ORIGINAL RESEARCH ARTICLE

Adverse Drug Reactions with HER2-Positive Breast Cancer Treatment: An Analysis from the Italian Pharmacovigilance Database

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Abstract

Background Anti-HER2 therapy has evolved in the last years and an important role in this transformation was that of monoclonal antibodies and tyrosine kinase inhibitors. Considering their extended use in clinical practice, some toxicity problems have been highlighted around these drugs.

Objective To analyze the onset of adverse drug reactions (ADRs) related to the use of HER2-positive breast cancer treatments through a spontaneous reporting system (SRS) database.

Methods All ADR reports having as suspected drug trastuzumab, pertuzumab, lapatinib, or trastuzumab emtansine (TDM-1), recorded into the Report Reazioni Avverse dei Medicinali (RAM) system database for national data and into the Italian SRS database for Sicilian data and collected from 2006 to 2020 have been evaluated. A descriptive analysis of basal demographic and drug-related characteristics was performed. A case-by-case methodology was conducted paying particular attention to the serious ADR reports collected in Sicily, focusing on type of seriousness, age, sex, concomitant drugs, comorbidities, time to onset (TTO), and time to resolution (TTR).

Results Of the 3609 Italian reports, 65.6% were related to trastuzumab ($n = 2367$), followed by pertuzumab, TDM-1, and lapatinib. Almost all reports occurred in female patients (94.3%) and were most frequent in the age group 18–65 years (69.6%). A higher number of cases were related to general disorders and administration site conditions ($n = 1079$; 29.9%), gastrointestinal disorders ($n = 1037$; 28.7%), skin disorders ($n = 821$; 22.7%), and blood disorders ($n = 599$; 16.6%). Cases involving trastuzumab and pertuzumab mainly reported general disorders ($n = 788$; 33.3% and $n = 194$; 32.1%, respectively) while more than half of the reports associated with lapatinib were related to gastrointestinal ($n = 184$; 59.7%) and skin diseases ($n = 146$; 47.4%). Regarding TDM-1, 40% of reports had at least one ADR belonging to blood and lymphatic system disorders. The case-by-case assessment of Sicilian ADR reports showed that 40 cases were serious (33.3%), with a median TTO of 37 (6–97) days. Serious ADR reports mainly involved the onset of thrombocytopenia ($n = 8$; 20.0%), diarrhea ($n = 6$; 15.0%), asthenia and cardiac failure (both with $n = 5$; 12.5%), vomiting, hypersensitivity, and ejection fraction decreased (all with $n = 4$; 10.0%) and stomatitis ($n = 3$; 7.5%).

Conclusion This study is fundamentally consistent with results from the literature. Given the serious clinical condition of breast cancer and taking into account the importance of preventing some clinically relevant ADRs related to the use of anti-HER2 therapy, further analyses are essential to better describe the safety profile of these target therapies.

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1 Introduction

Breast cancer was the most commonly diagnosed type of cancer worldwide in 2020, accounting for approximately 2.3 million new cases [1]. Moreover, it is also considered one of the main causes of cancer death in women. In recent years, the incidence of breast tumors increased considerably due to screening and surveillance programs and early identification, which resulted in a greater number of new diagnoses especially at early-stage cancer [2, 3]. In 6–7% of cases the neoplasm occurs in a metastatic form. About

Key Points

The importance of the Spontaneous Reporting System (SRS) database for the identification of adverse drug reactions (ADRs) related to the use of human epidermal growth factor receptor type 2 (HER2)-positive breast cancer treatments is shown in the present study.

A higher frequency of cardiac disorders, palmar-plantar erythrodysesthesia (PPE) syndrome, thrombocytopenia, and infusion-related reactions was noticed for anti-HER2 therapy.

The collaboration between oncologists and pharmacologists plays an essential role in early identification of ADRs, informing patients and improving their awareness to report any new symptoms or worsening of a pre-existing condition as soon as possible during anti-HER2 therapy.

12–15% of cases of early breast cancer (EBC) and 20–30% of cases of metastatic breast cancer (MBC) are characterized by protein overexpression or gene amplification of the human epidermal growth factor receptor type 2 (HER2) [4, 5]. HER2 is a member of the HER family with a tyrosine kinase activity. Homo- or heterodimerization leads to the autophosphorylation of tyrosine residues into the cytoplasmic domain with the subsequent activation of different signaling pathways that stimulate cell proliferation, migration, invasion, angiogenesis, and survival [6, 7]. These five mechanisms belong to the "Hallmarks of cancer" and are crucial for tumor growth [8].

The treatment of HER2-positive breast cancer has radically changed over the last 20 years. Before the introduction into the market of the HER2-targeted monoclonal antibodies, HER2-positive breast cancer was characterized by lower survival and high recurrence rates [5]. Today, the evolution of standard of care involves (neo) adjuvant and metastatic therapy, including the associated use of novel therapies [9, 10]. The first therapy approved for HER2-positive MBC included the use of trastuzumab or pertuzumab in association with chemotherapeutic agents such as taxanes and vinca alkaloids. In a recent clinical trial, it has been shown that the use of monoclonal antibodies with chemotherapy achieves a better response in terms of survival than chemotherapy alone [11]. These drugs have also been approved over time for the treatment of EBC. Moreover, in 2013 the drug-antibody conjugate trastuzumab emtansine (TDM-1) was approved for the adjuvant treatment of adult patients with HER2-positive EBC who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy and for unresectable locally advanced breast cancer or MBC who previously received trastuzumab and a taxane, separately or in combination [12]. In recent years, two tyrosine kinase inhibitors, lapatinib and neratinib, have been approved for breast cancer treatment: lapatinib for progressive or advanced breast cancer in combination with capecitabine, trastuzumab or aromatase inhibitors, and neratinib for HER2-positive EBC [13, 14].

Some toxicity problems have been highlighted in clinical trials and post-marketing studies. Cardiac toxicity is the main side effect of anti-HER2 monoclonal antibodies with an incidence ranging from 0.7% to 12.0% [15, 16]. Allergic reactions may also occur in approximately 40% of patients during or immediately after the infusion, characterized by a real cytokine release syndrome (fever, chills, hypotension, dyspnea, skin rash) [11, 17]. The monoclonal antibody pertuzumab prevents heterodimerization of the EGFR receptor and ErB2, and can lead to the onset of diarrhea (in from 45% to 72% of cases) [18–21]. Anti-HER2 drugs, particularly trastuzumab, TDM-1, and lapatinib, have also been associated with the onset of interstitial lung disease with an overall incidence of 2.4% that reached 21.4% with trastuzumab [22]. Treatment with tyrosine kinase inhibitors can lead to hepatotoxicity, diarrhea, neutropenia, leukopenia, and severe skin reactions such as palmar-plantar erythrodysesthesia syndrome (PPE) (more than 25%) [23–25].

Given the clinical relevance of the adverse effects that have appeared in clinical trials and considering the recent market introduction of new anti-HER2 therapy and its extensive use in clinical practice, it may be useful to identify new and unexpected adverse drug reactions (ADRs) that may arise during the use of these drugs in the real world. In view of the above findings, the aim of this study was to evaluate ADRs related to HER2-positive breast cancer treatment and reported into the Italian Spontaneous Reporting System (SRS) database focusing on the Sicilian region.

2 Methods

2.1 Data Source

The Italian SRS database is managed by the Italian Medicines Agency (AIFA), which works closely with Pharmacovigilance Regional Centers (PRCs) for every possible safety signal detection. The SRS database consists of all ADR reports sent by healthcare professionals and citizens or by the Marketing Authorisation Holders (MAHs) at national level. Each ADR report collected into the Italian SRS database includes detailed information on patient (e.g., name/surname initials, age, gender), description of ADRs (e.g., time to onset (TTO) and time to recovery (TTR), seriousness, outcome, dechallenge, rechallenge), suspected and concomitant drugs (e.g., dosage, frequency and route of

administration, therapeutic indication), clinical history, and comorbidities. Drug classification is carried out using the Anatomical Therapeutic Chemical (ATC) classification (WHOCC), while suspected ADRs are categorized according to the Medical Dictionary for Regulatory Activities (MedDRA®).

Each single PRC, such as the Sicilian Pharmacovigilance Center, operates through a National Pharmacovigilance network to support the pharmacovigilance system with full access to specific regional data collected in Italian SRS. Regarding overall national data, the AIFA has created an online open-access system (Report Reazioni Avverse dei Medicinali, RAM) that provides an overview of all Italian ADR reports collected into the Italian SRS database and allows access to aggregated data relating to Italian reports recorded since 2002, organised by year of entry in the Italian SRS database. Only the following information are available from the RAM system: information about the total number of reports recorded broken down by year; the number and percentage of reports by seriousness; the number and percentage of reports by sex and age group of subjects who have experienced the ADR(s); the number and percentage of aggregated ADRs classified by System Organ Class (SOC) and Preferred Term (PT).

In accordance with the seriousness, ADRs can be divided into serious and not serious. An ADR is classified as serious when it proves to be life-threatening or fatal, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is another important medical event (IME) [26].

2.2 Case Definition and Selection Criteria

A retrospective observational study was conducted between January 2006 and December 2020 to evaluate the safety of drugs approved for HER2-positive breast cancer in a real-world setting. First of all, we included all ADR reports from the RAM system for national data in aggregated form and from the SRS database for Sicilian data in detailed form. The selection of data concerned all reports having at least one of the following drugs registered as suspected: trastuzumab (L01XC03), trastuzumab emtansine (L01XC14), pertuzumab (L01XC13), and lapatinib (L01EH01). Trastuzumab deruxtecan and neratinib were not considered due to their recent authorization onto the Italian market. Literature and duplicate cases were excluded from analysis of Sicilian data, as well as reports with trastuzumab having as indication metastatic gastric cancer.

In detail, the analysis was performed at the case level and reports containing more than one ADR were counted only once.

2.3 Data Analysis

A descriptive analysis of regional data and aggregate national reports of study drugs was conducted to evaluate the basal demographic and drug-related characteristics. Specifically, we performed analyses by year, sex, age, seriousness, and outcome. Furthermore, ADRs were analyzed taking into account the MedDRA® System Organ Class (SOC) and Preferred Term (PT) grouping the same ADR reports into the equivalent SOC and clustering the synonymous PTs of the same clinical condition under one term (see Online Supplementary Material S1).

We also performed a case-by-case assessment paying particular attention to the serious ADR reports collected in the Sicilian region focusing on type of seriousness, age, sex, concomitant drugs, comorbidities, TTO, and TTR. TTO and TTR were expressed in days and were calculated considering the time elapsed between the start of the drug use and the onset of the ADR and the time elapsed between the onset and the resolution of ADR where possible, respectively. Moreover, the Naranjo algorithm was used to evaluate the potential causal relationship between the serious clinical event and the suspected drug. Each ADR can be classified as: high probable (score ≥ 9), probable (scores 5–8), possible (scores 1–4), or doubtful (score ≤ 0) [27]. Absolute and relative frequencies were evaluated for categorical variables, while medians with interquartile intervals (Q1–Q3) were used to evaluate continuous variables.

ADRs were defined as expected for each drug if reported into the Summary of Product Characteristics (SPCs) available at the time of the analysis by the European Medicines Agency (EMA) website [28].

3 Results

This study included all ADRs collected between 1 January 2006 and 31 December 2020. A total of 3609 reports, having as suspected drugs at least one of anti-HER2 medications, were collected in the SRS and listed in the RAM system database. Specifically, 65.6% were related to the active substance trastuzumab ($n = 2367$), followed by pertuzumab ($n = 604$), TDM-1 ($n = 330$), and lapatinib ($n = 308$). With regard to trastuzumab-related reports, 1986 (83.9%) reported the trade name of the medicinal product. More than 88% of reports were associated with the originator trastuzumab Herceptin® ($n = 1753$) and only 233 reports (11.7%) concerned trastuzumab biosimilars (in detail: Kanjinty®, $n = 83$, 4.2%; Herzuma®, $n = 77$, 3.9%; Ontruzant®, $n = 68$, 3.4%; Ogivri®, $n = 4$, 0.2%; Trazimera®, $n = 1$; 0.1%). The reporting of anti-HER2 drug-related ADRs gradually increased over the years until 2018, with an important peak in 2019; trastuzumab showed a similar trend in the considered reports

over the years and a major increase was highlighted for pertuzumab since 2015 (Fig. 1).

Demographic characteristics including seriousness, sex, and age group are described in Table 1. Regarding the seriousness, ADRs were mainly not serious ($n = 2490$; 69.0%). Almost all the reports occurred in female patients (94.3%) and were more frequently in the age group 18–65 years (69.6%) (Table 1).

The analysis of ADRs underlined a higher number of cases related to the SOC "general disorders and administration site conditions" ($n = 1079$; 29.9%) mainly focusing on asthenia and "gastrointestinal disorders" ($n = 1037$; 28.7%) mostly related to diarrhea. These SOCs were followed by "skin and subcutaneous tissue disorders" ($n = 821$; 22.7%) such as rash and "blood and lymphatic system disorders" ($n = 599$; 16.6%) including neutropenia and thrombocytopenia. Trastuzumab and pertuzumab cases mostly reported general disorders and administration site conditions ($n = 788$; 33.3% and $n = 194$; 32.1%, respectively) while about half of reports associated with lapatinib involved gastrointestinal disorders ($n = 184$; 59.7%) and skin diseases ($n = 146$; 47.4%). Regarding TDM-1, 40% of reports had at least one ADR belonging to the SOC blood and lymphatic system disorders (Table 2). Trastuzumab as the originator was mostly reported for the onset of diarrhea ($n = 127$; 7.2%) neutropenia ($n = 113$; 6.5%), asthenia ($n = 103$; 5.9%), pyrexia ($n = 94$; 5.4%), and decreased ejection fraction ($n = 90$; 5.1%). Trastuzumab biosimilars were mainly reported for the onset

of chills ($n = 54$; 23.2%), pyrexia ($n = 28$; 12.0%), diarrhea ($n = 26$; 11.2%), and asthenia ($n = 25$; 10.7%).

The Italian SRS database contains 28,383 reports related to Sicily and collected from 2001 to 2020; of them, 126 had as suspected drug at least one anti-HER2 therapy (0.4%). In accordance with the exclusion criteria, 120 reports were considered for this analysis, of which only 11 cases had pertuzumab and trastuzumab reported concomitantly as suspected (9.2%) (Fig. 2). Trastuzumab was the most reported active substance ($n = 59$; 49.2%) followed by lapatinib ($n = 27$; 22.5%), TDM-1 ($n = 18$; 15.0%), and pertuzumab ($n = 5$; 4.2%). Considering trastuzumab, only nine ADR reports were related to biosimilar formulations (15.3% of the total number of trastuzumab-related reports) and 14 cases reported trastuzumab administered subcutaneously as the suspected drug (23.7% of the total number of trastuzumab-related reports). An association of two or more antineoplastic agents was reported in 27 reports (22.5%) and mostly included lapatinib plus capecitabine ($n = 9$; 7.5%) and trastuzumab plus pertuzumab plus docetaxel ($n = 6$; 5.0%). The trend almost increased over the years with a peak in 2015 ($n = 34$; 28.3%) and subsequently decreased in later years. Almost all the Sicilian reports involved females ($n = 118$; 98.3%) with a median age of 54 (49–64.3) years. Regarding the characteristics, ADR reports were mostly not serious ($n = 75$; 62.5%), fully recovered ($n = 46$; 38.3%), and reported by a physician ($n = 79$; 65.8%) (Table 3).

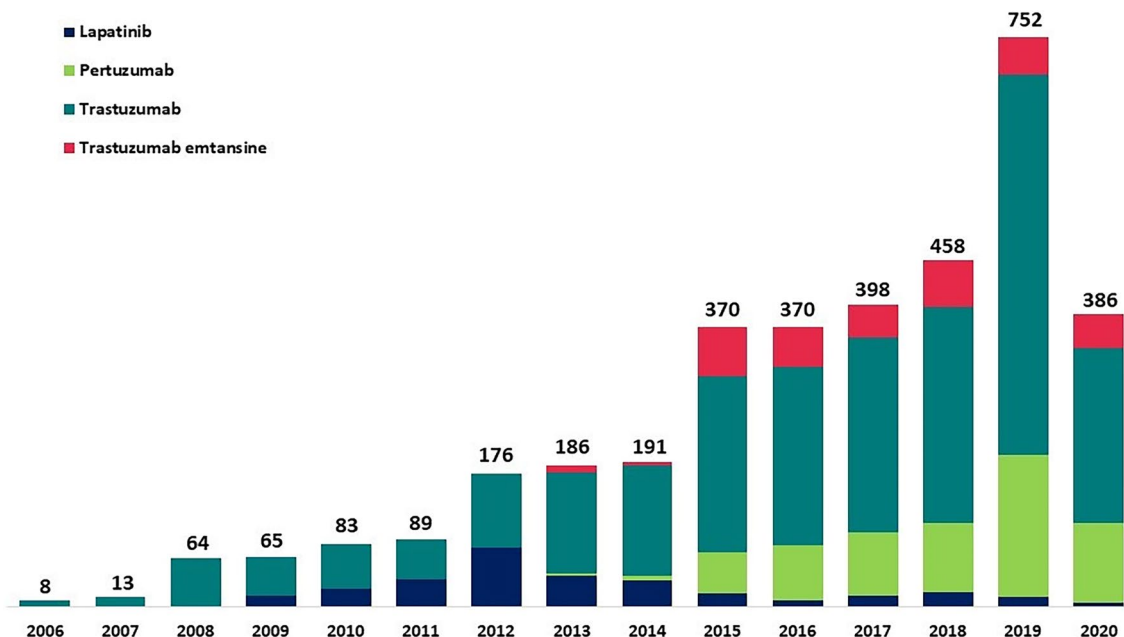ADR classifications of general and administration site disorders and gastrointestinal diseases were the most

Fig. 1 Italian trend of anti-HER2 therapy-related adverse drug reaction (ADR) reports collected into the RAM (Report Reazioni Avverse dei Medicinali) system over the years 2006–2020

Table 1 Descriptions of Italian anti-HER2 therapy-related adverse drug reaction (ADR) reports collected into the RAM (Report Reazioni Avverse dei Medicinali) system from January 2006 to December 2020.

Characteristic, n (%)	Lapatinib ($n = 308$)	Pertuzumab ($n = 604$)	Trastuzumab ($n = 2367$)	TDM-1 ($n = 330$)	Total ($n = 3609$)
Seriousness					
Serious	60 (19.5)	194 (32.1)	712 (30.1)	112 (33.9)	1078 (29.9)
Not serious	245 (79.5)	404 (66.9)	1,632 (68.9)	209 (63.3)	2490 (69.0)
Not available	3 (1.0)	6 (1.0)	23 (1.0)	9 (2.7)	41 (1.1)
Gender					
Male	1 (0.3)	8 (1.3)	167 (7.1)	3 (0.9)	179 (5.0)
Female	305 (99.0)	591 (97.8)	2189 (92.5)	319 (96.7)	3404 (94.3)
Not available	2 (0.6)	5 (0.8)	10 (0.4)	8 (2.4)	25 (0.7)
Age groups, years					
18–65	224 (72.7)	439 (72.7)	1637 (69.2)	210 (63.6)	2510 (69.6)
≥ 66	79 (25.6)	143 (23.7)	655 (27.7)	87 (26.4)	964 (26.7)
Not available	5 (1.6)	22 (3.6)	75 (3.2)	33 (10.0)	135 (3.7)

TDM-1 trastuzumab emtansine

reported ($n = 36$; 30.0% and 28; 23.3%, respectively) followed by cardiac ($n = 18$; 15.0%), skin ($n = 17$; 14.2%), and blood disorders ($n = 14$; 11.7%). Trastuzumab, including biosimilars, was mostly related to general conditions, in particular chills and cardiac disorders involving cardiac failure, while lapatinib was mostly associated with gastrointestinal diseases such as diarrhea and skin disorders including PPE syndrome; half of TDM-1-related ADRs reported blood disorders involving thrombocytopenia; in addition, the five cases of pertuzumab had at least one vascular disorder (Table 4). With regard to trastuzumab administered subcutaneously, seven ADRs concerned cardiac disorders, including heart disease and decreased ejection fraction, while four cases were associated with skin and allergic reactions.

The case-by-case assessment of serious Sicilian ADR reports is shown in Table 5. Of the 120 collected reports, 40 were serious (33.3%) and mostly concerned an IME ($n = 18$; 45.0%) with a median TTO of 37 (6–97) days. The totality involved females with a median age of 59 (50–66) years. Regarding the outcome, ADR reports were mostly improved or fully recovered ($n = 14$; 35.0% and $n = 12$; 30.0%, respectively), with a median TTR of 5 (0–33) days. The causality assessment showed that 21 ADRs were possible (52.5%), while 19 were probable (47.5%). Trastuzumab was the most reported suspected drug ($n = 14$; 35.0%) followed by TDM-1 ($n = 6$; 15.0%) and by the combinations of lapatinib + capecitabine and trastuzumab + pertuzumab (both with $n = 4$; 10.0%). Concomitant drugs mostly were paclitaxel and docetaxel ($n = 5$; 12.5% and $n = 2$; 5.0%, respectively). Serious ADR reports mainly involved blood, gastrointestinal, general, and cardiac disorders, especially with the onset of thrombocytopenia ($n = 8$; 20.0%), diarrhea ($n = 6$; 15.0%), asthenia and cardiac failure (both with $n = 5$; 12.5%), vomiting, hypersensitivity and decreased

ejection fraction (all with $n = 4$; 10.0%), and stomatitis ($n = 3$: 7.5%) (Table 5). Trastuzumab-related cardiac events had a median TTO of 103 (70.3–259.8) days. Looking at each single life-threatening event, ADR reports were mostly related to pertuzumab and trastuzumab. Specifically, cardiac failure and infusion-related reactions with hypersensitivity were more frequent.

4 Discussion

This study aimed to identify anti-HER2 therapy-related ADRs collected in the RAM system database for national data and in the SRS database for Sicilian data. Breast cancer in men is a rare disease, particularly in the metastatic setting, thus a higher prevalence of ADR reports has been recorded in women in accordance with other studies [29, 30]. Literature data confirmed patients' demographic characteristics, especially median age [31, 32], sex differences [33], and seriousness [34, 35]. No substantial differences were noted between national and Sicilian data. The 0.4% of ADRs collected into the Italian SRS database and coming from Sicily were related to anti-HER2 therapy. Trastuzumab shows the highest number of ADR reports, and this is presumably due to being on the market for the longest time, to entry into the Registries and web-based therapeutic plans of medicines subjected to AIFA monitoring from January 2011, and to the introduction of biosimilars from 2017 [36]. Moreover, pertuzumab-related ADRs increased in 2015 despite its authorization in March 2013; this could be explained by the greatest increase in consumption registered in 2015 compared to 2014, but also because pertuzumab was added into the AIFA registries from July 2014 [37].

Table 2 Descriptions of adverse drug reactions associated with HER2-positive breast cancer treatment and reported into the RAM (Report Reazioni Avverse dei Medicinali) system

Adverse drug reaction, n (%)[a]	Lapatinib (n = 308)	Pertuzumab (n = 604)	Trastuzumab (n = 2367)	TDM-1 (n = 330)	Total (n = 3609)
General disorders and administration site conditions	50 (16.2)	194 (32.1)	788 (33.3)	82 (2.8)	1079 (29.9)
Asthenia	24 (7.8)	56 (9.3)	173 (7.3)	23 (7.0)	276 (7 6)
Pyrexia	5 (1.6)	28 (4.6)	131 (5.5)	15 (4.5)	179 (5.0)
Chills		14 (2.3)	154 (6.5)	5 (1.5)	173 (4.8)
Hyperpyrexia	1 (0.3)	6 (1.0)	38 (1.6)	3 (0.9)	48 (1.3)
Gastrointestinal disorders	184 (59.7)	177 (29.3)	627 (26.5)	49 (14.8)	1037 (28.7)
Diarrhea	111 (36.0)	79 (13.1)	175 (7.4)	8 (2.4)	373 (10.3)
Nausea	16 (5.2)	23 (3.8)	114 (4.8)	8 (2.4)	161 (4.5)
Vomiting	19 (6.2)	15 (2.5)	88 (3.7)	5 (1.5)	127 (3.5)
Abdominal pain	10 (3.2)	15 (2.5)	70 (3.0)	5 (1.5)	100 (2.8)
Skin and subcutaneous tissue disorders	146 (47.4)	172 (28.5)	467 (19.7)	36 (10.9)	821 (22.7)
Rash	63 (20.5)	52 (8.6)	152 (6.4)	12 (3.6)	279 (7.7)
Pruritus	6 (1.9)	47 (7.8)	93 (3.9)	7 (2.1)	153 (4.2)
Alopecia		15 (2.5)	38 (1.6)	2 (0.6)	55 (1.5)
Palmar-plantar erythrodysesthesia syndrome	26 (8.4)	1 (0.2)	4 (0.2)	1 (0.3)	32 (0.9)
Blood and lymphatic system disorders	11 (3.6)	89 (14.7)	367 (15.5)	132 (40.0)	599 (16.6)
Neutropenia	4 (1.3)	32 (5.3)	160 (6.8)	21 (6.4)	217 (6.0)
Thrombocytopenia	2 (0.6)	9 (1.5)	62 (2.6)	88 (26.7)	161 (4.5)
Anemia	4 (1.3)	28 (4.6)	88 (3.7)	11 (3.3)	131 (3.6)
Leukopenia		11 (1.8)	41 (1.7)	5 (1.5)	57 (1.6)
Nervous system disorders	13 (4.2)	82 (13.6)	367 (15.5)	31 (9.4)	493 (13.7)
Paresthesia	3 (1.0)	28 (4.6)	97 (4.1)	8 (2.4)	136 (3.8)
Tremor		10 (1.7)	96 (4.1)	1 (0.3)	107 (3.0)
Headache	1 (0.3)	10 (1.7)	44 (1.9)	5 (1.5)	60 (1.7)
Dysgeusia		8 (1.3)	33 (1.4)	1 (0.3)	42 (1.2)
Respiratory, thoracic, and mediastinal disorders	10 (3.2)	94 (15.6)	314 (13.3)	36 (10.9)	454 (12.6)
Dyspnea	4 (1.3)	31 (5.1)	117 (4.9)	3 (0.9)	155 (4.3)
Epistaxis	3 (1.0)	11 (1.8)	36 (1.5)	14 (4.2)	64 (1.8)
Cough	1 (0.3)	11 (1.8)	28 (1.2)	7 (2.1)	47 (1.3)
Bronchospasm		7 (1.2)	21 (0.9)		28 (0.8)
Cardiac disorders	3 (1.0)	45 (7.5)	254 (10.7)	10 (3.0)	312 (8.6)
Cardiac failure		6 (1.0)	64 (2.7)		70 (1.9)
Tachycardia	1 (0.3)	12 (2.0)	43 (1.8)	2 (0.6)	58 (1.6)
Cardiotoxicity		2 (0.3)	22 (0.9)	4 (1.2)	28 (0.8)
Palpitations		5 (0.8)	16 (0.7)	1 (0.3)	22 (0.6)
Investigations	24 (7.8)	49 (8.1)	194 (8.2)	35 (10.6)	253 (7.0)
Ejection fraction decreased	4 (1.3)	23 (3.8)	107 (4.5)	9 (2.7)	143 (4.0)
Oxygen saturation decreased		7 (1.2)	12 (0.5)		19 (0.5)
Alanine aminotransferase increased		2 (0.3)	2 (0.1)	3 (0.9)	7 (0.2)
Aspartate aminotransferase increased	1 (0.3)	1 (0.2)	1 (0.0)	4 (1.2)	7 (0.2)
Musculoskeletal and connective tissue disorders	3 (1.0)	48 (7.9)	201 (8.5)	19 (5.8)	271 (7.5)
Arthralgia	2 (0.6)	8 (1.3)	52 (2.2)	3 (0.9)	65 (1.8)
Myalgia		7 (1.2)	38 (1.6)	3 (0.9)	48 (1.3)
Back pain		9 (1.5)	25 (1.1)	2 (0.6)	36 (1.0)
Pain in extremity		4 (0.7)	27 (1.1)	2 (0.6)	33 (0.9)

Table 2 (continued)

Adverse drug reaction, n (%)[a]	Lapatinib (n = 308)	Pertuzumab (n = 604)	Trastuzumab (n = 2367)	TDM-1 (n = 330)	Total (n = 3609)
Vascular disorders	9 (2.9)	49 (8.1)	152 (6.4)	7 (2.1)	217 (6.0)
Hypotension	3 (1.0)	8 (1.3)	34 (1.4)	1 (0.3)	46 (1.3)
Hypertension		8 (1.3)	35 (1.5)	1 (0.3)	44 (1.2)
Hot flushes		10 (1.7)	30 (1.3)	2 (0.6)	42 (1.2)
Flushing	1 (0.3)	15 (2.5)	24 (1.0)		40 (1.1)
Infections and infestations	23 (7.5)	32 (5.3)	117 (4.9)	10 (3.0)	182 (5.0)
Cystitis		6 (1.0)	18 (0.8)	2 (0.6)	26 (0.7)
Folliculitis	2 (0.6)	3 (0.5)	12 (0.5)		17 (0.5)
Conjunctivitis	1 (0.3)	3 (0.5)	9 (0.4)		13 (0.4)
Influenza		1 (0.2)	12 (0.5)		13 (0.4)
Hepatobiliary disorders	27 (8.8)	15 (2.5)	52 (2.2)	40 (12.1)	172 (4.8)
Hypertransaminasemia	13 (4.2)	15 (2.5)	56 (2.4)	30 (9.1)	114 (3.2)
Hyperbilirubinemia	16 (5.2)	3 (0.5)	10 (0.4)	13 (3.9)	42 (1.2)
Hepatotoxicity	8 (2.6)		2 (0.1)	7 (2.1)	17 (0.5)
Jaundice	2 (0.6)		1 (0.0)	1 (0.3)	4 (0.1)
Metabolism and nutrition disorders	15 (4.9)	19 (3.1)	47 (2.0)	8 (2.4)	89 (2.5)
Appetite decreased	9 (2.9)	7 (1.2)	17 (0.7)	5 (1.5)	38 (1.1)
Hypercalcemia		3 (0.5)	4 (0.2)	1 (0.3)	8 (0.2)
Hyperglycemia		1 (0.2)	5 (0.2)		6 (0.2)
Electrolyte imbalance	1 (0.3)	1 (0.2)	2 (0.1)		4 (0.1)
Injury, poisoning, and procedural complications	4 (1.3)	15 (2.5)	63 (2.7)	3 (0.9)	85 (2.4)
Infusion site reaction		7 (1.2)	51 (2.2)	1 (0.3)	59 (1.6)
Off-label use		2 (0.3)	5 (0.2)		7 (0.2)
Toxicity to various agents		4 (0.7)	3 (0.1)		7 (0.2)
Immune system disorders		11 (1.8)	40 (1.7)	4 (1.2)	55 (1.5)
Hypersensitivity		9 (1.5)	31 (1.3)	3 (0.9)	43 (1.2)
Anaphylactic shock		1 (0.2)	5 (0.2)		6 (0.2)
Anaphylactic reaction			3 (0.1)		3 (0.1)
Neoplasm benign, malignant, and unspecified (incl. cyst and polyps)	2 (0.6)	6 (1.0)	7 (0.3)	3 (0.9)	53 (1.5)
Neoplasm progression	1 (0.3)	18 (3.0)	15 (0.6)	13 (3.9)	47 (1.3)
Metastases to lymph nodes		1 (0.2)	2 (0.1)		3 (0.1)
Psychiatric disorders	1 (0.3)	7 (1.2)	38 (1.6)	1 (0.3)	47 (1.3)
Insomnia		5 (0.8)	14 (0.6)		19 (0.5)
Confusional state	1 (0.3)		5 (0.2)		6 (0.2)
Depression		1 (0.2)	4 (0.2)		5 (0.1)
Agitation			4 (0.2)		4 (0.1)
Eye disorders	3 (1.0)	8 (1.3)	30 (1.3)	3 (0.9)	44 (1.2)
Xerophthalmia		2 (0.3)	6 (0.3)		8 (0.2)
Lacrimation increased		1 (0.2)	5 (0.2)	1 (0.3)	7 (0.2)
Visual impairment		3 (0.5)	4 (0.2)		7 (0.2)
Ocular hyperemia		1 (0.2)	3 (0.1)		4 (0.1)
Renal and urinary disorders	5 (1.6)	5 (0.8)	19 (0.8)	6 (1.8)	35 (1.0)
Dysuria		2 (0.3)	7 (0.3)	3 (0.9)	12 (0.3)
Renal failure	1 (0.3)	1 (0.2)	2 (0.1)		4 (0.1)
Pollakiuria		1 (0.2)	2 (0.1)		3 (0.1)
Ear and labyrinth disorders	2 (0.6)	3 (0.5)	20 (0.8)		25 (0.7)

Table 2 (continued)

Adverse drug reaction, n (%)[a]	Lapatinib ($n = 308$)	Pertuzumab ($n = 604$)	Trastuzumab ($n = 2367$)	TDM-1 ($n = 330$)	Total ($n = 3609$)
Vertigo	2 (0.6)	3 (0.5)	15 (0.6)		20 (0.6)
Reproductive system and breast disorders	1 (0.3)	2 (0.3)	7 (0.3)	1(0.3)	11 (0.3)
Breast pain		1 (0.2)	1 (0.0)		2 (0.1)

TDM-1 trastuzumab emtansine

[a]Only the most reported adverse drug reactions by Preferred Term were described
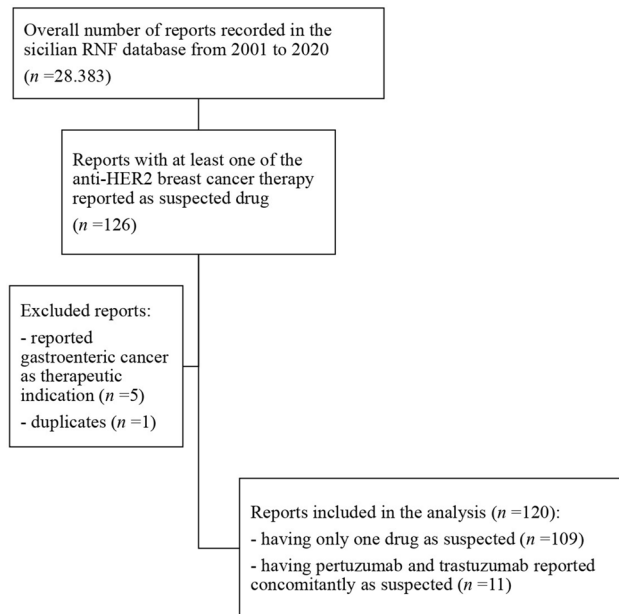
Fig. 2 Flowchart of Sicilian adverse drug reaction (ADR) report selection process. *RNF* Rete Nazionale di Farmacovigilanza, *HER2* human epidermal growth factor receptor type 2

Concerning ADRs, data were expected and confirmed what was reported in the SPCs. This analysis supported the hypothesis that anti-HER2 therapy is potentially related to the onset of gastrointestinal disorders mainly associated with diarrhea as shown in several studies with TDM-1, pertuzumab, and the combination of lapatinib and capecitabine [38, 39]. Lapatinib-induced diarrhea may be related to excessive chloride secretion and reduced sodium absorption. The estimated glomerular filtration rate (EGFR), the target of lapatinib, is a negative regulator of chloride secretion and it reduces the secretion of chlorides in intestinal epithelial cells through a mechanism involving protein kinase C and phosphatidylinositol 3-kinase. For this reason, the EGFR inhibitors can increase chloride secretion by blocking this cycle and consequently induce the discharge of diarrhea, representing a dose-limiting toxicity, particularly when co-administered with capecitabine [40, 41]. Moreover, a higher

number of general disorders, especially concerning asthenia, were reported, as also observed in other literature data [35]. Few cases involved pertuzumab-related vascular disorders, mainly hypertension, as shown in another study [42]. In relation to skin disorders, the onset of PPE syndrome with lapatinib was observed [38, 43]. Lapatinib is associated with a higher risk of PPE syndrome, probably related to the use of lapatinib in association with capecitabine; the metabolism of capecitabine occurs via the enzyme thymidine phosphorylase, which is widely expressed in the palms and is responsible of the massive production of 5-fluorouracil in this area with the consequent onset of PPE [44, 45]. Several published studies have reported a higher prevalence of thrombocytopenia during treatment with TDM-1 [46, 47]. The onset of thrombocytopenia could be explained by the use of TDM-1, which inhibits the megakaryocyte differentiation from hematopoietic stem cells and, consequently, the reduced production of platelets [48]. An association between the use of trastuzumab and the onset of cardiac disorders was seen. Unlike the cardiotoxicity induced by anthracyclines, the cardiac damage from anti-HER2 target therapy is not dose-dependent and is reversible upon discontinuation of treatment [15]. Moreover, it is unrelated to histological changes in cardiomyocytes and, consequently, it does not result in structural damage to the myocardium [49]. The mechanism of trastuzumab-induced cardiotoxicity is not well understood; it is proposed to be linked to the inhibition of the neuregulin-1/ErbB (NR-1/ErbB) signaling pathway [50]. Specifically, trastuzumab was associated with the onset of heart failure [51], and both pertuzumab and trastuzumab were associated with the onset of decreased ejection fraction [52]. Considering other serious ADRs, stomatitis occurred in reports having as suspected/concomitant drugs lapatinib + capecitabine [53] and pertuzumab + trastuzumab in association with docetaxel [54]. Oral mucositis (OM) induced by the anti-HER2 therapy is due to nuclear factor-κB (NF-κB), considered as the main transcriptional mediator of the OM process. NF-κB modulates the transcription of pro-inflammatory cytokines (tumor necrosis factor α, TNF-α; interleukin-6, IL-6; interleukin-1β, IL-1β) and promotes various drug-resistance mechanisms influencing the development

Table 3 Characteristics of Sicilian anti-HER2 therapy-related adverse drug reactions reports in the RNF (Rete Nazionale di Farmacovigilanza) database during the period 2006–2020

Characteristic, n (%)	Total reports (n = 120)
Year of reporting	
2007	2 (1.7)
2008	1 (0.8)
2010	4 (3.3)
2011	6 (5.0)
2012	5 (4.2)
2013	4 (3.3)
2014	16 (13.3)
2015	34 (28.3)
2016	14 (11.7)
2017	13 (10.8)
2018	5 (4.2)
2019	13 (10.8)
2020	3 (2.5)
Gender	
Female	118 (98.3)
Male	1 (0.8)
Missing	1 (0.8)
Median age (Q1–Q3), years	54 (49–64.3)
Seriousness	
Serious	40 (33.3)
Not serious	75 (62.5)
Not available	5 (4.2)
Type of seriousness	
Other medically important conditions	17 (14.2)
Hospitalization/prolongation of a pre-existing hospitalization	14 (11.7)
Life-threatening event	8 (6.7)
Outcome	
Fully recovered	46 (38.3)
Improved	24 (20.0)
Not yet recovered	15 (12.5)
Recovered with sequelae	2 (1.7)
Unknown	33 (27.5)
Reporter	
Physician	79 (65.8)
Other healthcare professional	24 (20.0)
Pharmacist	16 (13.3)
Patient/citizen	1 (0.8)
Therapeutic indication	
HER2+ breast cancer NOS	64 (53.3)
Metastatic breast cancer	37 (30.8)
Stage III breast cancer	3 (2.5)
Stage II breast cancer	2 (1.7)
Recurrent breast cancer	2 (1.7)
Breast cancer in situ	1 (0.8)
Stage I breast cancer	1 (0.8)
Not defined	10 (8.3)

Q1 quartile 1, *Q3* quartile 3, *HER2* human epidermal growth factor receptor type 2, *NOS* not otherwise specified

of OM and the progression of cancer [53]. Moreover, the present study highlighted serious infusion-related reactions characterized by hypersensitivity and related to pertuzumab and trastuzumab; the use of monoclonal antibodies causes a potential immunogenicity [55]. According to the BC Cancer Agency (BCCA) drug assessment report, infusion-related reactions, including symptoms of asthenia, chills, fatigue, and hypersensitivity, have been observed in from 13.0% to 40.0% of patients treated with pertuzumab or trastuzumab [56, 57].

The case-by-case assessment of serious Sicilian ADR reports showed that the median TTO was 37 (6–97) days. The median TTO of trastuzumab-related cardiac ADRs was 103 (70.3–259.8) days corresponding to 3.7 (2.5–9.3) months; this was slightly lower than it was observed in a recent study describing a median TTO of cardiac events of 6.6 (3.4–11.7) months [58]. Considering the causality assessment, the majority of ADRs were possible and probable.

4.1 Strengths and Limitations

This is the first study aimed as an overview of ADR reports related to treatment approved for HER2-positive breast cancer based on the SRS database. The spontaneous reporting of ADRs is one of the most commonly used methods of post-marketing surveillance, especially for drugs with recent approval [59–61]. Additionally, it is an important source of research into events not occurring in the pre-marketing clinical trial when the drug is administered to a relatively small number of selected patients and in controlled conditions. Nevertheless, SRS has some limitations; first, reports from patients and physicians are voluntary, thus they can result in being under-reported and inject heterogeneity into data; second, comorbidities, detailed treatment information, laboratory exam values, and diagnostic tests are not always available [62]. Moreover, the lack of data about the total number of drug-exposed patients (denominator) does not allow establishment of any meaningful conclusion around head-to-head comparison and about the incidence of anti-HER2 therapy-related ADRs [63]. Another important limitation of the present study lies in the fact that a detailed description of ADRs is available only for Sicilian data reported into the Italian SRS database. Indeed, the analysis of Italian data coming from the RAM system is made only in an aggregated form: the RAM system does not allow selection of each single report on the basis of the therapeutic indication only and the use of these drugs for other therapeutic indications cannot be excluded. Furthermore, the analysis of ADRs can potentially be influenced by other antineoplastic drugs used in the same therapeutic regimen or immediately prior to initiation of anti-HER2 therapy. The descriptive analysis only suggests a potential relationship that could be further

Table 4 Descriptions of adverse drug reactions associated with HER2-positive breast cancer treatment and reported into the Sicilian RNF (Rete Nazionale di Farmacovigilanza) database

Adverse drug reaction, n (%)[a]	Lapatinib (n = 27)	Pertuzumab (n = 5)	Trastuzumab (n = 59)	TDM-1 (n = 18)	Pertuzumab/trastuzumab (n = 11)	Total (n = 120)
General disorders and administration site conditions	3 (11.1)	3 (60.0)	23 (39.0)	3 (16.7)	4 (36.4)	36 (30.0)
Asthenia	1 (3.7)	1 (20.0)	2 (3.4)	3 (16.7)	1 (9.1)	8 (6.7)
Chills			6 (10.2)			6 (5.0)
Chest pain		1 (20.0)	4 (6.8)			5 (4.2)
Injection site reaction			4 (6.8)			4 (3.3)
Gastrointestinal disorders	14 (51.9)	2 (40.0)	7 (11.9)	1 (5.6)	4 (36.4)	28 (23.3)
Diarrhea	11 (40.7)	1 (20.0)	2 (3.4)		3 (27.3)	17 (14.2)
Vomiting	4 (14.8)		3 (5.1)		2 (18.2)	9 (7.5)
Nausea	4 (14.8)		2 (3.4)	1 (5.6)	1 (9.1)	8 (6.7)
Abdominal pain	1 (3.7)	2 (40.0)	2 (3.4)			5 (4.2)
Cardiac disorders		1 (20.0)	14 (23.7)		3 (27.3)	18 (15.0)
Cardiac failure			9 (15.3)			9 (7.5)
Skin and subcutaneous tissue disorders	10 (37.0)		4 (6.8)	1 (5.6)	2 (18.2)	17 (14.2)
Rash	4 (14.8)		4 (6.8)		1 (9.1)	9 (7.5)
Palmar-plantar erythrodysesthesia syndrome	4 (14.8)					4 (3.3)
Pruritus	2 (7.4)	1 (20.0)				3 (2.5)
Blood and lymphatic system disorders	2 (7.4)			9 (50.0)	3 (27.3)	14 (11.7)
Thrombocytopenia				9 (50.0)	2 (18.2)	11 (9.2)
Neutropenia	1 (3.7)				2 (18.2)	3 (2.5)
Investigations		1 (20.0)	10 (16.9)		2 (18.2)	13 (10.8)
Ejection fraction decreased			7 (11.9)		1 (9.1)	8 (6.7)
Respiratory, thoracic and mediastinal disorders		1 (20.0)	9 (15.3)	2 (11.1)		12 (10.0)
Dyspnea			6 (10.2)			6 (5.0)
Epistaxis				2 (11.1)		2 (1.7)
Vascular disorders	1 (3.7)	5 (100)	3 (5.1)	1 (5.6)	1 (9.1)	11 (9.2)
Hypotension	1 (3.7)	1 (20.0)	1 (1.7)			3 (2.5)
Nervous system disorders			7 (11.9)	1 (5.6)		10 (8.3)
Tremor		1 (20.0)	5 (8.5)	1 (5.6)		7 (5.8)
Headache						4 (3.3)
Hepatobiliary disorders	2 (7.4)	1 (20.0)	1 (1.7)	4 (22.2)	2 (18.2)	8 (6.7)
Hypertransaminasemia	1 (3.7)	1 (20.0)			1 (9.1)	6 (5.0)
Metabolism and nutrition disorders	3 (11.1)		1 (1.7)	2 (11.1)	1 (9.1)	7 (5.8)
Appetite decreased	2 (7.4)					4 (3.3)
Musculoskeletal and connective tissue disorders			3 (5.1)	1 (5.6)	1 (9.1)	5 (4.2)
Muscle spasms			1 (1.7)		1 (9.1)	2 (1.7)
Infections and infestations	2 (7.4)		3 (5.1)			5 (4.2)
Injury, poisoning and procedural complications			4 (6.8)			4 (3.3)
Immune system disorders		1 (20.0)	3 (5.1)			4 (3.3)
Hypersensitivity			3 (5.1)			3 (2.5)
Renal and urinary disorders	2 (7.4)	1 (20.0)				3 (2.5)
Renal failure	1 (3.7)	1 (20.0)				2 (1.7)
Neoplasm benign, malignant, and unspecified (incl. cyst and polyps)			1 (1.7)	1 (5.6)		2 (1.7)
Reproductive system and breast disorders			1 (1.7)			1 (0.8)

TDM-1 trastuzumab emtansine

[a]Only the most reported adverse drug reactions by Preferred Term were described

△ Adis

Table 5 Serious Sicilian adverse drug reaction (ADR) reports related to HER-2-positive breast cancer therapy

Case n.	Level of seriousness	Age (years)	Sex	Suspected drug(s) (therapeutic indication)	Concomitant drug(s) (therapeutic indication)	ADR(s)	TTO (days)	Outcome	TTR (days)	Causality assessment
1.	Hospitalization	65	F	Trastuzumab (not defined)	–	Atrial fibrillation	241	Fully recovered	5	Probable
2.	Hospitalization	68	F	Lapatinib (HER2+ breast cancer NOS)	Letrozole (not defined)	Diarrhea, dehydration, gastroenteritis, acute kidney injury, electrolyte imbalance	14	Fully recovered	9	Possible
3.	Hospitalization	70	F	Lapatinib plus capecitabine (metastatic breast cancer)	–	Gastroenteritis	72	Fully recovered	32	Probable
4.	Hospitalization	41	F	Lapatinib plus capecitabine (metastatic breast cancer)	–	Paronychia	155	Not yet recovered	–	Probable
5.	IME	49	F	Trastuzumab (HER2+ breast cancer NOS)	Paclitaxel (breast cancer NOS)	Feeling cold, infusion site reaction, vomiting	0	Improved	0	Probable
6.	IME	46	F	Lapatinib plus capecitabine (metastatic breast cancer)	–	Asthenia, stomatitis, vomiting, mucosal inflammation	6	Improved	–	Probable
7.	IME	49	F	Trastuzumab (HER2+ breast cancer NOS)	Tamoxifen (Breast cancer NOS)	Ejection fraction decreased	115	Not yet recovered	-	Possible
8.	IME	60	F	Trastuzumab (metastatic breast cancer)	Vinorelbine and zoledronic acid (metastatic breast cancer)	Asthenia, ejection fraction decreased	350	Not yet recovered	–	Possible
9.	Life-threatening	71	F	Pertuzumab (HER2+ breast cancer NOS)	Folic acid, flecainide, ezetimibe, repaglinide, lercanidipine and fenofibrate (not defined)	Hypotension, chest discomfort, pallor	0	Fully recovered	0	Probable
10.	IME	50	F	TDM-1 (HER2+ breast cancer NOS)	–	Thrombocytopenia	68	Not yet recovered	–	Possible
11.	IME	59	F	TDM-1 (HER2+ breast cancer NOS)	–	Thrombocytopenia	97	Improved	–	Probable
12.	IME	64	F	TDM-1 (HER2+ breast cancer NOS)	–	Thrombocytopenia	37	Improved	54	Probable
13.	Hospitalization	64	F	TDM-1 (metastatic breast cancer)	–	Asthenia, thrombocytopenia	21	Not yet recovered	–	Possible

Table 5 (continued)

Case n.	Level of seriousness	Age (years)	Sex	Suspected drug(s) (therapeutic indication)	Concomitant drug(s) (therapeutic indication)	ADR(s)	TTO (days)	Outcome	TTR (days)	Causality assessment
14.	IME	55	F	Trastuzumab (HER2+ breast cancer NOS)	Paclitaxel (not defined)	Ejection fraction decreased, cardiac failure	54	Unknown	–	Possible
15.	Life-threatening	41	F	Trastuzumab (HER2+ breast cancer NOS)	Tamoxifen and triptorelin (not defined)	Cardiac failure	316	Improved	–	Possible
16.	IME	65	F	Trastuzumab (HER2+ breast cancer NOS)	Paclitaxel (not defined)	Cardiac failure, forced expiratory volume decreased	92	Unknown	–	Possible
17.	IME	59	F	Trastuzumab and pertuzumab (HER2+ breast cancer NOS)	–	Diastolic dysfunction, ventricular dysfunction	336	Not yet recovered	–	Possible
18.	Life-threatening	55	F	Trastuzumab and pertuzumab (metastatic breast cancer)	Docetaxel (not defined)	Atrial fibrillation	48	Unknown	–	Possible
19.	IME	58	F	Lapatinib and capecitabine (stage III breast cancer)	–	Mucosal inflammation, neutropenia	13	Fully recovered	36	Probable
20.	Life-threatening	NA	F	Pertuzumab (not defined)	Docetaxel (not defined)	Diarrhea, hypertensive crisis, renal failure	NA	Fully recovered	–	Possible
21.	Hospitalization	50	F	Docetaxel, pertuzumab, and trastuzumab (HER2+ breast cancer NOS)	Metformin	Stomatitis, dysphagia, hyperpyrexia, odynophagia, weight decreased, abdominal pain	30	Improved	–	Possible
22.	IME	40	F	Trastuzumab, TDM-1, tamoxifen, carboplatin, docetaxel (HER2+ breast cancer NOS)	-	Thrombocytopenia, hypertransaminasemia, hyperbilirubinemia	NA	Fully recovered	–	Possible
23.	Life-threatening	66	F	Trastuzumab (metastatic breast cancer)	–	Laryngeal edema, hypersensitivity	0	Fully recovered	0	Probable
24.	IME	NA	F	Trastuzumab (not defined)	–	Hypersensitivity	21	Unknown	–	Possible
25.	IME	NA	F	Trastuzumab (not defined)	–	Hypersensitivity	21	Unknown	–	Possible

Table 5 (continued)

Case n.	Level of seriousness	Age (years)	Sex	Suspected drug(s) (therapeutic indication)	Concomitant drug(s) (therapeutic indication)	ADR(s)	TTO (days)	Outcome	TTR (days)	Causality assessment
26.	IME	76	F	Docetaxel, pertuzumab and trastuzumab (HER2+ breast cancer NOS)	–	Asthenia, diarrhea, nausea, vomiting	0	Improved	–	Probable
27.	Hospitalization	66	F	Trastuzumab (recurrent breast cancer)	–	Cardiac failure	NA	Improved	–	Possible
28.	IME	55	F	Lapatinib and capecitabine (metastatic breast cancer)	–	Palmar-plantar erythrodysesthesia syndrome	66	Improved	235	Probable
29.	IME	63	F	TDM-1 (HER2+ breast cancer NOS)	Zoledronic acid (not defined)	Thrombocytopenia	351	Unknown	–	Possible
30.	IME	58	F	TDM-1 (HER2+ breast cancer NOS)	–	Thrombocytopenia	188	Improved	–	Probable
31.	Hospitalization	60	F	Lapatinib and capecitabine (HER2+ breast cancer NOS)	–	Stomatitis, diarrhea, abdominal pain, dyspepsia, appetite decreased	12	Improved	-	Probable
32.	Hospitalization	43	F	Trastuzumab (metastatic breast cancer)	Docetaxel and pertuzumab (metastatic breast cancer)	Dyspnea, oxygen saturation decreased	0	Fully recovered	4	Probable
33.	Life-threatening	34	F	Trastuzumab (HER2+ breast cancer NOS)	Paclitaxel (not defined)	Cardiac failure, forced expiratory volume decreased	62	Unknown	0	Possible
34.	Hospitalization	41	F	Docetaxel, pertuzumab and trastuzumab (metastatic breast cancer)	–	Anemia, neutropenia, dehydration, asthenia, diarrhea, hypercalcemia, thrombocytopenia, vomiting, hyperfibrinogenemia	6	Improved	–	Probable
35.	Hospitalization	59	F	Trastuzumab and pertuzumab (metastatic breast cancer)	Denosumab and docetaxel (Metastatic breast cancer), atorvastatin (dyslipidemia), bisoprolol and ramipril (hypertension), acetylsalicylic acid (not defined)	Acute myocardial infarction	27	Recovered with sequelae	31	Possible

Table 5 (continued)

Case n.	Level of seriousness	Age (years)	Sex	Suspected drug(s) (therapeutic indication)	Concomitant drug(s) (therapeutic indication)	ADR(s)	TTO (days)	Outcome	TTR (days)	Causality assessment
36.	Hospitalization	77	F	Trastuzumab (HER2+ breast cancer NOS)	Paclitaxel (not defined)	Angina pectoris	73	Fully recovered	5	Probable
37.	Life-threatening	63	F	Trastuzumab and paclitaxel (HER2+ breast cancer)	–	Tachycardia, sense of oppression, chest pain	0	Improved	0	Probable
38.	Hospitalization	74	F	Lapatinib and capecitabine (metastatic breast cancer)	–	Diarrhea, renal failure	0	Fully recovered	43	Possible
39.	Hospitalization	67	F	Trastuzumab and pertuzumab (HER2+ breast cancer NOS)	–	Ejection fraction decreased	309	Improved	–	Possible
40.	Life-threatening	74	F	Pertuzumab (HER2+ breast cancer NOS)	–	Cyanosis, pruritus, edema, hypersensitivity	0	Fully recovered	0	Probable

F female, *HER2* human epidermal growth factor receptor type 2, *IME* important medical event, *NA* not available, *NOS* not otherwise specified, *TDM-1* trastuzumab emtansine, *TTO* time to onset, *TTR* time to recovery

investigated to generate a real signal [59, 64]. Despite these limitations, it is mainly recognized that SRS contributes to the characterization of safety profiles, which is particularly important for preventing some ADRs related to the use of anti-HER2 therapy in the treatment of breast cancer.

5 Conclusion

The importance of the SRS database for the identification of ADRs induced by anti-HER2 therapy is shown in the present study. The obtained data are mainly consistent with results in the literature. However, more attention should be paid to the occurrence of serious ADRs including heart failure, PPE syndrome, thrombocytopenia, and infusion-related reactions. Moreover, breast cancer is a heterogeneous disease and sometimes presents a very aggressive behavior causing clinically relevant symptoms and limitations to quality of life. This is particularly relevant in older patients or those with multiple comorbidities, underlining the importance of preventing some relevant ADRs, related to the use of anti-HER2 therapy, to improve patients' compliance. Further analyses are essential to better describe the safety profile of these target therapies and to develop proactive management strategies. The collaboration between oncologists and pharmacologists plays an essential role in early identification of ADRs, informing patients and improving their awareness of needing to report any new symptoms or worsening of a pre-existing condition as soon as possible during anti-HER2 therapy.

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