Abstract: P1221

Takotsubo-like syndrome in a patient with BRAF mutated metastatic lung cancer

Authors:
LC Belarte Tornero¹, A Taus Garcia², M Ble Gimeno³, T Martos Cardenas⁴, S Servitja Tormo⁴, E Gimeno Vazquez⁵, A Salar Silvestre⁵, X Sanz Latiesas⁶, F Martinez Medina³, A Miguel Gutierrez⁷, E Sole Gonzalez⁷, S Ruiz Bustillo⁷, N Farre Lopez⁷, J Marti Almor⁸, ¹Hospital del Mar, Cardiology Department, Heart Failure Unit, Cardio-Hematology-Oncology Unit - Barcelona - Spain, ²Hospital del Mar, Oncology Department - Barcelona - Spain, ³Hospital del Mar, Cardiology Department. Cardio-Hematology-Oncology Unit - Barcelona - Spain, ⁴Hospital del Mar, Oncology Department, Cardio-Hematology-Oncology Unit - Barcelona - Spain, ⁵Hospital del Mar, Hematology Department, Cardio-Hematology-Oncology Unit - Barcelona - Spain, ⁶Hospital del Mar, Department of Radiation Oncology, Cardio-Hematology-Oncology Unit - Barcelona - Spain, ⁷Hospital del Mar, Cardiology Department, Heart Failure Unit - Barcelona - Spain, ⁸Hospital del Mar, Head of Cardiology Department - Barcelona - Spain,

Topic(s):
Cardio-Oncology

Citation:
A 72-year-old woman was admitted to hospital with dysnea. She had a history of lung adenocarcinoma with liver metastasis and bilateral carcinomatous lymphangitis diagnosed one year before. She received treatment with carboplatin and pemetrexed and nivolumab without response. Initial molecular testing revealed a BRAF V600E mutation so treatment with trametinib/dabrafenib was initiated 4 months before admission. The patient complained of progressive shortness of breath, orthopnea and intermittent oppressive chest pain the last 4 days before admission. Heart failure was diagnosed based on bilateral pulmonary crackles on examination, an X-ray that showed bilateral pulmonary oedema and NT-pro-BNP of 7339 pg/mL. The treatment with trametinib/dabrafenib was stopped because of suspected cardiotoxicity. High-sensitivity cardiac troponin was elevated (peak level 261.5 ng/L) with ischemic kinetic and ECG showed left axis with profound negative anterolateral T waves and prolonged QT. A coronary angiography was performed and showed coronary arteries without stenosis. The echocardiogram revealed normal left ventricle (LV) size with severe systolic dysfunction due to extensive anterolateral and apical akinesia with hyperkinetic basal LV. Thus the diagnosis of Takotsubo-like syndrome was established. In the following hours the patient progress to cardiogenic shock with elevated serum lactate and inotropic support with levosimendan was required. Rapid improvement was observed with hemodynamic recovery and resolution of heart failure. Treatment with B-blockers and ACE inhibitors was started. A cardiac magnetic resonance, done 1 week after, evidenced normal LV function without regional wall motion abnormalities. No myocardial oedema or late gadolinium enhancement was proved. The ECG after 1 week was normal.

To our knowledge this is the first case report of tramefinib cardiotoxicity presented as Takotsubo-like syndrome. The treatment with BRAF and MEK inhibitors is usually used in melanoma. However, as persistent hyperactivation of the RAS-RAF-MEK-ERK pathway is common in solid tumours; their use is being extended. Trametinib is a selective inhibitor of MEK 1/2. Cardiac adverse events include elevated blood pressure, prolonged QT duration, LV dysfunction and myocarditis. LV systolic dysfunction incidence varies from 3 to 9% and although it is not very frequent it can be life-threatening. The specific effect of trametinib over cardiac cells is not well studied. It is likely the result of suppression of ERK1/2 activation in the heart; a receptor with cardioprotective effects. As MEK/ERK receptor is inhibited with trametinib beta-adrenergic signalling shunts toward the cardiotoxic p38 MAP kinase pathway. That’s why levosimendan was preferred instead of other inotropics with beta-adrenergic effect as dobutamine. Periodic cardiac function monitoring must be implemented in patients treated with trametinib for early detection of cardiotoxicity.
Abstract: Takotsubo-like syndrome in a patient with BRAF mutated metastatic lung cancer

Authors: LC Belarte Tornero, A Taus Garcia, M Ble Gimeno, T Martos Cardenas, S Servitja Tormo, E Gimeno Vazquez, A Salar Silvestre, X Sanz Latiesas, F Martinez Medina, A Miguel Gutierrez, E Sole Gonzalez, S Ruiz Bustillo, N Farre Lopez, J Marti Almor

Hospital del Mar, Cardiology Department, Heart Failure Unit, Cardio-Hemato-Oncology Unit - Barcelona - Spain, 2 Hospital del Mar, Oncology Department - Barcelona - Spain, 3 Hospital del Mar, Cardiology Department. Cardio-Hemato-Oncology Unit - Barcelona - Spain, 4 Hospital del Mar, Oncology Department, Cardio-Hemato-Oncology Unit - Barcelona - Spain, 5 Hospital del Mar, Hematology Department, Cardio-Hemato-Oncology Unit - Barcelona - Spain, 6 Hospital del Mar, Department of Radiation Oncology, Cardio-Hemato-Oncology Unit - Barcelona - Spain, 7 Hospital del Mar, Cardiology Department, Heart Failure Unit - Barcelona - Spain, 8 Hospital del Mar, Head of Cardiology Department - Barcelona - Spain

Topic(s): Cardio-Oncology

Citation: A 72-year-old woman was admitted to hospital with dysnea. She had a history of lung adenocarcinoma with liver metastasis and bilateral carcinomatous lymphangitis diagnosed one year before. She received treatment with carboplatin and pemetrexed and nivolumab without response. Initial molecular testing revealed a BRAF V600E mutation so treatment with trametinib/dabrafenib was initiated 4 months before admission.

The patient complained of progressive shortness of breath, orthopnea and intermittent oppressive chest pain the last 4 days before admission. Heart failure was diagnosed based on bilateral pulmonary crackles on examination, an X-ray that showed bilateral pulmonary oedema and NT-pro-BNP of 7339 pg/mL. The treatment with trametinib/dabrafenib was stopped because of suspected cardiotoxicity. High-sensitivity cardiac troponin was elevated (peak level 261.5 ng/L) with ischemic kinetic and ECG showed left axis with profound negative anterolateral T waves and prolonged QT. A coronary angiography was performed and showed coronary arteries without stenosis. The echocardiogram revealed normal left ventricle (LV) size with severe systolic dysfunction due to extensive anterolateral and apical akinesia with hyperkinetic basal LV. Thus the diagnosis of Takotsubo-like syndrome was established.

In the following hours the patient progressed to cardiogenic shock with elevated serum lactate and inotropic support with levosimendan was required. Rapid improvement was observed with hemodynamic recovery and resolution of heart failure. Treatment with β-blockers and ACE inhibitors was started. A cardiac magnetic resonance, done 1 week after, evidenced normal LV function without regional wall motion abnormalities. No myocardial oedema or late gadolinium enhancement was proved. The ECG after 1 week was normal.

To our knowledge this is the first case report of trametinib cardiotoxicity presented as Takotsubo-like syndrome. The treatment with BRAF and MEK inhibitors is usually used in melanoma. However, as persistent hyperactivation of the RAS-RAF-MEK-ERK pathway is common in solid tumours; their use is being extended. Trametinib is a selective inhibitor of MEK 1/2. Cardiac adverse events include elevated blood pressure, prolonged QT duration, LV dysfunction and myocarditis. LV systolic dysfunction incidence varies from 3 to 9% and although it is not very frequent it can be life-threatening. The specific effect of trametinib over cardiac cells is not well studied. It is likely the result of suppression of ERK1/2 activation in the heart; a receptor with cardioprotective effects. As MEK/ERK receptor is inhibited with trametinib β-adrenergic signalling shunts toward the cardiotoxic p38 MAP kinase pathway. That's why levosimendan was preferred instead of other inotropics with β-adrenergic effect as dobutamine. Periodic cardiac function monitoring must be implemented in patients treated with trametinib for early detection of cardiotoxicity.