**VIA MEDICA**

Review article

# Are molecular target therapies limited by cardiotoxicity — causes and symptoms of cardiovascular damage

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Since the introduction of new drugs, (commonly referred to as 'Molecular Target Therapies'), into oncological clinical practice both the number of objective indicators/endpoints of achieved treatment response and cancer survival duration have increased. Nevertheless, the risk of cardiovascular complications has also risen. Optimistic reports on the relatively low cardiotoxicity of these drugs have been verified through experience. Routine clinical practice has witnessed growing numbers of new drug groups that have different molecular target points and also a varied cardiotoxicity.

This paper presents the most important cardiovascular complications associated with the use of molecularly targeted drugs and includes their mechanisms of development.

NOWOTWORY J Oncol 2017; 67, 1: 34–40

**Key words:** cardiotoxicity, molecular target therapy, arterial hypertension, cardiac failure, arrhythmias, drug side-effects

## Introduction

Administering molecularly targeted systemic cancer treatment represents a new and valued benefit in oncology. An important element to this approach is recognising that certain genetic abnormalities are associated with malignant transformation, growth factors and their receptors. The proliferation and differentiation of malignant cells caused by the triggering of the 'molecular pathway' arises from activation of membrane receptors. When modified, these molecular mechanisms may allow prolonged progression-free survival and also in some cancer patients, their overall survival. Nevertheless, despite the optimistic toxicity profiles reported initially, it became apparent very soon that many

were associated with adverse reactions (including significant cardiac toxicity) making their withdrawal necessary or even resignation from the anti-cancer treatment [1]. It must of course be remembered that such drugs are often given to patients, who had been previously treated with conventional chemotherapy and which had also affected their cardiovascular system [2]. Furthermore, a significant number of cancer patients suffered from concomitant diseases. Data from the National Cancer Registry shows that cancer develops over the age of 60 years in 70% of men and in 60% of women, and is most common in the eighth decade of life; this being very well illustrated in prostate cancer cases [3]. In some clinical settings, just a solitary

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characteristic of the tumour (for instance its localisation) may cause cardiovascular disturbances.

Within this context tumours of the heart are of minor importance; both primary and secondary. The former are very rare (accounting for about 0.02%) and are usually present as sarcomas and lymphomas [4], whilst metastatic lesions are more common (accounting for approximately 21% cases; mainly including the pericardium by direct infiltration and less commonly, through metastasising via blood vessels or lymphatic routes). Clinical manifestations of secondary heart tumours are relatively late and are often accidentally recognised during imaging diagnostics, unfortunately, usually when vital structures of the heart have been affected [5].

The key issue underlying molecular target therapy is to block signal transfer which, in turn, adversely affects cellular division. This is usually achieved either by inactivating the ligand or blocking the receptor by specific antibody binding, blocking auto-phosphorylation or inhibiting the signalling of intracellular pathways. Cell cycle inhibitors and proteasome inhibitors may also be used. The mechanisms listed above, ie. signal pathways and/or kinase targets are also present within normal structures of the heart and/or the vascular system and therefore it is impossible to avoid targeted drugs interfering with healthy cardiomyocytes, that affect the function and the survival of myocardial cells [6].

## Cardiotoxic mechanisms of molecular target therapy

The working experience of molecular target therapy acquired over the last few years has allowed two types of cardiovascular toxicity mechanisms to become identified:

1. Toxicity associated with specific mechanisms of action, ie. associated with the activation of an identical target point within the cardiomyocyte (e.g. kinase or receptors).
2. Toxicity associated with indirect or direct inhibition of other signalling pathways which, in effect, causes symptoms of cardiotoxicity (e.g. the affinity of sunitinib to block serotonin alpha and beta adrenergic receptors, the potassium channel protein receptor (hERG) and the Purkinje fibres, which is not observed in the case of sorafenib, which blocks only the hERG receptor protein and the Purkinje fibres) [7].

Table I shows the most common kinases which act as therapeutic targets for treating cancer and their potential effect on the cardiovascular system [8]. At present it is impossible to predict all potential forms of cardiotoxicity for molecular target therapy drugs because of the complicated nature of molecular targets. The vast majority of these drugs have multikinase effects and are characterised by different binding sites within the cardiomyocytes

## Cardiovascular disturbances

### Hypertension

One of the more common and critical clinical complications is arterial hypertension. It is usually associated whenever tyrosine kinase inhibitors (TKI) or anti-angiogenic drugs are given, such as bevacizumab. Among these drugs are also sunitinib, sorafenib and pazopanib. Their molecular action is based on blocking the internal domain of the vascular endothelial growth factor receptor (VEGFR). Bevacizumab has a slightly different mechanism of action, as it binds directly to the vascular endothelial growth factor (VEGF). TKIs decrease the production of nitric oxide and thereby increase vascular resistance and blood flow deficits within capillaries. This may either cause arterial hypertension or exacerbate any pre-existing condition [9]. Murine studies have shown that mechanical factors are not important for inducing changes within large blood vessels, however the decrease in afterload brought on by TKIs directly affects the end-systolic resistance and eventually, the systolic function of the heart. Thus it can be ruled out that administering TKIs significantly decreases the 'functional' density of capillaries.

Developing hypertension is also likely to be associated with renal changes. Animal studies have shown lesions within glomerular vessels, microangiopathic thrombosis, proliferation of the glomerular mesangium and excessive generation of fibrin. Normally, the activation of type 2 VEGFR activates phosphoinositide 3-*kinase* (PI3K)-AKT) and induces phosphorylation and activation of endothelial nitric oxides synthesis. This causes a secondary increase in guanylate cyclase activity and due to smooth muscle relaxation, blood vessels then dilate. During the production of nitric oxide, endothelin synthesis increases which causes vascular obturation. Unfortunately, the factor responsible for the endothelin synthesis increase remains unknown [10].

Most researchers agree that it is difficult to assess the number of patients with hypertension caused by TKI-treatment. One reason being that there are a number of definitions of hypertension applied according to the purposes of clinical trials. Also its measurement methods vary. The incidence of hypertension depends upon the type of drug. It is estimated that for all patients treated with TKIs, hypertension develops in 15% to 60% cases and is more serious as regards to systolic hypertension. In the instance of bevacizumab, arterial hypertension is observed in some 20–30% cases (of whom in 11–16% cases it was observed for the first time). Severe hypertension is found in 8% cases, while hypertensive crisis in as many as 1% of subjects [11, 12]. Chu et al. have shown arterial pressure to be 150/100 mmHg or higher in 47% of patients during sunitinib therapy [13]. In a meta-analysis designed to assess the risk of hypertension in approximately 4600 patients treated for renal cancer with sorafenib, Wu reported grade 3 and 4 hypertension in 23%

**Table I.** The most common kinases and their potential effects on the cardiovascular system

| Kinase | Role of kinase in the cardiovascular system |
|---|---|
| RAF1/ BRAF | Anti-apoptotic action, maintains the function of the left ventricle under increase load (stress) |
| PI3K (p110a) | Physiologic heart growth, affects cardiomyocyte survival |
| PI3K (p110y) | Regulation of contractility and pathological hypertrophy |
| PDK1 | Affects cardiomyocyte survival and beta-adrenergic response |
| Akt 1, 2 or 3 | Regulation of cardiomyocyte survival, growth and metabolism |
| mTOR | Regulation of protein synthesis, inhibition causes energy preservation under duress; regulation of protein synthesis; inhibition leads to energy saving under stress, regulation of Akt (mTORC2) activation process |
| AMPK | Supervision of energetic stress, mTOR1 inhibition while maintaining energy reserves |
| GSK3 a/b | mTORC1 inhibition (together with AMPK), GSKbeta deletion acts protectively in postinfarct remodelling; GSKalfa deletion causes cardiac insufficiency under stress |
| CDKs | CDK2 inhibition limits heart damage in the course of ischemia-reperfusion acting through retinoblastomy protein |
| Aurora | Regulator of phase M of the cellular cycle |
| PLKs | Plk1 is involved in Cdc2 activation, chromosome segregation, centrosome maturation, forming of the spindle apparatus and cytokines |
| PDGFR | Participates in angiogenesis and in cardiac response to pressure stress (beta isoform) |
| VEGFR | Participates in angiogenesis and in cardiac response to pressure stress (antihypertensive effect) |
| EGFR (ErbB1) | Preserving function of the; left ventricle under prolonged katecholamine stimulation; mediating the signaling pathway stimulating cell survival |
| ERBB2 ERBB4 | Influences the survival and homeostasis of cardiomyocytes and maintains function of left ventricle |
| Kit | Promotion of progenital cells in the heart and differentiation differentiation of immature cardiomyocytes, direction towards post-ischaemic sites, promoting repair |
| Abl/ARG | Maintenance of homeostasi, in rofents treated with imatinib left ventricular dysfunction is observed |
| JAK2 | Together with STAT3 act protectively in many pathologic situations |
| FAK | Activation decreases heart hypertrophy and fibrosis |
| DMPK | Type 1 myotonic dystrophy is brought on by additive repetitions of the 3'UTR regioon of the DMPK kinase |
| LTK | Activation causes hypertrophy and degeneration of cardiomyocytes |
| ROCK | Activation of fibrosis and apoptosis under hypertensive stress |
| LKB1 | Activation of AMPK which is proangiogenic within the heart |
| LDB3, ZASP and/or Cypher | Induction of ZASP mutations associated with skeletal muscle myopathies |
| ERK 1/2 | Promotion of cardiomyocyte survival, ability to modulate physiologic (but not pathologic) hypertrophy |
| PKC alfa | Destructive influence on the heart under hypertensive stress |
| cGMP-dependent PK | One of the four main kinases influencing cardiac failure; activated by PDE5 receptors; inhibits apoptosis, hypertrophy and beta-adrenergic response |
| PIM kinase | Influences the survival of cardiomyocytes (activated by Akt, regylated at the gene expression level) |
| CAMKII | Main kinase in cardiac failure; influences heart hypertrophy; promotes decompensation under hypertensive stress |
| GRK2 and/or GRK5 | Decrease in beta-adrenergic signalling through beta-arrestin recruitment |
| ASK1 | Promotes pathologic hypertrophy and remodelling. Pro-apoptotic |
| PTEN phosphatase | Inhibition of hypertrophy, decrease in cardiomyocyte survival under stress; PI3K antagonist |

and 6% of subjects, respectively. The total risk of developing hypertension for sorafenib therapy was 6.11, p < 0.001 [14]. Another meta-analysis on 5000 patients with gastrointestinal stromal tumours (GIST), demonstrated that the risk of developing hypertension was 22.72, p < 0.001 [15].

Many workers stress that during TKIs administration, the rise in blood pressure may be rapid; especially in the case of sunitinib and sorafenib. This concerns patients who have not been previously treated for hypertension and may lead to a hypertensive crisis.

### Prolonged QT interval

The QT interval represents the time of ventricular repolarisation. Its length may be affected by many factors (e.g. age, autonomic stress, electrolyte levels, drugs or even the time of day). QT interval duration depends upon heart rhythm; during bradycardia it is long, in tachycardia it shortens. Measuring the QT interval is possible using a standard 12-channel ECG. In clinical practice, a correction of the QT interval is performed based upon heart rate, and a corrected value (QTc) is given.

Clinical symptoms of prolonged QT may cause syncope or a dangerous form of arrhythmia known as *torsade de pointes* which may cause ventricular fibrillation and eventually death. Many drugs administered as targeted therapy may prolong QT. Those include TKIs, histone deacetylase inhibitors, SRC/ABL inhibitors, FTpase, protein-Ckinase inhibitors, serine/threonine kinase protein-specific BRAF inhibitors and even inhibitors (blockers) of the type 3 serotonin receptor [12, 16, 17].

### Prolonged QT interval — tyrosine kinase inhibitors

In both preclinical and phase I trials of sunitinib in patients with solid tumours, prolonged repolarisation of the ventricular functional potential has been observed as represented by prolonged QT in a standard ECG. Changes in the QT interval of more than 60 ms (as compared to the initial values) were observed in 5% of the 84 subjects who had entered the study [18]. In a clinical trial involving 24 patients aged 24–87 years, the longest QT interval was seen on day 3, 24 hours after administering the drug (intended initial dose of 50 mg). This abnormality was not associated with any clinical problems. In none of the patients was the QT longer than > 500 ms [19]. It is important that sunitinib has a binding affinity to 5HT2a serotonin receptors, alpha and beta adrenergic receptors, hERG receptor protein and Purkinje fibres; blocking them all, which may affect repolarisation. Besides, electron microscopy investigations have shown both the presence of lesions and the activation of degenerative processes, particularly within the mitochondria as well as a significant decrease in the concentration of adenosine triphosphate (ATP) in the sunitinib and sorafenib groups [20].

Wandetanib, a tyrosine kinase inhibitor administered for treating medullary thyroid cancer in patients with the *RET* gene mutation, may significantly prolong ventricular repolarisation. A probable mechanism causing repolarisation disorders is interaction with ferrum channels within the heart. During a phase 1 study, QTc was prolonged in at least 10% of subjects; however this had no clinical implications and did not affect the course of drug administration [21]. In a phase II study of patients with breast cancer in whom wandetanib was administered 100 mg per day together with docetaxel, QTc was prolonged in almost 5% of patients compared with the group receiving wandetanib 300 mg per day with docetaxel, in whom prolonged QTc was observed in as many as 11% of subjects.

QTc prolongation was not observed in patients receiving docetaxel as monotherapy [22]. In a clinical study of wandetanib administered for non-small cell lung cancer, QTc was prolonged in 15% cases as compared to the non-wandetanib controls [23].

In a phase II trial of wandetanib on plasmocytoma patients there was also no QTc prolongation [24]. In another phase II wandetanib study on skin melanoma, it was found that during the first 6 months of treatment as many as 90 out of 132 patients had a QTc prolonged by 15.1 ms (in 2 patients, QTc exceeded 500 ms, and in one case it reached 60 ms compared to the initial value) [25].

In view of such findings, it must be remembered that the cardiotoxicity seen for this group of drugs is probably triggered by a different mechanism and may be associated with a mitochondrial effect; it also arises from receptors being blocked to various extents within the cardiomyocytes. This might be the underlying issue responsible for the varied cardiotoxicity of TKIs.

### Prolonged QT interval — histone deacetylase inhibitors

Deacetylases are regulatory proteins affecting the expression of genes dependent upon the presence of acetyl groups within histones. In many malignancies, acetylation abnormalities have been observed and this is the rationale behind attempts to apply these type of drugs for anticancer treatment [26].

Vorinostat and romidepsin have recieved FDA approval in the treatment of T-cell lymphoma of the skin, while the Committee for Medicinal Products for Human Use (CMHP) issued a negative opinion for romidepsin, stating that any clinical benefits have not been analysed (including longer overall survival). In the case of vorinostat, the submission for CMHP opinion had been withdrawn. In Europe therefore, histone deacetylase inhibitors are only administered in the course of clinical trials. Most of the data regarding their effects on the QT interval shows, that it is reversible and, usually of short duration. For the majority of patients, no symptomatic arrhythmias have been observed [12, 26].

### Prolonged QT interval — SRC/ABL inhibitors

Common SRC/ABL inhibitors include nilotinib and dasatinib which are widely used in routine clinical practice.

Dasatinib is used for treating chronic myelogenous leukaemia (CML) during the chronic phase in patients with the newly diagnosed disease who present with the Philadelphia chromosome (Ph+) as well as in cases of acute lymphoblastic leukaemia with Ph(+). In a phase II study on

467 patients, the median QTc prolongation was between 3 and 6 msec and in 64 patients the QTc was 60 ms longer as compared to initial values whilst in 3 patients the QTc was prolonged over 500 msec; this study demonstrating that exclusion criteria be applied also to patients with concomitant cardiovascular diseases. Thus, there seems to be a rationale behind the clinical observation that the hERG receptor within the heart is blocked 100 times less when compared to nilotinib [27].

Nilotinib may cause QT prolongation. In a clinical trial on patients resistant to imatinib, 4% of subjects presented with a QT pronged by 60 ms compared to baseline values. No prolongations over 500 ms were observed. Sudden death was observed in 0.6% cases and it was impossible to tell whether they were not associated with abnormal ventricular repolarisation [28, 29]. It has been noted that other drugs which damage blood vessels, e.g. FTpase inhibitors and protein C kinase inhibitors (which are currently undergoing phase I trials), may potentially also prolong QTc [30].

### Cardiac ischemia

Bevacizumab combined with standard chemotherapy may increase the number of emboli within the cardiovascular system and within the central nervous system. In a retrospective analysis, Scappaticci et al. showed a statistically significant risk of thromboembolism with combined therapy (standard + bevacizumab). The absolute risk of thromboembolic episodes reached 5.5 per 100 patient-years in the combined treatment group compared to 3.1 in the group receiving standard chemotherapy only. Risk factors included age over 65 yrs and previous thromboembolic episodes [31]. Schimdinger reported thrombo-embolic incidents in 24% of patients treated with sunitinib [18]. In 17.6% of patients treated with sunitinib, a significant increase in the troponin level has been reported [13].

### Dysfunction of the left ventricle

Different mechanisms underlie left ventricle dysfunction resulting from molecular target therapy. The best known is that associated with trastuzumab.

HER2 protein (ErB2) belongs to the family of epidermal growth factor receptors; EGFR. It is found on the malignant cells in some 20% of breast cancer patients. The protein consists of an external domain which binds the ligand, a transmembrane part and a cytoplasmatic part, which bears the characteristics of tyrosine kinase. The ErB2 receptor does not possess its own ligands, but it may undergo heterodimerisation with the remaining receptors, thus becoming activated.

Clinical trials have shown symptomatic and asymptomatic heart dysfunction in 4.7% of patients treated with trastuzumab only and in 27% of patients in whom trastuzumab is combined with anthracyclines. Risk factors of cardiotoxicity of trastuzumab include older age, previous treatment with anthracyclines and forms of heart injuries associated with concomitant diseases.

Under physiological conditions, activation of the Erb2 receptor within the heart is responsible for maintaining the correct structure and function of the myocardium. Binding with type 1 neuregulin (NRG1) activates the enzymatic pathway which determines the response to oxidative stress and initiates repairing mechanisms through the ERK and AKT routes. PI3K activation catalyses phosphorylation of the PK domain of AKT kinase, thus in turn initiating cellular mechanisms responsible for the growth and survival of myocytes. PI3K activation is possible through active RAS proteins. Additionally, NRG1 inhibition indirectly blocks the SRc and Fak routes, which exacerbates left ventricular dysfunction. Studies conducted on murine neonates in which the over-expression of antiapoptotic Bcl-X$_L$ cardiomyocyte protein has been genetically induced, has supported its protective role for developing dilation and hypertrophy of the myocardium on reaching adulthood [32–34].

It is important, that the type of cardiotoxicity induced by trastuzumab is classified as type II and reversible. The decrease in the ejection fraction is, in most cases, asymptomatic [6, 7, 32]. The HERA study has shown an asymptomatic decrease of the ejection fraction in 7% of patients, while symptomatic patients accounted for 1.7%. In the NSABP B1 study, this ratio was 14.2% and 4.7%, respectively (these differences arose mainly from qualification criteria and from methods used to assess cardiotoxicity) [35].

Ewer conducted a study in order to assess the clinical course of cardiotoxicity over a period of four years from the termination of anthracyclines treatment and under trastuzumab follow-up treatment [36].

The ejection fraction increased in 56% of patients after the withdrawal of trastuzumab and in 66% of cases treatment was recommenced. The median time for the ejection fraction to increase was 1.5 months. Only 12% of subjects developed left ventricle dysfunction.

A humanised monoclonal antibody which blocks the external subdomain of the ErbB2 receptor through inhibiting the dimerisation of the receptor, especially with the ErbB3 receptor, is pertuzumab which is yet another antibody which may be potentially useful for treating patients both with early and advanced breast cancer. Hitherto, studies have shown that for pertuzumab, cardiac failure is relatively rare and does not exceed a 1.2% rate in subjects. This difference is likely because of a different mechanism of action on the ErbB2 receptor. Within the cardiomyocyte, an important part of its protective mechanism is activating the ErbB2/ /ErbB4 dimer through NRG1 ligand binding to ErbB4. Pertuzumab inhibits the dimerisation process through inhibiting the ligand binding to the ErbB3 receptor [7].

When assessing the potential risk of developing cardiotoxicity (including heart failure associated with target therapy), one must always remember the different mechanisms of the two different molecular groups, that is the mAbs antibodies and the small molecules. Evidence for this has been provided by Spector et al, who has shown the possible protective function of lapatinib on the cardiomyocyte, which acts through the activation of a cardioprotective AMP-dependent kinase [37].

Published results of cardiovascular complication rates from randomised trials may actually show significantly different outcomes.

Populations qualified for treatment under pre-set and under 'normal' conditions vary significantly according to their cardiac status. A study by Tarantini shows that in 160 patients aged over 60 years, 32% had serious concomitant cardiovascular diseases. This is significantly more than in trial populations; the N-31 trial, the N9831 and the HEART of approximately 16% rates. Symptomatic cardiac failure was observed in 6% and in 2% before the age of 60. Trastuzumab was stopped in 10% of patients aged over 60 years and in 4% of patients below 60 years, whilst treatment was recommenced in 44% of patients over 60 years and in 58% of patients aged below 60.

Whenever ABL inhibitors are used for treatment, it is assumed that left ventricular dysfunction for imatinib does not exceed 1%. During electron microscopy investigations, myocyte necrosis was found; probably associated with apoptosis. It is likely that this mechanisms is similar to that observed in CML cells. Imatinib inhibits cellular processes responsible for deactivating oxidative stress, which become activated by the listed kinases.

Dilative cardiomyopathy was found in 4% patients treated with dasatinib and was caused by blocking the ABL//SRC route within the heart [12].

Cardiac incidents (including myocardial infarction, cardiac failure sudden cardiac death) are found in around 11% of GIST patients resistant to imatinib. In a retrospective study on a group of 224 patients, heart failure developed in 2.7% of patients and the median time to developing symptoms of cardiac failure was 22 days from the onset of sunitinib therapy, which supports the concept of the cumulative effect of sunitinib cardiotoxicity and its dependence on the duration of treatment [39]. It is estimated that cardiac failure, defined as a decrease in ejection fraction by over 15%, occurs in about 9–18% of patients. In a clinical trial on 75 patients, Chu had shown a below 50% fall of the ejection fraction in 20% of patients; 8% of subjects having had symptoms of NYHA III or IV cardiac failure [13]. In 4.6% of patients studied by Telli, systolic dysfunction was seen; defined as a fall in ejection fraction below 20% of the initial value. The listed risk factors included previous cardiac disease (cardiac failure, angina) and low BMI values [40].

An interesting meta-analysis was prepared based upon the results published in the Medline database between January 1996 and February 2011. Subjects consisted of almost 7000 patients treated with sunitinib. In 45 cases, cardiac dysfunction was observed (in 1.5% of patients this was found to be significant), but no differences in the frequency of cardiac incidents were seen; neither depending on the type of disease nor on cardiac observation (renal cancer as compared to other malignancies; cardiac observation vs none) [41].

Pathologic features observed by electron microscopy showed cardiomyocyte hypertrophy with damaged mitochondria (oedema, altered structure, increased permeability of the mitochondrial membrane without necrosis nor intracellular tissue hypertrophy). Murine studies have only revealed cardiomyocyte necrosis in cases of arterial pressure stress induced by phenylephrine [20].

Numerous published observations from a significant number of clinical trials show that cardiac toxicity is usually reversible and disappears after treatment withdrawal in the majority of patients. However in some patients they may be severe, even resulting in death [17].

## Summary

The use of modern diagnostic and therapeutic modalities has both significantly increased the number of complete recoveries and the survival of cancer patients. Nevertheless, the problem of treatment side-effects (incl. cardiovascular) remains a critical issue in oncology. This paper presents the most important issues of cardiotoxicity particularly regarding everyday practice of the oncologist. It also points out areas in which direct collaboration between the oncologist and the cardiologist may be necessary in order to provide optimal therapy for dealing with cardiac complications arising from oncological treatment.

**Conflict of interest:** none declared

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