$, 10.6%). Most of reported cases concerned the anti-CTLA4 antibody ipilimumab in monotherapy ($n=34$, 40.0%). Median time from immune checkpoint inhibitor initiation to ICU admission was 1.4 (0.2–16) months with a median number of received courses of two (1–32).

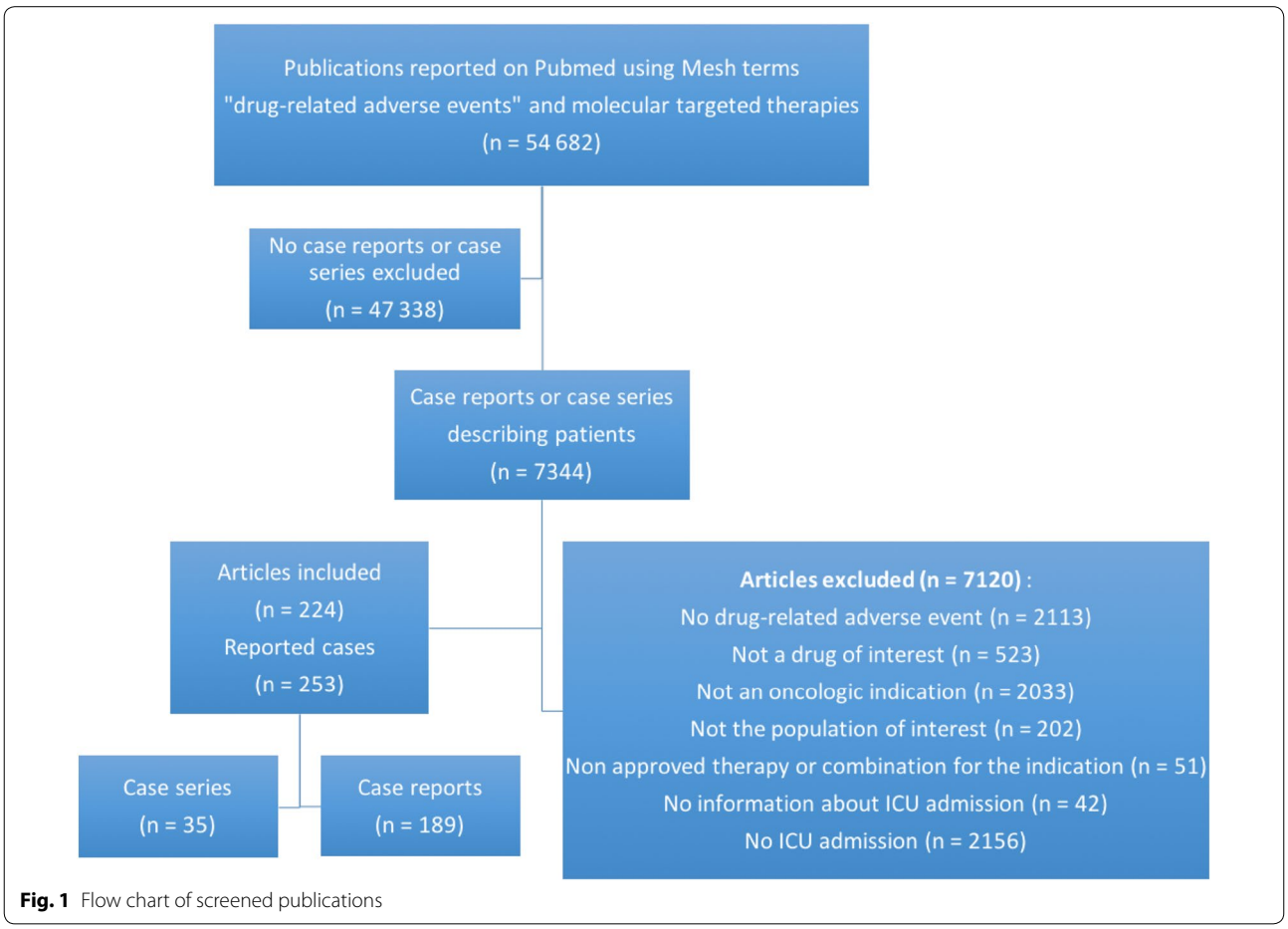


Fig. 1 Flow chart of screened publications

Table 2 Molecular targeted therapy-related toxicity that required ICU admission

	n (%)					*n*			
	All (*n* = 253)	**Anti-angiogenic agents (*n* = 102)**	**Immune checkpoint inhibitors (*n* = 85)**	**EGFR inhibitors (*n* = 33)**	**Anti-HER2 (*n* = 10)**	**mTOR inhibitor (*n* = 8)**	**BRAF inhibitors (*n* = 7)**	**ALK inhibitor (*n* = 3)**	**Other[d] (*n* = 5)**
Gastrointestinal	69 (27.3)	42	20	3		1	1	1	1
Colitis/ileitis	3	26[a]	3	2[c]		1	1[c]	1	1
Digestive perforation	44	6	15	1					
Digestive fistula	6	3	2						
Digestive hemorrhagia	6	7							
Hepatitis	10								
Cardiovascular	58 (22.9)	23	27	3	4				1
Toxic cardiomyopathy	15	7	2	2	3				1
Takotsubo syndrome	6	5	1	1	1				
Coronary vasospasm	3	2	1						
Myocardial infarction	3	2	1						
Acute aortic dissection	3	3	1						
Pericarditis	1	1	8						
Tamponade	9	1	13						
Myocarditis	13	1							
Pulmonary embolism	1	1							
Ischemic colitis	1								
Intracardiac thrombus	1								
Ischemic cerebral vasculopathy	2								
Respiratory	29 (11.5)	7	7	11	1	2		1	
Pneumonitis/ILD*	13	2	3	6	1	2		1	
ARDS**	11	1	4	4					
Pneumothorax	5	4[b]		1[c]					
Neurological	39 (15.4)	12	23	2			1		1
PRES***	11	10	9	1			1		1
Guillain–Barre syndrome	9	1	2	1					
Meningoradiculoneuritis	2	1	2						
Meningoencephalitis	2		9						
Myasthenia gravis	9		1						
Bulbar myopathy	1								
Intracranial hemorrhagia	2								
Unexplained coma	2								
Unexplained seizure	1								
Infectious events	13 (6.3)	4		4		4			1
Necrotizing fasciitis	6	4		2		2			1
Pneumocystis pneumonia	2			2		1			
B hepatitis virus reactivation	2					1			
Other[d]	3								
Renal	10 (4.8)	6	2		2				
Acute renal failure	3	3	2		2				
Acute interstitial nephritis	2	3							
Thrombotic microangiopathy	5								
Hypersensitivity/infusion reaction	9 (4.3)			7		1	1		

Table 2 (continued)

	n (%)					*n*			
	All (*n* = 253)	Anti-angiogenic agents (*n* = 102)	Immune checkpoint inhibitors (*n* = 85)	EGFR inhibitors (*n* = 33)	Anti-HER2 (*n* = 10)	mTOR inhibitor (*n* = 8)	BRAF inhibitors (*n* = 7)	ALK inhibitor (*n* = 3)	Other[d] (*n* = 5)
Dermatologic	4 (1.9)			1			3		
Toxic epidermal necrolysis	4			1			3		
Tumor lysis syndrome	4 (1.9)	1		1	1				1
Muscular	3 (1.4)		3						
Polymyositis	3		3						
Endocrinal	3 (1.4)	3							
Severe hypothyroidism	3	3							
Other events[d]	12 (4.7)	4	3	1	2		1	1	

*Interstitial lung disease

**Acute respiratory distress syndrome

***Posterior reversible encephalopathy syndrome

[a] Three out of 26 cases were related to metastatic lesions necrosis

[b] Two out of four events were related to tumor necrosis

[c] One of these events was related to tumor necrosis

[d] Details of other events and drugs are available in supplementary data

Mechanical ventilation, vasopressors, and plasmapheresis were required in 49 (57.6%), 23 (27.1%), and 22 (25.9%) patients, respectively. Sixty-nine (81.2%) patients received high-dose steroids, 23 (27.1%) intravenous immunoglobulins, 11 (12.9%) infliximab, and eight (9.4%) another immunosuppressive drug. ICU mortality rate after irAEs was 28.2% ($n = 24$). Immune-related adverse events associated with highest rate mortality the in ICU were fulminant myocarditis (7 deaths out of 13 cases, 53.8%) and neurologic events (9/23, 39.1%). Three patients presenting with ipilimumab-related perforated enterocolitis died during ICU stay from postoperative multiple-organ dysfunction syndrome [10–12]. One patient died from nivolumab-related acute respiratory distress syndrome, despite aggressive treatment including infliximab use [13]. Four out of ten (40.0%) patients who had received a combination of ipilimumab and nivolumab died in the ICU: two patients died from fulminant myocarditis [14], of which one was infliximab-refractory, one patient from immune-related myasthenia gravis with no response to intravenous immunoglobulins [15], and one from septic shock secondary to immunosuppression induced with high-dose steroids and mycophenolate mofetil, initiated as immune-related nephritis treatment [16].

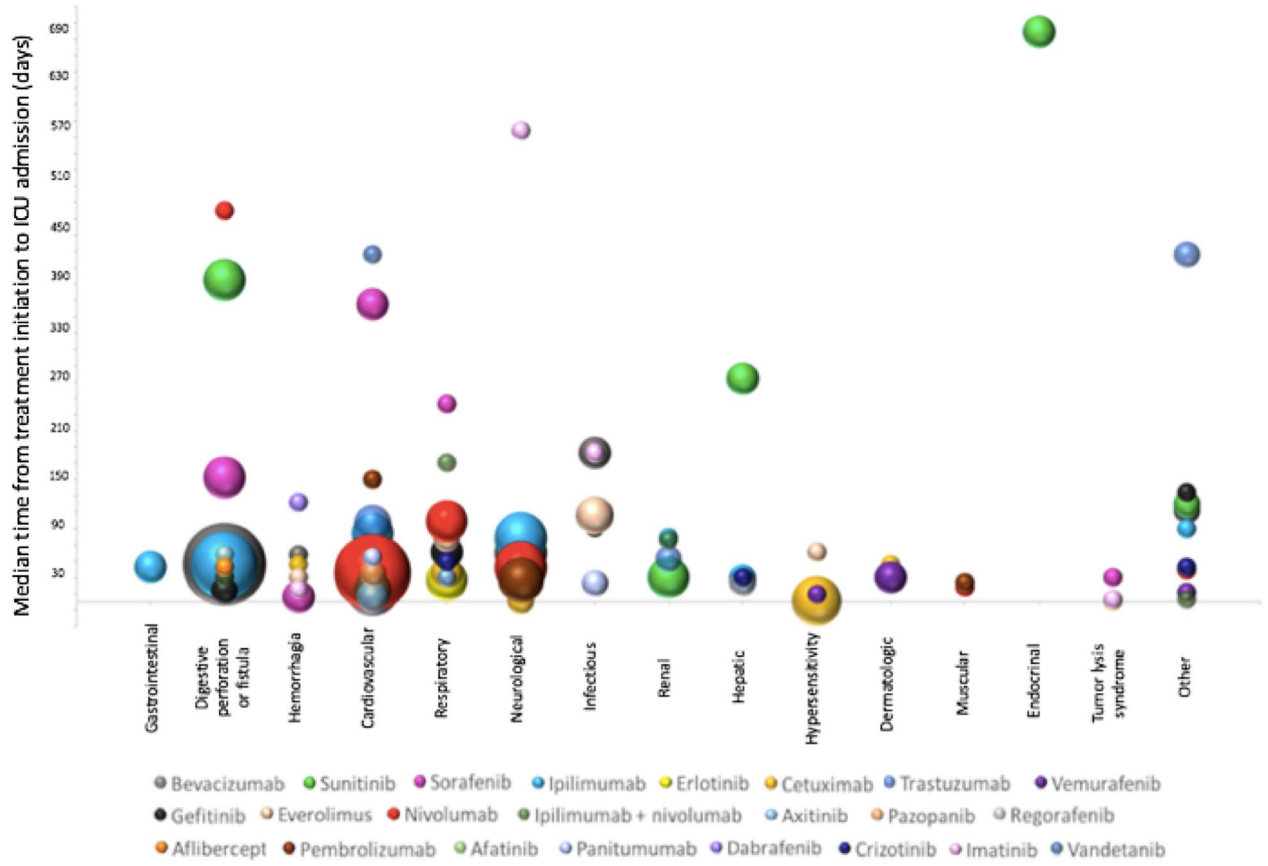
EGFR inhibitors: erlotinib, gefitinib, cetuximab (Table 4S)

Thirty-three cases of anti-EGFR-related AEs requiring an ICU management were identified, of which ten (30.3%) cases were diagnosed as interstitial lung disease and seven (21.2%) as cetuximab-related hypersensitivity. ICU admission occurred after anti-EGFR initiation with a median time of 1.0 (0.2–4.5) month, except for cetuximab, for which related infusion reactions were observed during the first injection. Three (9.1%) cases of tumor necrosis-related events were reported, in addition to one case of cetuximab-related tumor lysis syndrome. Conceivably, all three cases occurred in patients with non-small cell lung cancer harboring an epidermal growth factor receptor (EGFR) mutation.

Most patients required mechanical ventilation (78.8%) and seven (21.2%) needed vasopressor. High-dose steroids were administered in 13 (39.4%) patients. Thirteen patients (39.4%) out of 33 died during ICU hospitalization. Acute respiratory distress syndrome occurred in four patients admitted with interstitial lung disease (40.0%), and all four died in the ICU. Two patients (28.6%) died on the day of ICU admission from cetuximab-related hypersensitivity.

Other molecular targeted therapies (Table 5S)

Ten patients were treated with trastuzumab, resulting in three (30.0%) cases of toxic cardiomyopathy with a median time from anti-HER2 initiation of 4.0 (2.3–6.0) months, corresponding to nine (3–12) received injections. There was no evidence of previous cardiac history or cardiotoxic medications. One of the three patients died in the ICU. Everolimus was administered to eight patients.



ICU: Intensive Care Unit
Bubbles surface areas are proportional to the number of patients reported for each drug-related adverse event.

Fig. 2 Systematic review of molecular targeted therapy adverse events leading to ICU in oncology

Two patients (25.0%) were admitted to the ICU for life-threatening interstitial lung disease, of which one was fatal. Strikingly, two patients developed *Pneumocystis* pneumonia after a median treatment time of 1.5 (1.0–2.0) months, with a favorable outcome [17]. Life-threatening AEs related to BRAF inhibitors, crizotinib, imatinib, and vandetanib are shown in Table 5S (supplementary data).

Discussion

Molecular targeted therapies, mainly immune checkpoint inhibitors, have drastically modified the therapeutic paradigm in solid oncology. In the years to come, an increasing number of patients with solid tumors will be treated with new drugs. While many AEs have been well-described in clinical trials, others remain unknown, due either to their sporadicity or their late onset during follow-up. Therefore, it is of clinical importance to collect data about drug-related AEs, including life-threatening complications during patient follow-up.

Our search yielded 253 cases of life-threatening drug-related AEs requiring an admission into an ICU in patients presenting with solid tumors. Almost half of these cases were related to use of antiangiogenic agents, involved in 26 (25.5%) reported cases of digestive perforation with a 30.8% mortality rate in the ICU. Of these, three cases (11.5%) were attributed to necrosis of metastatic digestive lesions. As reported in Table 1, digestive perforations were already described in 1–6% of patients in clinical trials assessing bevacizumab in several types of cancer [18–26]. In addition, we collected 23 (22.5%) cases of antiangiogenic-related cardiovascular issues, of which seven (30.4%) were lethal. Although the molecular mechanisms through which VEGF inhibitor use leads to cardiotoxicity remain unclear, it is suggested that patients with proteinuria and hypertension immediately after beginning antiangiogenic therapy are at increased risk for later cardiac AEs [27]. These findings pinpoint the importance of cardiovascular assessment before and during treatment with angiogenesis inhibitors, particularly

for multi-targeted small molecules such as sunitinib and sorafenib [28].

The most significant reported immunotherapy-related serious toxicity was colitis or ileitis ($n=18$, 21.2%), which is consistent with immunotherapy clinical trial results [29–37]. Surprisingly, only one case of life-threatening perforated enterocolitis due to ipilimumab and nivolumab combination was reported in literature [38], although the latter further increased the risk of autoimmune-like issues in clinical trials [30, 31]. Conceivably, the novelty of immunotherapies explains the small number and the heterogeneity of published cases we report. As recently reported by Wang et al., irAEs associated with the highest rate of mortality in the ICU in our cohort were fulminant myocarditis and neurologic events. However, analysis of the pharmacovigilance database indicates that fatal irAEs remain uncommon, occurring at a rate of 0.3–1.3% [39].

ICU mortality in our review was 31.6%. Although the paucity and variability regarding case reporting do not allow us to generalize this result, this figure is consistent with some previous studies focusing on survival of solid cancer patients admitted to the ICU [40]. Taken together, all these data emphasize the need for a careful selection of patients who are candidates for a targeted molecular therapy. An exhaustive and personalized evaluation of toxicity risk before treatment initiation is warranted. In particular, an autoimmune work-up aiming to rule out a subclinical systemic disease should be consistently undertaken. As recently shown by Johnson et al., patients with underlying pre-existing autoimmunity disease should not be de facto ineligible for immunotherapy, but would imperatively require thorough monitoring during and after treatment [41]. Critical care specialists and oncologists should be aware of warning symptoms for a prompt diagnosis of drug-related AEs, which might be resolved early with a dose reduction or transient discontinuation of treatment. Furthermore, although management of steroid-refractory irAEs with immunomodulatory medications such as infliximab, mycophenolate mofetil, or tacrolimus may be efficient in some cases [42–45], prospective trials assessing different treatment modalities are needed. Here, we report a published case of ipilimumab-related hepatitis refractory to mycophenolate mofetil but which resolved with use of T cell depleting antibody anti-thymocyte globulin [46]. Ultimately, more data are needed regarding optimal dose and administration schedule of ipilimumab to curtail the risk of autoimmune-like or immune-related toxicity [8], given the possible dose-toxicity relationship [37, 47].

There are several limitations inherent to this review. First of all, the small number of reported cases and their retrospective nature hamper assessment of molecular treatment imputability, particularly in the case of therapeutic combinations including chemotherapy and other drugs. Moreover, administered doses of targeted molecules are not always mentioned. Secondly, patients with life-threatening anticancer drug-related AEs may have declined, or were denied for ICU referral and were not included in this review. Furthermore, we could not differentiate ICU patients from HDU patients in some reported cases. Last, another important bias of this review lies in the reporting of only published cases (Fig. 1S). However, hierarchy in terms of proportions is maintained between AEs with respect to those described in pivotal clinical trials for each drug (Table 1), suggesting that our review may be representative of real-world patients, although widely underestimating the absolute number of serious drug-related AEs.

We believe that this review provides substantial information on the management and outcomes of patients presenting with life-threatening anticancer drug-related AEs. Our findings advocate for a thoughtful selection of patients likely to benefit from molecular targeted therapy and improved clinical and biological monitoring during and after treatment initiation. Further studies should identify optimal therapeutic doses and schedules to adopt and determine predictive biomarkers for adverse events, primarily those related to immune checkpoint inhibitors [48], in order to enhance the risk/benefit profile for each individual.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05650-w) contains supplementary material, which is available to authorized users.

Abbreviations
ICU: Intensive care unit; AEs: Adverse events; irAEs: Immunotherapy-related adverse events; HDU: High-dependency unit; CCU: Coronary care unit; EGFR: Epidermal growth factor receptor.

Compliance with ethical standards

Conflicts of interest
Authors declare no conflict of interest in relation with this publication.

Publisher's Note

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