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ORIGINAL ARTICLE

Fatal events during clinical trials: an evaluation of deaths during breast cancer studies

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Abstract

Background Information on deaths occurring during oncological clinical trials has never been systematically assessed. Here, we examine the incidence of death and the profile of patients who died during randomized clinical breast cancer (BC) trials.

Methods Information on fatal events during German Breast Group (GBG) led BC trials was prospectively captured. Data were derived from the trial databases and death narratives. All deaths were evaluated for possible causes, underlying conditions, treatment relatedness, time point and rate of autopsies.

Results From 12/1996 to 01/2017, 23,387 patients were treated within 32 trials. Of those 88 (0.4%) died on therapy within 17 trials. Median age was 64 [range 35–84] years, 63.2% of patients had a body mass index (BMI) ≥ 25 kg/m^2; 65.9% 1–3 and 22.7% ≥ 4 comorbidities; 61.4% 1–2 cardiovascular risk factors (CRFs); 26.4% took > 3 drugs; 81.7% had ECOG 0; 50.0% stage III, 76.7% luminal BC. The main causes of death were infection (38.6%; of those, 82.3% sepsis, 17.6% pneumonia), heart failure (14.8%), and pulmonary embolism (13.6%). Fatal events mainly occurred within the first 4 therapy cycles (55.7%), in the investigational arm (66.7%) and under anthracycline–taxane-based chemotherapy (51.1%). A relationship with the treatment was declared in 27.3% of the cases. An autopsy was performed in 13.6% of patients.

Conclusions Death during study treatment was mainly related to infections, and patients with advanced disease, high BMI, underlying comorbidities, CRFs and concomitant medications. If considered for study participation these patients need careful monitoring due to their higher risk for death on study.

Keywords Death in clinical trial · Cause of death · Chemotherapy-related death · Serious adverse events · Rate of autopsy

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Introduction

Clinical trials are essential to investigate novel treatment approaches to improve patients' outcome. Even though the conduct of clinical trials is strictly regulated to provide for patient safety and despite careful monitoring at different levels, the death of patients on study still remains a major concern that needs to be reported rapidly and accurately. Nevertheless, underreporting of safety results is a common phenomenon that may lead to an overestimation of the health benefit of a certain intervention. From 1990 to 2000, only eight deaths have been reported among 70 million participants in the USA [1]. To obviate the problem of incomplete reporting and to increase patient safety, the FDA expects the legal trial sponsor to submit annual reports that include a list of participants who died during the investigation, along with the underlying death cause. All deaths must be reported to the FDA as a serious adverse event (SAE), regardless of the relationship to the investigational agent [2]. Even though the CONSORT guidelines do not specify the need to report all deaths, the authors should disclose fatal events in each study group [3]. The assessment of the causal relationship with study treatment is of major importance to obtain a reliable balance between efficacy and safety of the investigated drugs. An autopsy may be necessary to definitively clarify the causality. However, the role of autopsy for patients who died during clinical trials is not well established and the use varies among different countries. Studies investigating the incidence of death among participants of clinical trials including the profile of dead patients and the possible relationship with the investigational drugs are lacking. Such investigations, however, are necessary to increase the safety of future patients enrolled in clinical trials. Only one review examined toxic deaths in 92 clinical oncology trials and found a mortality rate of 0.7% related to the study medication among 34,734 patients [4]. In our analysis, we studied the incidence of death among patients involved in randomized clinical breast cancer (BC) trials conducted by the German Breast Group (GBG), and described risk factors (RFs) that should be carefully monitored and examined the role of autopsy.

Materials and methods

Information on patients' deaths during GBG led BC trials was prospectively captured. Rules for death reporting were as follows: any death during treatment and within 30 days following last treatment had to be reported to the sponsor regardless of the relation to the study drug; after this period, only deaths considered to be related to study treatment had to be reported. International trials where the GBG was not the sponsor were excluded due to lack of access to all data. Therefore, a total of 32 phase II and III interventional randomized BC studies were initially considered. The present analysis included a total of 17 trials in which fatal events

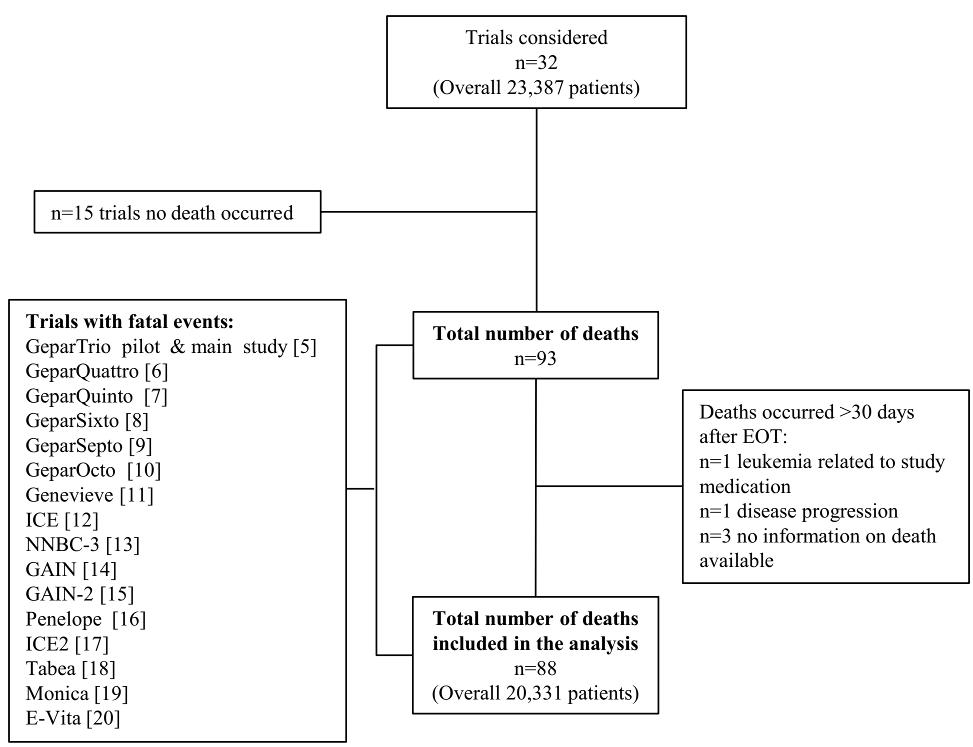

Fig. 1 Consort diagram. *EOT* end of treatment

occurred (Fig. 1). Inclusion and exclusion criteria and all trial designs were previously published [5–20]. All patients starting on study medication were included in the analysis. For the 6 trials still ongoing at the time of the analysis, all randomized patients were taken into account (data cut-off 30th January 2017). Data on patient and tumor baseline characteristics, treatment-related variables (standard or investigational arm, anticancer therapy, number of cycles received), last SAE submitted before death, and type of study center (hospital, practice) were derived from the trial databases. Data on cause of death, last study drug received and investigator-assessed relationship with the study drug were derived from death narratives that included autopsy results, if performed. All deaths were evaluated for possible causes, underlying conditions, treatment relatedness, time point and autopsy rate. An evaluation of the relatedness with the study medication was performed by a central medical reviewer, based on death narratives.

Statistical analysis

Baseline patient and tumor characteristics as well as treatment-related variables, last submitted SAE, death SOC (System Organ Class) and autopsy rates are presented as absolute numbers, frequency and median/ranges, if applicable. Fisher's exact test was used to compare binary variables and Pearson Chi square tests to evaluate the correlation between type of center and last SAE submitted before death as well as the death SOC and the relationship between treatment-related variables (standard or investigational arm, type of treatment) and death-related variables (cause of death and SOC, cycle when death occurred, last agents administered before death, relationship with the study drug as assessed by the investigator and the central medical review). Patients ($n=4$) enrolled in double-blind studies were excluded from the analysis assessing the relationship between death and study treatment as there were no unblinded information on the investigational treatment received at the time of the analysis. All reported p values were two sided and $p \leq 0.05$ was considered statistically significant. The analysis was performed using SPSS 21.0 (SPSS, Chicago, IL, USA).

Results

Patients and baseline characteristics

From December 1996 to January 2017, a total of 23,387 patients were randomized within 32 trials. Overall, 88 out of 23,387 (0.4%) patients died during or 30 days after completion of study treatment. When considering only the trials were fatal events occurred, 32/11,165 patients died in neoadjuvant (0.3%), 45/9332 in adjuvant (0.5%) and 11/436 (2.5%) in metastatic studies. Baseline characteristics of dead patients are presented in Table 1. In particular, 66 (75.0%) patients were treated and followed up in hospitals and 22 (25.0%) in practices. Patients with advanced disease (stage III/IV) were more frequently overweight or obese (90.9% vs 59.2%; $p=0.042$), had more frequently 3 or more comorbidities (72.7% vs 37.7%; $p=0.071$) or 3 or more CRFs (45.5% vs 7.8%; $p=0.001$) and took more frequently 1–3 concomitant medications (63.6% vs 36.8%; $p=0.041$) compared to patients with early disease stage (stage I/II).

Last severe adverse event submitted before death

A total of 87 SAEs were submitted (for one patient no SAE was submitted before death) (Fig. 2). The majority were classified by SOC as follows: 26.1% ($n=23$) blood and lymphatic system disorders ($n=9$ febrile neutropenia (FN), $n=6$ severe neutropenia, $n=6$ pancytopenia, $n=2$ anemia), 18.2% ($n=16$) infections and infestations ($n=12$ pneumonia, $n=1$ central venous catheter infection, $n=1$ peritonitis, $n=1$ endocarditis, $n=1$ cystitis) and 12.5% ($n=11$) respiratory, thoracic and mediastinal disorders ($n=9$ pulmonary embolism, $n=1$ lung failure, $n=1$ severe pulmonary hypertension). There was no statistically significant difference in terms of SOC of last SAE between patients treated at a hospital or an oncology practice ($p=0.255$). When focusing on the most common last SAE SOCs, no differences were found according to the type of treatment center (blood and lymphatic system disorders 30.3% vs 13.6%, $p=0.165$ infections and infestations 15.2% vs 27.3%, $p=0.202$; respiratory, thoracic and mediastinal disorders 13.6% vs 9.1%, $p=0.577$). There were no differences in terms of the most common last SAEs submitted before death (pneumonia 12.1% vs 18.2%, $p=0.485$; pulmonary embolism 12.1% vs 9.1%, $p=1.000$; FN 12.1% vs 4.5%, $p=0.440$). However, for patients treated with dose-dense chemotherapy the last SAE submitted before death was categorized within SOC "infections and infestations" more commonly than for patients treated with standard dose chemotherapy (36.0 vs 11.1%, $p=0.012$), whereas no statistically significant difference was found for SOC "blood and lymphatic system disorders" (32.0% vs 23.8%, $p=0.433$).

Cause of death

Causes of death were mainly classified under: infections and infestation (38.6%), respiratory, thoracic and mediastinal disorders (17.0%) and cardiac disorders (14.8%) (Fig. 3). The main cause of death was infection ($n=34$; 38.6%; with $n=28$ sepsis, $n=6$ pneumonia), heart failure ($n=13$; 14.8%) and pulmonary embolism ($n=12$; 13.6%). The remaining causes of death were: new primary tumor ($n=1$), depression ($n=1$), seizure ($n=1$), hemorrhage ($n=4$), lung failure

Table 1 Baseline patient and tumor characteristics

Patients characteristics	Patients ($N=88$)		Tumor characteristics	Patients ($N=88$)	
	n	Valid (%)		*n*	Valid (%)
Age			Tumor stage c/p		
≤ 45 years	4	4.5	T1	18	20.5
46–65 years	45	51.1	T2	41	46.6
> 65 years	39	44.3	T3	12	13.6
Median [range], years	64 [35–84]		T4	17	19.3
BMI			Nodal stage c/p		
18.5–24.9	32	36.8	N0	21	24.7
25.0–29.9	26	29.9	N1	31	36.5
30.0–39.9	25	28.7	N2	20	23.5
≥ 40	4	4.6	N3	13	15.3
Missing	1		Missing	3	
Comorbidities			Disease stage		
None	10	11.4	I	7	8.0
1–3	58	65.9	II	26	29.5
≥ 4	20	22.7	III	44	50.0
Median [range]	2 [0–8]		IV	11	12.5
Cardiovascular risk factors[a]			HR status		
None	23	26.1	Negative	20	23.3
1–2	54	61.4	Positive	66	76.7
≥ 3	11	12.5	Missing	2	
Median [range]	1 [0–4]		HER-2 status		
Concomitant medications[b]			Negative	53	75.7
None	29	33.3	Positive	17	24.3
1–3	35	40.2	Missing	18	
> 3	23	26.4	Tumor grade		
Median [range]	2 [0–9]		1	4	4.7
Missing	1		2	46	54.1
ECOG performance status			3	35	41.2
0	67	81.7	Missing	3	
1	12	14.6	Subgroups		
2	3	3.7	HR+/HER2−/G1–G2	26	38.8
Missing	6		HR+/HER2−/G3	14	20.9
Treatment setting			HR+/HER2+	11	16.4
Neoadjuvant	32	36.4	HR−/HER2+	6	9.0
Adjuvant	45	51.1	TNBC	10	14.9
Metastatic	11	12.5	Missing	21	

BMI body mass index, *c/p* clinical/pathological, *M* metastases, *HR* hormone receptor, *G* grade, *TNBC* triple negative breast cancer

[a]Overweight/obesity, hypertension, dyslipidemia or diabetes

[b]Medications taken to treat underlying conditions (i.e., thyroid hormones, antihypertensives, anti-hyperlipidemia therapy…)

($n=3$), enterocolitis ($n=2$), gastrointestinal perforation ($n=1$), liver failure ($n=2$), renal failure ($n=1$), accident ($n=1$), drug intoxication ($n=1$). For 7 patients, the cause of death could not be identified (sudden deaths). Overall, in 9 (12.5%) patients a disease progression was diagnosed and indicated as the cause of death for 4 patients. No statistically significant difference was observed between death SOC and type of center ($p=0.502$). When considering the most common death SOCs, no statistically significant difference was found between hospitals or in practices (infections and infestations 36.4% vs 45.5%, $p=0.460$; respiratory, thoracic and mediastinal disorders 18.2% vs 13.6%, $p=0.752$; cardiac disorders 16.7% vs 9.1%, $p=0.504$). The use of dose-dense chemotherapy was associated with an increased incidence of

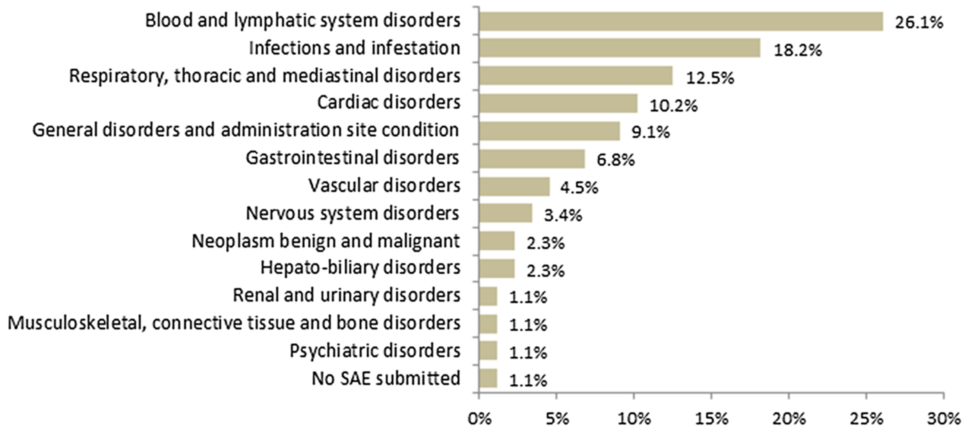

Fig. 2 Distribution per SOC of the last SAE submitted before death according to the WHO-System Organ Class-Body system. *SAE* serious adverse event, *SOC* system organ class, *WHO* World Health Organization

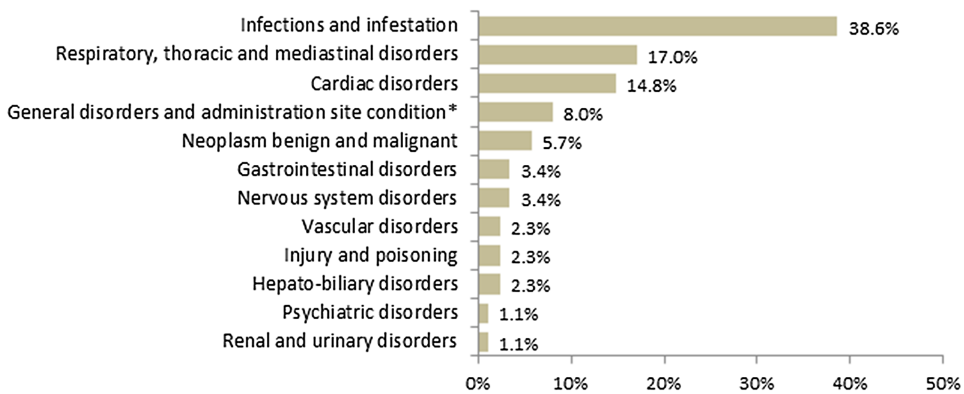

Fig. 3 Distribution per SOC of the cause of death according to the WHO-System Organ Class-Body system. *Death unknown. *SAE* serious adverse event, *SOC* system organ class, *WHO* World Health Organization

death due to infection (standard dose vs dose-dense chemotherapy 60.0% vs 30.2%, $p=0.015$), but not due to cardiac disorders (8.0% vs 17.5% $p=0.334$).

Autopsy rate

The overall autopsy rate was 13.6% ($n=12$). In two patients, the autopsy confirmed the initially supposed cause of death, while in 9 patients it led to the definition of the death cause. In one case, the autopsy result was not available. While for seven patients the cause of death was unknown, an autopsy was only performed in one of them. This death was initially attributed to the study medication, after autopsy, however, it became clear that the patient died due to tumor progression with massive hemangiosis.

Relationship between death and anticancer treatment

Deaths during clinical studies occurred mainly on treatment, in particular within the first 4 cycles (55.7%) (Table 2). The majority of fatal events happened when an investigational treatment/schedule was given (66.7%) and fatalities were slightly more common when an anthracycline–taxane (AT)-based combination was administered (51.1%). Anti-HER2 or anti-VEGF (vascular endothelial growth factor)-targeted therapies were involved in 18.2% of the fatal events. The use of an investigational drug or of a new drug combination compared to the use of a conventional well-known drug or drug combination did not influence the time (i.e., cycle) when death occurred ($p=0.236$). When the death occurred within the first 4 cycles (38.8%), as well as during cycles 5–8 (80.0%), the treatment received was mainly AT based, if after cycle 8, mainly other therapy (44.4%) or hormone treatment alone (33.3%) ($p<0.001$). A relationship between death and anticancer treatment received was declared by the investigator in 27.3% of the cases, not related in 40.9% and unknown in 31.8%. The decision was neither influenced by the type of treatment arm ($p=0.460$), nor by treatment setting ($p=0.125$), nor by the number of comorbidities ($p=0.093$). In patients who took more than 3 concomitant medications the relationship was mainly defined as not related (60.9%), in patients who took 1–3 or no concomitant medication the relationship was mainly defined as unknown (31.4% if 1–3 drugs, 34.5% if no drug) ($p=0.022$). Relatedness to chemotherapy was declared mainly when an AT-based chemotherapy was given (66.7%, $p=0.006$). After re-assessment of patients' death narratives, a relationship

Table 2 Cycle, treatment and relationship of the event with the study drug

Treatment-related variables	Patients (N = 88)	
	n	Valid (%)
Cycle when death occurred		
1–4	49	55.7
5–8	30	34.1
> 8[a]	9	10.2
Median (range)	4 [1–21]	
Standard or investigational arm		
Standard treatment	28	33.3
Investigational treatment	56	66.7
Missing[b]	4	
Chemotherapy density		
Standard	63	71.6
Dose-dense	25	28.4
Treatment received till death		
Anthracyline-based	8	9.1
Taxane-based	15	17.1
Anthracycline- and taxane-based	45	51.1
Hormone treatment alone	3	3.4
Other[c]	17	19.3
Targeted therapy		
Anti-HER2/anti-VEGF therapy	16	18.2
No targeted agent	72	81.8
Last treatment received before death		
Anthracycline based	12	13.6
Taxane-based	36	40.9
Anthracycline- and taxane based	14	15.9
Hormone treatment alone	4	4.5
Other[d]	22	25.0
Relation to study drug assessed by investigator		
Not related	36	40.9
Related	24	27.3
Unknown	28	31.8
Relation to study drug assessed by medical reviewer		
Not related	38	43.2
Related	50	56.8

EOT end of treatment, *VEGF* vascular endothelial growth factor

[a]two patients died after the end of treatment, but within 30 days after EOT

[b]n = 4 unknown (patients included into double-blind placebo controlled study)

[c]n = 8 capecitabine with/without bisphosphonate, n = 1 CMF (cyclophosphamide, methotrexate, 5-fluorouracil), n = 1 bisphosphonate alone, n = 2 eribulin, n = 4 unknown (patients included into double-blind placebo controlled study)

[d]n = 1 bevacizumab, n = 4 biphosphonate alone, n = 6 capecitabine with/without biphosphonate, n = 3 cyclophosphamide, n = 1 CMF, n = 2 eribulin and lapatinib, n = 1 lapatinib, n = 4 unknown

with the study medication was defined in 56.8% of the cases and no relationship in 43.2%.

Discussion

Fatal events in clinical trials are rare but represent a key ethical issue. In our analysis, we showed that deaths during study occurred mostly in elderly patients, patients with a high BMI, comorbidities, CRFs, advanced disease and patients taking concomitant medications. Infection was the main cause leading to patients' deaths as well as one of the most frequent last SAEs submitted before death, being less frequent only with respect to FN and severe neutropenia. Both the tumor and chemotherapy compromise the immune system, predisposing to infection. Fatal events related to infection could be reduced through a careful assessment of patients' RFs and the early use of diagnostic procedures and treatment. Online tools can help to classify a patient's risk. Moreover, patient education is essential to help caregivers to set up appropriate treatment measures in due time [21]. MASCC Risk Index can be used to classify patient's risk for serious complications of FN, including death [22]. Furthermore, the use of antibiotic prophylaxis might help to reduce the incidence of fever, infections and all-cause mortality [23]. Age is the most important RF for hematological toxicities, as the bone marrow reserves decrease with age, increasing the probability of myelosuppression. In a pooled analysis of 4 randomized (neo)adjuvant trials, including A-based chemotherapy, the per-patient incidence of grade 3–4 hematological AEs increased with age, regardless of the chemotherapy regimen administered [24]. The prophylactic use of G-CSF can prevent the higher rate of hematological AEs and provide protection against potentially fatal complications for patients at risk for FN. Moreover, prevention of FN, seen especially during the first treatment cycles, is of major importance also to avoid treatment reductions and dose delays that could adversely affect tumor control [25]. Moreover, in elderly patients, the decreased renal function can increase the risk of toxicities and the increased occurrence of cardio- and neurotoxicity can further complicate treatment [26]. Taken together all these issues translate into the increased incidence of deaths observed in our study among elderly patients. Elderly patients are under-represented in clinical studies. Increasing their enrollment is a major issue, to better define cancer treatment recommendations in this patient population and to determine the most effective supportive therapy. In our analysis, cardiovascular events are the second most common cause of death, likely due to the fact that more than half of the patients were treated with A or AT combinations and around 20% received anti-HER2/anti-VEGF-targeted treatment, known to increase the risk for cardiac events, especially in patients with RFs.

Notably, two-thirds of patients in our cohort had 1–2 CRFs. This not only underlines the importance of a wise choice of inclusion and exclusion criteria in clinical trials, but also the responsibility of investigators to choose the right patients for the right trial irrespective of the possibility of inclusion of the patient. Patients with cancer have a higher risk of developing venous thromboembolism (VTE) as compared to patients without cancer that is a sevenfold greater chance if they received chemotherapy [27]. Being the third most common cause of death in our patient collective, the correct application of guidelines and of predictive models for chemotherapy-associated VTE is recommended to improve prophylaxis and treatment [28]. Advanced disease and high BMI are two additional RFs associated with fatal events in our analysis. Patients with advanced BC are more likely to experience treatment-related toxicities due to the debilitating impact of the cancer itself and due to the cumulative toxicities of the previous chemotherapy lines. Not surprisingly, drug intake is a further RF for fatal events, probably linked to comorbidities as well. Overweight and obesity are also associated with an increased risk of a wide range of chronic diseases [29]. Even though a meta-analysis showed that obese patients receiving chemotherapy based on actual body weight experience similar or lower rates of toxic effects compared with normal weight patients [30], we previously demonstrated that obese patients receiving dose-dense AT-containing chemotherapy according to actual body weight experienced a higher rate of severe toxicities [31]. Moreover, excess body weight is associated with an increased risk of cancer as well as non-cancer-related deaths [32]. All these points may lead to the increased risk of death shown in our analysis for patients with high BMI. We have further investigated the role of dose-dense chemotherapy. In line with the recently published EBCTCG meta-analysis [33], dose-dense or dose-intensified regimen seems not to be associated with higher mortality compared to standard dose chemotherapy in our analysis. Interestingly, in our cohort of patients who died during clinical trials, we found that the use of a dose-dense chemotherapy regimen was associated with an increased incidence of mortality due to infection. This aspect was not reported by the EBCTCG meta-analysis, potentially because, as pointed out by the authors, the causes of fatal events were not sufficiently documented. However, in accordance with the EBCTCG work, no difference was found for mortality due to cardiac events.

The causality assessment for a non-specific event such as death may be challenging. On the one hand, it is common for physicians to confuse the underlying cause of death with mechanism of death. On the other hand, definition of causality may suffer from a serious bias of attribution, especially for patients enrolled in clinical trials and/or with multiple comorbidities. Furthermore, many clinicians feel uncomfortable to implicate a drug that they do not frequently use in clinical practice and that they are responsible to monitor [34], especially in case of new investigational drugs for which the safety profile is not yet well established. It is noteworthy that two-thirds of fatal events occurred in the investigational arm and that for more than one-third the relationship with the study drug was not declared by the investigators. After re-assessment, more than half of the cases were attributed to the study medication. Moreover, there is no standard assessment for cause of death, except for autopsy, which can lead to a change of the attribution of death to an entirely different etiology category in about 29% of cases [35]. Nevertheless, this examination is infrequently performed. In our study, the autopsy rate was 13%. In 81% of the cases, the procedure helped to clarify the initially supposed cause of death. Surprisingly, only in 1 out of 7 patients with an unknown cause of death an autopsy was performed, but that could reflect the refusal of relatives, particularly in Germany, to give their consent for the procedure. Despite death during study being a rare event, the great number of trials included here enables us to obtain information on fatal events in a large cohort of patients. All data were prospectively captured. This is the first study that systematically analyzed fatal events in clinical BC trials. The medical revision of all death narratives enabled us to obtain a careful re-assessment of the relationship between the fatal events and the study medication. Moreover, the autopsy rate has never been reported for patients who died during BC treatment. Our analyzed studies are multicentric and partly international which makes the cohort very heterogeneous. Therefore, the death rate might have been influenced by the different approaches in prevention and management of SAEs and the treatment of complications leading to fatal events. Moreover, the autopsy rate might have been influenced by local habits and regulations. Due to the very small number of patients who died during clinical studies compared to the cohort of patients who did not, a formal comparative analysis of these two cohorts was not feasible as the statistical power would have been too low. Therefore, we performed a merely descriptive analysis in the cohort of patients with a fatal event. The retrospective nature of the investigation only allows us to generate hypotheses on factors that could enhance the risk of dying during clinical trials. In conclusion, we showed that death on study treatment was mainly related to infections and occurred mainly in elderly patients, in patients with advanced disease, high BMI, underlying comorbidities and CRFs, and taking concomitant medications. While the identified risk factors might also apply to patients treated outside the clinical trials, it is crucial that, if considered for study participation, these patients need more careful monitoring due to their higher risk of death. In particular, patients with metastatic disease need special attention being at higher risk of complications and death. To ensure patient's safety, it is fundamental that investigators adhere to study protocol guidelines and promptly report SAEs and fatal events. Furthermore, for the safeguard of future patients involved in clinical trials and the improvement of clinical trial designs, an analysis of fatal events should be part of the main publication.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest related to this work.

Statement of ethics All patients included in the studies analyzed have provided written informed consent for study participation and data collection. All the analyzed trials were approved by the relevant ethics committees.

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