# Clinical Features and Outcomes of Patients with Chemotherapy-induced Takotsubo Syndrome

Katelyn Storey, BA, and Scott W Sharkey, MD

*Minneapolis Heart Institute and Foundation, Minneapolis, MN*

## Abstract

Chemotherapy treatment of malignancy accounts for 1–2% of takotsubo syndrome (TS) triggers. Women comprise 60–70% of patients with chemotherapy-associated TS, a distinctly lower prevalence than the 90% female prevalence in TS overall. Fluorouracil is the most commonly reported TS-triggering chemotherapeutic agent, although this must be interpreted in the context of the frequency of worldwide use of this agent. The onset of TS relative to chemotherapy initiation is quite variable, ranging from the initial administration to subsequent chemotherapy cycles several weeks beyond initiation. Limited information suggests chemotherapy can be safely reinitiated once the patient has recovered from the initial TS event. Having a TS event in the setting of chemotherapy treatment for malignancy is associated with substantial mortality.

## Keywords

Takotsubo syndrome, chemotherapy, cardio-oncology

**Disclosure:** Funding: Minneapolis Heart Institute Foundation, Minneapolis, MN, US.
**Received:** 19 March 2019 **Accepted:** 18 June 2019 **Citation:** *US Cardiology Review* 2019;13(2):74–82. **DOI:** https://doi.org/10.15420/usc.2019.10.1
**Correspondence:** Scott W Sharkey, MD, Minneapolis Heart Institute Foundation, 920 East 28th St., Suite 620, Minneapolis, MN 55407. E: scott.sharkey@allina.com



During the past 25 years, takotsubo syndrome (TS) has emerged as an important form of acute myocardial injury characterized by a distinctive regional left ventricular (LV) contraction abnormality, often with marked reduction of the LV ejection fraction, and typically completely reversible. At presentation, TS is often indistinguishable from acute coronary syndrome, yet its occurrence is independent of epicardial coronary artery obstruction.[1–4] Other features include a predilection for older women and an association with antecedent stressful event acting as the TS trigger. During the early experience with this condition, these triggering events were largely related to emotional trauma.[5–10] As experience has expanded, a greater association with physical stressors has emerged.[3,4,11–13] The increased association with a physical trigger likely reflects greater awareness of secondary TS complicating acute illness. Within the realm of physical triggers, a number of reports have documented pharmacological agents as TS triggers, including cocaine, nortriptyline, venlafaxine, albuterol, flecainide, epinephrine, duloxetine, and a number of chemotherapeutic agents.[14] In this article, we examine the association of chemotherapeutic agents with TS.

## Takotsubo Syndrome and Malignancy

Surprisingly little information is available regarding the association of chemotherapy with TS triggering. The most commonly used chemotherapeutic agents for malignancy among Medicare recipients in the US are listed in *Table 1*. A 2015 international systematic review of 1,109 TS patients reported malignancy as a comorbid condition in 10%, although malignancy itself was not necessarily the TS trigger and no information was provided regarding chemotherapy use.[15] A 2010–2014 analysis of 1,067,977 adult chemotherapy-related admissions from the US National Inpatient Sample database noted 562 patients (average age 63 ± 12 years, 69% female) with a TS diagnosis, representing an incidence of 37.0 (female) and 16.6 (male) per 100,000 chemotherapy-related hospitalizations.[16] The annual incidence of chemotherapy-associated TS is increasing by an estimated 8.6 per 100,000 patients.[16]

A 2008–2014 analysis from a tertiary cancer center noted 30 patients (average age 65 ± 9 years, 73% female) with cancer and TS. Among these patients, cancer treatment was identified as the TS trigger in 17 (57%), dominated by surgical procedures in 10 (33%), with chemotherapy as the apparent trigger in only 5 (17%) patients.[17]

The International Takotsubo Registry (1,750 patients) noted malignancy in only 1.3% of 630 patients (8 individuals) with physical TS triggers, although details regarding use of chemotherapy were not provided.[12] Therefore, examining the association of chemotherapy with TS is limited by the relatively small number of patients and the lack of detail surrounding these events.

## Methods

A computer-assisted search of the electronic database MEDLINE (1996–January 2019) was conducted. References were also examined for relevant articles, including review papers. The main search terms were: "takotsubo cardiomyopathy", "takotsubo syndrome", "chemotherapy", "stress cardiomyopathy", "apical ballooning syndrome", and "cancer". Published case reports of TS and chemotherapy were chosen. We excluded studies in which cancer itself (not chemotherapy) was reported as the primary physical stressor.

## Results

From 2007 to 2018, we identified 36 unique patients with chemotherapy-associated TS (female patients 19 [61%], average age 64 ± 13 years, range 24–85 years; *Table 2*). ST-elevation was the most frequent initial ECG finding, present in 56% of reports providing this detail, and the average initial ejection fraction was 28 ± 12%. The onset of TS relative to initiation of chemotherapy was highly variable, ranging from the initial administration to subsequent chemotherapy cycles several weeks beyond initiation. In some cases, the temporal delay between chemotherapy administration and TS onset was lengthy, raising the question of whether the chemotherapeutic agent was actually the TS trigger.

The antimetabolite class of drugs (5-fluorouracil, capecitabine and cytarabine) represented the agents most commonly reported as TS triggers (*Table 2*). A variety of other chemotherapeutic classes were also represented, including tyrosine kinase inhibitors (sunitinib, axitinib, and pazopanib), HER2 monoclonal antibodies (trastuzumab and pertuzamab), angiogenesis inhibitors (bevacizumab), CD20 monoclonal antibodies (rituximab), microtubule-targeting drugs (paclitaxel and combretastatin), and anthracyclines (doxorubicin and daunorubicin). The TS event was associated with the use of a single chemotherapeutic agent in 69% of patients. Among patients with chemotherapy-associated TS, the most frequent malignancies were colorectal (n=10, 28%), leukemia (n=4, 11%), lymphoma (n=3, 8%), and renal (n=3, 8%).

### Additional Considerations

Chemotherapeutic agents have a long-established reputation for cardiotoxicity, including left ventricular dysfunction and heart failure, acute myocardial ischemia and infarction, thromboembolism, hypertension, and arrhythmia.[47] Several of these drugs (e.g., fluorouracil, capecitabine, paclitaxel, docetaxel, bevacizumab, erlotinib, and sorafenib) have been associated with an acute MI-like syndrome that may be difficult to distinguish from a TS event.

### Acute Myocarditis Mimicking Takotsubo Syndrome

Recently, immune checkpoint inhibitors have been associated with acute myocarditis characterized by onset of new cardiovascular symptoms, troponin elevation, and abnormal ECG, typically within days to weeks of treatment initiation.[48] Acute myocarditis and TS share clinical features, including presentation, ischemic ECG changes, troponin release, and absent acute coronary artery obstruction. In rare circumstances, acute myocarditis may result in a TS-like regional LV contraction abnormality, in which case it may be challenging to distinguish the two conditions.[49] In this setting, cardiac MRI may be useful because TS is characterized by myocardial edema in a transmural distribution (T2-weighted imaging) without late gadolinium enhancement.[50,51]

Table 1: US Medicare Claims Chemotherapy Drugs 2016

| Drug | Typical Use | Medicare Claims in 2016 (n) |
|---|---|---|
| Methotrexate | Multiple | 2,480,000 |
| Anastrozole | Breast cancer | 1,370,000 |
| Tamoxifen | Breast cancer | 475,000 |
| Hydroxyurea | Multiple | 381,000 |
| Fluorouracil | Multiple | 380,000 |
| Revlimid® (lenalidomide) | Multiple | 239,000 |
| Xtandi® (enzalutamide) | Prostate cancer | 101,000 |
| Imbruvica® (ibrutinib) | Multiple | 101,000 |
| Zytiga® (abiraterone) | Prostate cancer | 96,800 |
| Ibrance® (palbociclib) | Breast cancer | 95,400 |
| Gleevecv (imatinib mesylate) | Chronic myeloid leukemia | 76,500 |
| Cyclophosphamide | Multiple | 9,565 |
| Rituxan® (rituximab) | Non-Hodgkins lymphoma | 4,867 |
| Avastin® (bevacizumab) | Colorectal cancer | 4,594 |
| Velcade® (bortezomib) | Multiple myeloma and mantle cell lymphoma | 2,734 |
| Carboplatin | Multiple | 2,487 |
| Herceptin® (trastuzumab) | Breast and gastric cancer | 2,450 |
| Paclitaxel | Multiple | 1,666 |

### Acute Coronary Syndrome Mimicking Takotsubo Syndrome

The apical LV ballooning phenotype is not pathognomonic of TS and urgent coronary angiography is necessary to exclude an unstable coronary obstruction that would require revascularization.[3,4] In particular, TS-like apical ballooning may be the consequence of acute myocardial ischemia in the setting of proximal stenosis involving the left anterior descending (LAD) coronary artery, which extends beyond the LV apex to supply the inferior wall ('wrap around' LAD).[52] In uncertain situations, such as late presentation, suspected coronary embolism, or when coronary angiographic findings are equivocal, CMR is useful because late gadolinium enhancement is rarely evident in TS, but frequently present in a vascular distribution in patients with ischemic injury from coronary artery obstruction.[3,4,53]

### Outcomes

In the largest study to date, all-cause in-hospital mortality was substantially greater among chemotherapy-treated patients with versus without a TS event (18.3% versus 3.2% respectively; p<0.001).[16] Advanced age (>85 years), sepsis, fluid–electrolyte disorders, respiratory failure, and cardiogenic shock were univariate predictors of in-hospital mortality in patients with chemotherapy-associated TS. Metastatic cancer was present in only 17%.[16] There is limited information regarding the safety of continuing or reinitiating chemotherapy after a TS event. A study involving a small number of patients (n=30) noted the majority of patients were able to resume chemotherapy cancer treatment after normalization of LV ejection fraction (generally within 3 weeks of the TS event), without TS recurrence.[54]

## Discussion

The current body of information regarding chemotherapy-triggered TS reveals a patient profile that differs from that of the larger TS

experience. In particular, women account for only 60–70% of patients with chemotherapy-associated TS, yet comprise > 90% of all TS cases,[3] an anomaly without an obvious explanation. In women, the five most common malignancies are breast, lung, colorectal, uterine, and thyroid, versus prostate, lung, colorectal, bladder, and melanoma in men.[55] Although publication bias may explain some of these findings, it is possible that men have a particular TS vulnerability in the setting of malignancy and chemotherapy. In fact, physical TS triggers are more common in men, and men have a higher 1-year TS-related mortality than women.[56]

The frequency of reports noting 5-fluorouracil as a TS trigger is curious. This drug is on the WHO's list of essential medicines for cancer; therefore, fluorouracil likely represents one of the most commonly used chemotherapy agents worldwide.[57] Consequently, the frequency of fluorouracil-associated TS may be driven by exposure of a greater number of patients to this agent (*Table 1*). Alternatively, fluorouracil may have pharmacological properties that can trigger a TS event. For example, there is evidence that fluorouracil is an arterial vasoconstrictor,[40] and coronary microvascular vasoconstriction is proposed as a mechanism in TS pathophysiology.[58]

## Conclusion

Chemotherapy treatment of malignancy is a relatively uncommon TS trigger, with a significantly greater proportion of men than is typically observed with TS. Fluorouracil is the most commonly reported chemotherapeutic agent, although this must be interpreted in the context of the frequency of worldwide use of this agent.

Whether certain chemotherapeutic agents are more likely to trigger TS is unresolved. Based on limited information, chemotherapy can be safely reinitiated, with careful observation, once the patient has recovered from the initial TS event. A TS event in the setting of chemotherapy treatment of malignancy is associated with substantial mortality. ■


1. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol* 2010;55:333–41. https://doi.org/10.1016/j.jacc.2009.08.057; PMID: 20117439.
2. Bossone E, Erbel R. The "takotsubo syndrome": from legend to science. *Heart Fail Clin* 2013;9: xiii–xv. https://doi.org/10.1016/j.hfc.2013.01.001; PMID: 23562127.
3. Sharkey SW, Maron BJ. Epidemiology and clinical profile of Takotsubo cardiomyopathy. *Circ J* 2014;78:2119–28. https://doi.org/10.1253/circj.CJ-14-0770; PMID: 25099475.
4. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;39:2032–46. https://doi.org/10.1093/eurheartj/ehy076; PMID: 29850871.
5. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation* 2005;111:472–9. https://doi.org/10.1161/01.CIR.0000153801.51470.EB; PMID: 15687136.
6. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. *J Am Coll Cardiol* 2001;38:11–18. PMID: 11451258.
7. Kurisu S, Sato H, Kawagoe T, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* 2002;143:448–55. PMID: 11868050.
8. Abe Y, Kondo M, Matsuoka R, et al. Assessment of clinical features in transient left ventricular apical ballooning. *J Am Coll Cardiol* 2003;41:737–42. PMID: 12628715.
9. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539–48. https://doi.org/10.1056/NEJMoa043046; PMID: 15703419.
10. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation* 2008;118:397–409. https://doi.org/10.1161/CIRCULATIONAHA.106.677625; PMID: 18645066.
11. Sharkey SW, Pink VR, Lesser JR, et al. Clinical profile of patients with high-risk tako-tsubo cardiomyopathy. *Am J Cardiol* 2015;116:765–72. https://doi.org/10.1016/j.amjcard.2015.05.054; PMID: 26144453.
12. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015;373:929–38. https://doi.org/10.1056/NEJMoa1406761; PMID: 26332547.
13. Kurisu S, Kihara Y. Tako-tsubo cardiomyopathy: clinical presentation and underlying mechanism. *J Cardiol* 2012;60:429–37. https://doi.org/10.1016/j.jjcc.2012.06.015; PMID: 23078863.
14. Summers MR, Prasad A. Takotsubo cardiomyopathy: definition and clinical profile. *Heart Fail Clin* 2013;9:111–22. https://doi.org/10.1016/j.hfc.2012.12.007; PMID: 23562112.
15. Pelliccia F, Parodi G, Greco C, et al. Comorbidities frequency in Takotsubo syndrome: an international collaborative systematic review including 1109 patients. *Am J Med* 2015;128:654.e11–19. https://doi.org/10.1016/j.amjmed.2015.01.016; PMID: 25660245.
16. Desai R, Abbas SA, Goyal H, et al. Frequency of takotsubo cardiomyopathy in adult patients receiving chemotherapy (from a 5-year nationwide inpatient study). *Am J Cardiol* 2019;123:667–73. https://doi.org/10.1016/j.amjcard.2018.11.006; PMID: 30538037.
17. Munoz E, Iliescu G, Vejpongsa P, et al. Takotsubo stress cardiomyopathy: "good news" in cancer patients? *J Am Coll Cardiol* 2016;68:1143–4. https://doi.org/10.1016/j.jacc.2016.06.027; PMID: 27585514.
18. Voit J, Tibrewala A, Akhter N. Heart of the matter: reverse takotsubo syndrome in an anthracycline-exposed oncology patient. *BMJ Case Rep* 2018 Oct 3. https://doi.org/10.1136/bcr-2018-226378.
19. Grunwald MR, Howie L, Diaz LA Jr. Takotsubo cardiomyopathy and fluorouracil: case report and review of the literature. *J Clin Oncol* 2011;30:e11–14. https://doi.org/10.1200/JCO.2011.38.5278.
20. Goel S, Sharma A, Garg A, et al. Chemotherapy induced Takotsubo cardiomyopathy. *World J Clin Cases* 2014;2:565. https://doi.org/10.12998/wjcc.v2.i10.565; PMID: 25325068.
21. Franco TH, Khan A, Joshi V, et al. Takotsubo cardiomyopathy in two men receiving bevacizumab for metastatic cancer. *Ther Clin Risk Manag* 2008;4:1367–70. PMID: 19337443.
22. Damodaran S, Mrozek E, Liebner D, et al. Focal takotsubo cardiomyopathy with high-dose interleukin-2 therapy for malignant melanoma. *J Ntl Compr Canc Netw* 2014;12:1666–70. https://doi.org/10.6004/jnccn.2014.0168; PMID: 25505207.
23. Basselin C, Fontanges T, Descotes J, et al. 5-fluorouracil-induced tako-tsubo-like syndrome. *Pharmacotherapy* 2011;31:226. https://doi.org/10.1592/phco.31.2.226; PMID: 21275498.
24. Malley T, Watson E. A case of takotsubo cardiomyopathy after chemotherapy. *Oxf Med Case Reports* 2016;2016:55-58. https://doi.org/10.1093/omcr/omw014; PMID: 27066260.
25. Coen M, Rigamonti F, Roth A, et al. Chemotherapy-induced Takotsubo cardiomyopathy: a case report and review of the literature. *BMC Cancer* 2017;17:394. https://doi.org/10.1186/s12885-017-3384-4; PMID: 28578653.
26. Baumann S, Huseynov A, Goranova D, et al. Takotsubo cardiomyopathy after systemic consolidation therapy with high-dose intravenous cytarabine in a patient with acute myeloid leukemia. *Oncol Res Treat* 2014;37:487–90. https://doi.org/10.1159/000365536; PMID: 25231689.
27. Coli S, Pigazzani F, Gaibazzi N. Midventricular takotsubo cardiomyopathy after oxaliplatin infusion: an unreported side effect. *J Cardiovasc Med* 2015;16:646–9. https://doi.org/10.2459/JCM.0000000000000204; PMID: 25333375.
28. Lees C, Yazdan-Ashoori P, Jerzak KJ, et al. Takotsubo cardiomyopathy during anti-HER2 therapy for metastatic breast cancer. *Oncologist* 2019;24:e80-e82. https://doi.org/10.1634/theoncologist.2018-0285; PMID: 30389744.
29. Giza DE, Lopez-Mattei J, Vejpongsa P, et al. Stress-induced cardiomyopathy in cancer patients. *Am J Cardiol* 2017;120:2284–8. https://doi.org/10.1016/j.amjcard.2017.09.009; PMID: 29096885.
30. Kobayashi N, Hata N, Yokoyama S, et al. A case of takotsubo cardiomyopathy during 5-fluorouracil treatment for rectal adenocarcinoma. *J Nippon Med Sch* 2009;76:27–33. https://doi.org/10.1272/jnms.76.27; PMID: 19305108.
31. Geisler BP, Raad RA, Esaian D, et al. Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. *J Immunother Cancer* 2015;3:4. https://doi.org/10.1186/s40425-015-0048-2; PMID: 25705383.
32. Lim SH, Wilson SM, Hunter A, Hill J, et al. Takotsubo cardiomyopathy and 5-fluorouracil: getting to the heart of the matter. *Case Rep Oncol Med* 2013;2013:206765. https://doi.org/10.1155/2013/206765; PMID: 24368954.
33. Van de Donk NW, America YG, Zelissen PM, et al. Takotsubo cardiomyopathy following radioiodine therapy for toxic multinodular goitre. *Neth J Med* 2009;67:350–2. PMID: 19915229.
34. Numico G, Sicuro M, Silvestris N, et al. Takotsubo syndrome in a patient treated with sunitinib for renal cancer. *J Clin Oncol* 2012;30:e218–20. https://doi.org/10.1200/JCO.2012.42.4911; PMID: 22802320.
35. Ovadia D, Esquenazi Y, Bucay M, et al. Association between takotsubo cardiomyopathy and axitinib: case report and review of the literature. *J Clin Oncol* 2014;33:e1–3. https://doi.org/10.1200/JCO.2013.48.7280; PMID: 24567431.
36. Shams Y, Tornvall P, Törnerud M, et al. Capecitabine caused cardiogenic shock through induction of global Takotsubo syndrome. *Cardiovasc Revasc Med* 2013;14:57–61. https://doi.org/10.1016/j.carrev.2012.10.001; PMID: 23218901.
37. Gianni M, Dentali F, Lonn E. 5 flourouracil-induced apical ballooning syndrome: a case report. *Blood Coagul Fibrinolysis* 2009;20:306–8. https://doi.org/10.1097/MBC.0b013e328329e431; PMID: 19300240.
38. White AJ, LaGerche A, Toner GC, et al. Apical ballooning syndrome during treatment with a vascular endothelial growth factor receptor antagonist. *Int J Cardiol* 2009;131:e92–4. https://doi.org/10.1016/j.ijcard.2007.07.066; PMID: 17920711.
39. Khanji M, Nolan S, Gwynne S, et al. Tako-Tsubo syndrome after trastuzumab: an unusual complication of chemotherapy for breast cancer. *Clin Oncol* 2013;25:329. https://doi.org/10.1016/j.clon.2012.12.007; PMID: 23434354.
40. Smith SA, Auseon AJ. Chemotherapy-induced takotsubo cardiomyopathy. *Heart Fail Clin* 2013;9:233–42. https://doi.org/10.1016/j.hfc.2012.12.009; PMID: 23562124.
41. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. *Intern Med J* 2010;40:303–7. https://doi.org/10.1111/j.1445-5994.2009.02144.x; PMID: 20529041.
42. Bhakta S, Flick SM, Cooney MM, et al. Myocardial stunning following combined modality combretastatin-based chemotherapy: two case reports and review of the literature. *Clin Cardiol* 2009;32:E80–4. https://doi.org/10.1002/clc.20685; PMID: 20014213.
43. Ng KH, Dearden C, Gruber P. Rituximab-induced takotsubo syndrome: more cardiotoxic than it appears? *BMJ Case Rep* 2015;2015. https://doi.org/10.1136/bcr-2014-208203; PMID: 25733089.
44. Ozturk MA, Ozveren O, Cinar V, et al. Takotsubo syndrome: an underdiagnosed complication of 5-fluorouracil mimicking acute myocardial infarction. *Blood Coagul Fibrinolysis* 2013;24:90–4. https://doi.org/10.1097/MBC.0b013e3283597605; PMID: 23249567.
45. Kim L, Karas M, Wong SC. Chemotherapy-induced takotsubo cardiomyopathy. *J Invasive Cardiol* 2008;20:E338–40. PMID: 19057042.
46. Fernandez SF, Basra M, Canty JM. Takotsubo cardiomyopathy following initial chemotherapy presenting with syncope and cardiogenic shock-a case report and literature review. *J Clin Exp Cardiol* 2011;2:124. https://doi.org/10.4172/2155-9880.1000124.
47. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231–47. https://doi.org/10.1016/j.jacc.2009.02.050; PMID: 19520246.
48. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755–64. https://doi.org/10.1016/j.jacc.2018.02.037; PMID: 29567210.
49. Caforio AL, Tona F, Vinci A, et al. Acute biopsy-proven

lymphocytic myocarditis mimicking Takotsubo cardiomyopathy. *Eur J Heart Fail* 2009;11:428–31. https://doi.org/10.1093/eurjhf/hfp008; PMID: 19193625.
50. Eitel I, Schuler G, Thiele H. Myocarditis mimicking Takotsubo cardiomyopathy or Takotsubo cardiomyopathy with secondary inflammation? *Eur J Heart Fail* 2009;11:809, author reply 810. https://doi.org/10.1093/eurjhf/hfp089; PMID: 19605454.
51. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on Takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018;39:2047–62. https://doi.org/10.1093/eurheartj/ehy077; PMID: 29850820.
52. Chao T, Lindsay J, Collins S, et al. Can acute occlusion of the left anterior descending coronary artery produce a typical 'takotsubo' left ventricular contraction pattern? *Am J Cardiol* 2009;104:202–4. https://doi.org/10.1016/j.amjcard.2009.03.018; PMID: 19576347.
53. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, et al. Clinical characteristics and cardiovascular magnetic resonance findings in stress (takotsubo) cardiomyopathy. *JAMA* 2011;306:277–86. https://doi.org/10.1001/jama.2011.992; PMID: 21771988.
54. Giza DE, Lopez-Mattei J, Vejpongsa P, et al. Stress-induced cardiomyopathy in cancer patients. *Am J Cardiol* 2017;120:2284–8. https://doi.org/10.1016/j.amjcard.2017.09.009; PMID: 29096885.
55. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat databases [research data 1973–2015]. DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. Bethesda, MD: National Cancer Institute. Available at: https://seer.cancer.gov/data-software/documentation/seerstat/ (accessed 9 July 2019).
56. Murugiah K, Wang Y, Desai NR, et al. Trends in short-and long-term outcomes for takotsubo cardiomyopathy among medicare fee-for-service beneficiaries, 2007 to 2012. *JACC Heart Fail* 2016;4:197–205. https://doi.org/10.1016/j.jchf.2015.09.013; PMID: 26746377.
57. Robertson J, Barr R, Shulman LN, et al. Essential medicines for cancer: WHO recommendations and national priorities. *Bull World Health Organ* 2016;94:735. https://doi.org/10.2471/BLT.15.163998; PMID: 27843163.
58. Sharkey SW, Maron BJ, Kloner RA. The case for takotsubo cardiomyopathy (syndrome) as a variant of acute myocardial infarction. *Circulation* 2018;138:855–7. https://doi.org/10.1161/CIRCULATIONAHA.118.035747; PMID: 30354447.

Table 2: Takotsubo Syndrome and Chemotherapy

| Authors | Study Type | Unique Patients | Age (Years) | Sex | Malignancy | Chemotherapy | ST-elevation | EF | Triggering Circumstances | Outcome | Authors' Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Voit et al. 2018[18] | Case report | 1 | 24 | M | Acute myeloid leukemia | Daunorubicin and cytarabine | No | 25 | Chemotherapy | Echocardiography 3 weeks later revealed improvement of EF to 63% | Given the complete recovery of LVEF within 12 weeks of presentation, concluded consistent with TS |
| Grunwald et al. 2012[19] | Case report, review | 1 | 60 | F | Stage III colon cancer | Fluorouracil, leucovorin, oxaliplatin | Yes | 10 | Chemotherapy, was 26 h into planned 46 h infusion when developed chest pain | At 16-month follow-up had not experienced any additional cardiac events. However, colon cancer recurred 5 months after the episode of TS | Contributes to growing literature on TS that occurs with fluorouracil, which is frequently administered for colorectal cancers |
| Goel et al. 2014[20] | Case report | 1 | 55 | M | Acute myeloid leukemia | Cytarabine and daunorubicin | Yes | 30 | Day 6 of chemotherapy | 20 days after event, patient had EF of 50% with mild anterolateral and anterobasal hypokinesia | Anthracycline agents may have especially cardiotoxic effects |
| Franco et al. 2008[21] | Case report | 2 | 76,61 | M | Colon cancer, metastatic non-small-cell lung cancer | Bevacizumab | Yes | | Patient 1: 2 days PTA started receiving chemotherapy<br>Patient 2: at 3 weeks prior to admission, patient had received second chemotherapy dose | At approximately 1 month, echocardiography showed significant recovery of LV function | Bevacizumab is a novel chemotherapeutic agent that inhibits VEGF |
| Damodaran et al. 2014[22] | Case report | 1 | 55 | F | Malignant melanoma | High-dose IL-2 | No | 45 | Admitted for course two, cycle 1 of high-dose IL-2, T-wave inversions were seen on EKG after initiation | Complete resolution of LV function | First reported instance of TS with high-dose IL-2 |
| Basselin et al. 2011[23] | Case report | 1 | 48 | M | Colic adenocarcinoma | 5-fluorouracil, oxaliplatin, calcium folinate (FOLFOX protocol) | Yes | 15 | Underwent first round of chemotherapy, ~24 h later, developed chest pain and EKG abnormalities; recurrence after third round of chemotherapy | 4 months later, discovery of liver metastasis led to new chemotherapy regimen including irinotecan and bevacizumab under close monitoring<br>No recurrence of cardiac manifestations was subsequently noted | Interesting case because patient had recurrent TS after third round of chemotherapy, which was the next dose of FOLFOX protocol |
| Malley and Watson 2016[24] | Case report | 1 | 73 | F | Tonsillar stage IV B diffuse large B-cell lymphoma | Lomustine, cytarabine, cyclophosphomide, etoposide (LACE) | No | 45 | Underwent 7 days of chemotherapy prior to TS event | No adverse events in follow-up | First case of TS in a patient receiving LACE chemotherapy |
| Voit et al. 2018[18] | Case report | 1 | 24 | M | Acute myeloid leukemia | Daunorubicin and cytarabine | No | 25 | Chemotherapy | Echocardiography 3 weeks later revealed improvement of EF to 63% | Given the complete recovery of LVEF within 12 weeks of presentation, concluded consistent with TS |

*(Continued)*

Table 2: Cont.

| Authors | Study Type | Unique Patients | Age (Years) | Sex | Malignancy | Chemotherapy | ST-elevation | EF | Triggering circumstances | Outcome | Authors' Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Coen et al. 2017[25] | Case report, review | 1 | 45 | F | Locally advanced epidermoid carcinoma of the anal canal | 5-fluorouracil and mitomycin C | Yes | 30 | Developed TS after receiving intra-arterial and intravenous polychemotherapy | EF normalized. Was not rechallenged with intra-arterial chemotherapy | TS is a rare and unpredictable event among oncologic patients. Patients under significant stress (physical or psychological) and those with cardiovascular risk factors complaining of cardiac symptoms should be carefully examined for signs of TS |
| Baumann et al. 2014[26] | Case report | 1 | 58 | M | Acute myeloid leukemia | Cytarabine | No | 20 | After receiving intravenous cytarabine, developed severe dyspnea at rest, with cardiogenic shock after central venous catheter was removed | During 18 months of follow-up, no hospitalization or clinical signs of heart failure occurred | TS can occur in patients with acute myeloid leukemia under systemic chemotherapy, which possibly represents a triggering factor for TS development |
| Coli et al. 2015[27] | Research letter/case report | 1 | 67 | F | Local advanced colon cancer | Oxaliplatin | Yes | | At end of third session of oxaliplatin infusion, patient reported chest pain, dyspnea, jugular constriction | 1 month later, MRI showed complete recovery of regional and global LV function. Patient restarted capecitabine monotherapy only, and did not experience any other adverse events | Represents the first description of TS induced by oxaliplatin during combined capecitabine and oxaliplatin regimen |
| Lees et al. 2018[28] | Case report | 1 | 63 | F | Metastatic HER2-positive breast cancer | Dual anti-HER2 therapy (pertuzumab + trastuzumab in addition to nabpaclitaxel chemotherapy) | Yes | 20 | After completing third cycle of pertuzumab + trastuzumab, presented to ED with progressive dyspnea | Patient ultimately pursued comfort care and died in palliative care unit ~1 month later | First reported case of TS associated with pertuzumab + trastuzumab combination therapy. Given these agents are relatively novel, clinicians might consider TS as differential diagnosis upon severe cardiac presentation in these patients |

(Continued)

Table 2: Cont.

| Authors | Study Type | Unique Patients | Age (Years) | Sex | Malignancy | Chemotherapy | ST-elevation | EF | Triggering Circumstances | Outcome | Authors' Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Giza et al. 2017[29] | Research article | 5 | 41–77 | N/A | 64% either advanced malignancy or recurrent disease | 3 patients after treatment with paclitaxel, 1 patient after bevacizumab and capecitabine, and 1 patient after 5-fluorouracil | No | ≤50% | Occurred during chemotherapy session | No in-hospital immediate mortality or cardiac-related mortality occurred | Compared with the general population, TS is more common in cancer patients |
| Kobayashi et al. 2009[30] | Case report | 1 | 62 | F | Rectal adenocarcinoma | 5-fluorouracil | Yes | 28 | 4 weeks after start of chemotherapy, intermittent shortness of breath and slight chest pain developed, progressively worsened | N/A | The cause of heart failure in this patient (i.e., TS induced by multivessel coronary vasospasm including microcirculation disorders only during 5-fluorouracil administration) is notable |
| Geisler et al. 2015[31] | Case report | 1 | 83 | F | Metastatic melanoma | Ipilimumab | Yes | 50 | Had received four standard doses of ipilimumab in the 3 weeks prior to admission | N/A | First reported case of TS in patient treated with ipilimumab. Post-marketing surveillance should capture cases of ipilimumab cardiac toxicity and physicians should be aware of this potential adverse event |
| Lim et al. 2013[32] | Case report | 1 | 66 | F | Rectal adenocarcinoma | 5-fluorouracil | No | 30 | Presented to ED after third week of chemotherapy, had been feeling unwell since the third day after this dose | Died 2 years later from complications of cancer | TS has been increasingly noted to occur in association with 5-fluorouracil. Oncologists and cardiologists need to recognize TS as a potential toxicity of this drug |
| van de Donk et al. 2009[33] | Case report | 1 | 73 | M | Toxic multinodular goiter | Radioiodine therapy (iodine-131) | Yes | 25 | At 4 weeks after radiodine therapy, presented with rapidly progressive dyspnea and significant increase in free thyroxin | Echocardiography after just 4 days showed significant LVEF improvement to 57% | First report of TS provoked by thyrotoxicosis resulting from radiation thyroiditis induced by radioiodine. Suggest determination of thyroid function in all patients with TS |
| Numico et al. 2012[34] | Case report | 1 | 57 | F | Clear-cell renal cancer | Sunitinib | Yes | 15 | During treatment with sunitinib at a dose of 12.5 mg/day for 4 weeks every 6 weeks | No sign of cardiomyopathy at 3-month evaluation | To their knowledge, only one other reported case exists of TS with sunitinib |
| Ovadia et al. 2014[35] | Case report | 1 | 71 | F | Renal cell carcinoma | Axitinib | Yes | 20 | Within 24 h of administration of axitinib, patient developed chest pain and shortness of breath | EF 50% at 3 weeks after initial presentation | The presumed association between the initiation of axitinib therapy and TS deserves further prospective clinical observation |

*(Continued)*

Table 2: Cont.

| Authors | Study Type | Unique Patients | Age (Years) | Sex | Malignancy | Chemotherapy | ST-elevation | EF | Triggering Circumstances | Outcome | Authors' Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shams et al. 2013[36] | Case report | 1 | 55 | M | Adenocarcinoma of cecum | Capecitabine | Yes | 15 | Chest pain started ~ 28 h after beginning oral capecitabine therapy | 1 week after admission, EF >55% | A case of capecitabine-induced global TS presenting with cardiogenic shock and STEMI |
| Gianni et al. 2009[37] | Case report | 1 | 79 | F | Colorectal cancer with metastatic involvement of liver | 5-fluorouracil | Yes | 34 | Last chemotherapy had been administered 2 weeks prior to presentation | 4 weeks later EF improved to 70% with no akinesis | First report of TS secondary to chemotherapy with fluorouracil for colon cancer |
| White et al. 2009[38] | Case report | 1 | 61 | M | Renal cell carcinoma with pulmonary metastases | Pazopanib | Yes | | Had been taking pazopanib for 8 weeks, at a dose of 800 mg daily | Repeat echocardiography 3 weeks later showed normal LV function | Successful treatment with a beta-blocker in a case of TS complicated by severe LV outflow tract obstruction |
| Khanji et al. 2013[39] | Case report/ letter | 1 | 50 | F | Breast cancer | Trastuzumab | No | | During 11th infusion of trastuzumab, developed crushing chest pain and T-wave inversion | N/A | Association of trastuzumab with TS has not been previously reported, and whether patients should be rechallenged with the drug is unclear |
| Smith and Auseon 2013[40] | Case report | 1 | 60 | F | Gray-zone lymphoma | Rituximab | Yes | 20 | During infusion of rituximab, ST-elevation seen on EKG (she was asymptomatic) | Rituximab was discontinued, LVEF 1 month later was 42% | Although exact mechanisms behind cardiotoxic effects of chemotherapeutic agents remain unclear, there is an association with a small cohort of medications |
| Stewart et al. 2010[41] | Case report | 1 | 81 | F | Stage III colorectal cancer | 5-fluorouracil | No | 35 | Acute onset of chest pain after 5-fluorouracil therapy | 1 week later, LVEF normalized to 60% | Although vasospasm is a well-recognized side-effect of this class of chemotherapeutic agent, broader cardiotoxicity is commonly seen and an increased awareness of the range of toxicity is necessary if repeat toxicity is to be avoided |
| Bhakta et al. 2009[42] | Case report, review | 2 | 71, 78 | F | Anaplastic thyroid carcinoma in both patients | Combretastatin | No | 40, 50 | Patient 1: 18 h after day 6 of combretastatin Patient 2: after combretastatin therapy, complained of nausea followed by left breast pressure | Patient 1: follow-up echocardiography 1 month later showed EF = 55% Patient 2: follow-up echocardiography 1 month later showed EF = 60% | These patients are unique for several reasons because they did not have emotional stressors and remained asymptomatic. Patients who develop cardiac events following combretastatin should be followed closely |

*(Continued)*

Table 2: Cont.

| Authors | Study Type | Unique Patients | Age (Years) | Sex | Malignancy | Chemotherapy | ST-elevation | EF | Triggering Circumstances | Outcome | Authors' Conclusions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ng et al. 2015[43] | Case report | 1 | 66 | M | Chronic lymphocytic leukemia | Rituximab | Yes | 40 | Within 40 min of infusion, developed acute shortness of breath, spikes in temperature | No recurrence of cardiac symptoms | First case at the time of rituximab with TS, exceptional case because most TS and chemotherapy-linked reactions have occurred during initial infusions, but this patient had already completed treatments with rituximab |
| Ozturk et al. 2013[44] | Case report | 1 | 48 | M | Metastatic gastric cancer | 5-fluorouracil | No | 15 | At the 34th hour of the planned 46-h infusion, patient developed tachycardia followed by dyspnea | Repeat echocardiography 27 days later with EF = 50%. Died of complications from cancer 13.5 months later | TS appears to occur more frequently than was previously thought, especially in relation to chemotherapy. Need to increase awareness |
| Kim et al. 2008[45] | Case report | 2 | 67, 75 | M, F | Patient 1: laryngeal squamous cell carcinoma Patient 2: colon cancer | Patient 1: cetuximab Patient 2: oxaliplatin and capecitabine | Patient 1: yes Patient 2: no | 20, 35 | Patient 1: 3 days after single dose of cetuximab, while having MRI of brain, became acutely hypoxic, then developed pulseless electrical activity arrest. Patient 2: immediately following first chemotherapy session with new regimen experienced acute onset of severe dyspnea | Patient 1: repeat echocardiography 2 weeks later showed EF = 45% Patient 2: follow-up echocardiography 2 weeks later showed EF = 59% | The exact mechanism remains unclear and the possible link between chemotherapy and TS needs to be further examined |
| Fernandez et al. 2011[46] | Case report, review | 1 | 85 | F | | Rituximab, cyclophosphamide, liposomal doxorubicin, vincristine | Yes | 20 | Underwent first cycle of chemotherapy in an outpatient setting, 5 days later had chest pain, dizziness, diaphoresis | 8 months later, echocardiography was completely normal | TS may represent as a form of cardiac dysfunction within the spectrum of chemotherapy-induced cardiac toxicity. Emphasize that rechallenging should only be considered if no other viable option |

*ED = emergency department; EF = ejection fraction; EKG = electrocardiography; HER2 = human epidermal growth factor receptor 2; IL = interleukin; N/A = not available; TS = takotsubo syndrome; VEGF = vascular endothelial growth factor.*