Molecules, Drugs, and First-Line Therapies: A Guide for the Cardiologist

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6.1 Introduction: Cardiovascular Toxicity with First-Line Therapy in Solid Tumors, Risk, and Benefit

Neoplastic conditions are diseases of aged subjects, generally already suffering of different medical comorbidities and likely to assume polypharmacy for these conditions. This leads to a potentially increased risk of drug interactions and may increase the likelihood of cardiovascular events when they have to be treated with certain cardiotoxic anticancer drugs.

- Cancer therapy has evolved, becoming more selective and potentially less toxic, sparing normal tissue from acute and chronic damage.
  - However, the "off-target" toxicities (an unexpected toxic effect linked to the presence of the drug target on healthy organs, like the heart, vessels, skin, etc.) may be a problem [1].
- Treatment of main solid tumors encloses more commonly a *combination of cytotoxic drugs* (e.g., chemotherapy) that portend a different but existing risk of cardiovascular side effects, *with molecular targeted agents*, that can be associated with adverse events that are the consequence of critical pathways inhibited by these targeted therapies on vessels and the heart [e.g., vascular endothelial growth factor receptor (VEGFR)] [2].
  - This combination has the potential to delay progression of disease, to increase overall survival (OS), and also to increase the burden of toxicity of cancer patients suffering from various cancers [3].
  - The risk of cardiotoxicity can also be augmented if patients were previously exposed to cardiotoxic drugs during the primary treatment of disease or in the past (in case of relapsing or second cancer). Some classical examples are the treatments with anthracyclines for hematologic malignancies and/or for breast cancer that have a cumulative (cardiotoxic) dosage beyond which the risk of heart failure becomes clinically significant. A pretreatment with these agents can also make a (subclinical) cardiac damage not clinically apparent until a further toxic damage is added in the metastatic phase of cancer.

The scope of oncological treatment, when potentially cardiotoxic drugs have planned to be used, must include a comprehensive clinical history of patient for preexisting medical condition, anticancer treatments, other risk factors and polypharmacy, and a careful cardiologic evaluation.

With these data in mind, any oncologist should estimate the real added benefit of any oncological therapy, as a function of prognosis of metastatic cancer to be treated, balanced with the risk of life-threatening adverse events.

Cancer patients receiving chemotherapy or targeted therapies have an increased risk of developing cardiovascular complications, and the risk is even greater, in particular, if there is a known history of heart disease. Several meta-analyses have demonstrated a small risk of fatal adverse events [approximately 1.5–2.5 %, relative risk (RR) 1.5–2.2] with both anti-angiogenic tyrosine kinase inhibitors (TKIs) and bevacizumab [4–6]. In one analysis, bevacizumab was associated with an increased risk of fatal events when used in combination with taxanes or platinum agents (RR, 3.49) but not in combination with other agents (RR, 0.85) [4]. In two meta-analyses, bleeding was the most common fatal adverse event with both classes of agents; however, other causes of treatment-related death were also cardiac [4,5]. In another meta-analysis examining fatal events with anti-VEGFR TKIs, death due to heart failure were higher on the TKI treatment arms [6].

Among the main serious cardiovascular events that have been reported and will be discussed here, there are:

- Arrhythmias
- Myocardial damage causing a dilated cardiomyopathy
- Angina or myocardial infarction
- Pericardial disease (rare)
- Hypertension
- Arterial or venous thromboembolic events

Drug-associated cardiovascular toxicity in oncology patients treated with upfront treatment for advanced stages of disease is the primary argument of this chapter and will be analyzed according to different types of cancer, taking into consideration in particular the combinations of agents used as first-line therapy.

6.2 First-Line Therapy in Different Cancers: Challenges and Pitfalls with Cardiotoxic Drugs

6.2.1 Breast Cancer

Chemotherapy

Anthracyclines and Taxanes Alone or in Combinations

- Systemic treatment of metastatic breast cancer includes the use of one or more of:
  - Hormonal therapies
  - Cytotoxic agents
  - Target therapies

The choice of the strategy is based mostly on the biology of disease, and the extent of lymph node and metastatic burden.

- Hormonal therapies are used in patients whose cancer expresses estrogen and/or progesterone receptors. The most used drugs are tamoxifen and aromatase inhibitors (as letrozole and fulvestrant.). *Tamoxifen* is given for 5 years in the adjuvant setting.
- Cytotoxic therapies are used in patients whose cancer is not hormone-sensitive and in advanced disease.
  - Anthracyclines (monotherapy or with cyclophosphamide).
  - Doxorubicin, epidoxorubicin, and liposomal doxorubicins (pegylated or non-pegylated).
- Taxanes (paclitaxel, docetaxel)—either as a single agent or in combinations with anthracyclines—is the preferred regimen as first-line therapy for metastatic patients. A taxane-based (anthracycline-free) combination has significantly fewer adverse events of neutropenia, infection/febrile neutropenia, nausea, and vomiting compared to anthracyclivnes/cyclophosphamide [7].
- Combination chemotherapy is preferred with visceral and/or symptomatic disease.
- Combination chemotherapy in metastatic setting is not associated with a significant increase in OS, with response rate and time to progression being moderately increased.
- Cardiac toxicity of anthracyclines has been known for many years and is mostly evident as left ventricular dysfunction possibly leading to congestive heart failure.

- *Epirubicin* is less cardiotoxic than doxorubicin on a mg per mg basis [8]. In a meta-analysis of 13 studies comparing doxorubicin with epirubicin, use of epirubicin significantly decreased the risks of both clinical and subclinical cardiotoxicity [9].
- In *liposomal formulations*, doxorubicin is included in liposomes which do not cross healthy capillary vessels and concentrate in tumor. A randomized trial compared *pegylated liposomal doxorubicin* (PLD, 50 mg/m^2 every 4 weeks) with doxorubicin (60 mg/m^2 every 3 weeks) as first-line therapy in patients with metastatic BC; 56 % of them previously received anthracyclines. With a similar PFS and OS for the two arms, risk of cardiotoxicity was significantly higher with doxorubicin than PLD ($P < 0.001$) [10]. Similar results, with low rates of cardiac toxicity, were found with *non-pegylated liposomal doxorubicin* + cyclophosphamide compared to conventional anthracycline + cyclophosphamide combination [11].
  - The limit of liposomal formulations is mostly the high cost.

- Cardiotoxicity of taxanes is rare and asymptomatic. Paclitaxel is mainly associated with bradycardia and heart block.
  - However, they may potentiate the cardiotoxicity of anthracyclines.
  - Heart failure has described in up to 20 % of patients treated with paclitaxel plus doxorubicin in different studies [12,13], although an increased incidence of cardiotoxicity was not seen in all studies, even in patients pretreated with adjuvant anthracyclines [14]. The risk of heart failure is apparent at cumulative doxorubicin doses that are much lower than would be expected with single-agent doxorubicin [15–17]. Even docetaxel is associated with potentially related cardiac events and can potentiate the cardiac toxicity of anthracyclines [18]. In two randomized first-line trials comparing combinations of anthracycline + cyclophosphamide with anthracycline + taxanes, in anthracycline-naïve patients, the rate of grade 3–4 cardiac toxicity is similar and about 3 % in both arms [19,20].

The choice of treatment is according to comorbidities, risk factors, and previous therapies.

- The cardiotoxicity of doxorubicin and epirubicin may become relevant with cumulative doses above 300 and 700 mg/m^2, respectively.

The added toxicity is evident even for treatments given years apart (i.e., the *cumulative dose of anthracyclines is calculated during the lifespan).*

To better evaluate the cumulative dose of different anthracyclines, a conversion factor of 0.66 may be used for epidoxorubicin.

- Age, preexisting cardiovascular disease (e.g., cardiomyopathies, coronary artery disease, hypertension, peripheral vascular disease, diabetes), and concurrent or prior chest irradiation increase the risk of cardiotoxicity.
- The concomitant use of trastuzumab also increases the risk of cardiac dysfunction.
- In patients at high risk, an anthracycline-free regimen should be preferred. If anthracyclines are considered necessary, liposomal formulations or epidoxorubicin should be used.

Anti-HER2 Agents

Two drugs are currently approved for treatment of HER2+ breast cancer: the monoclonal antibodies trastuzumab and pertuzumab, which are combined with taxanes in a triplet combination showing a better OS that chemotherapy plus trastuzumab alone.

Both drugs bind to the extracellular domain IV of ErbB2 receptor, belonging to the HER family of tyrosine kinase receptor class. Pertuzumab binds instead the domain II, but both prevent dimerization of HER2 with other receptor members of HER family (homo- or heterodimerization). Pivotal early trials in 2000's association of trastuzumab with chemotherapy lead to a 1–4 % of heart failure and up to 18 % of LVEF drop when used in the adjuvant phase of treatment. Risk factors specific for trastuzumab-associated cardiotoxicity have not been clearly discovered. The analyses of the potential risk factors, including age, weight, hypertension, cumulative dose, and HER2 expression level, have revealed, however, that only age and concurrent doxorubicin therapy were significantly associated with an increased risk of cardiac disease [21]. In particular the risk is higher when the concomitant administration of anthracyclines is planned. After the introduction of trastuzumab therapy in early disease after 2005, almost all patients with HER2+ breast cancer are pretreated with anthracyclines as adjuvant therapy, so few women are anthracycline naive in metastatic setting. In the pivotal phase III trial by Slamon et al., the combination of paclitaxel and trastuzumab leads to a NYHA class III–IV cardiac dysfunction in 2 and 1 % of patients treated with paclitaxel + trastuzumab and paclitaxel alone, respectively [22]. In the pivotal phase III CLEOPATRA trial that randomly assigned 808 patients with HER2+ breast cancer to first-line treatment with trastuzumab and docetaxel plus either pertuzumab or placebo [23], combined therapy arm (triple combination) was not associated with significantly worse cardiac toxicity compared to docetaxel/trastuzumab alone. However, only a few patients had received trastuzumab in adjuvant setting. A decline of ≥10 % age points that resulted in an LVEF of <50 % occurred in 3.8 % of the pertuzumab group versus 6.6 % of the control group. Among them, 72 % of patients in the placebo arm and 87 % of those on the pertuzumab arm recovered to a normal value. The prescribing information package suggests monitoring LVEF about every 3 months. When LVEF fall to value <45 % or 45–50 % but with a ≥10 % absolute decrease below the pretreatment value, both pertuzumab and trastuzumab have to be withhold, and LVEF assessment should be repeated within approximately 3 weeks.

Endocrine Therapy (Tamoxifen, Aromatase Inhibitors, Fulvestrant)

Among hormonal therapies used for treating metastatic breast cancer, the most worrisome side effect is venous thromboembolism due to tamoxifen. It manifests as venous thrombosis or pulmonary embolism. Both aromatase inhibitors and fulvestrant are not known cardiotoxics in studies of advanced disease. Probably the limited time on treatment in metastatic patients limits the risk of vascular events.

6.2.2 Colorectal Cancer and Other Upper Gastrointestinal Malignancies

Fluoropyrimidines

The antimetabolite agents 5-fluorouracil (5-FU) and capecitabine are the cornerstone of all treatments for advanced GI cancers, either alone or in combination with oxaliplatin and irinotecan (plus or minus biological agents). Another similar agent, S-1, is now approved for treatment of advanced gastric cancer in association with cisplatin, but has the potential to be associated with lower risk of cardiotoxicity compared to 5-FU continuous infusion. Cardiotoxicity associated with these drugs is frequently reported in

the literature, with rates varying according to the series reported from 1 to 20 %. The most frequent cardiac symptom due to FU is an angina-like syndrome and is associated with ECG changes. Angina is reported up to 45 % of patients with 5-FU-related cardiotoxicity, myocardial infarction, and arrhythmia in 22 % of cases. Symptoms and ECG signs usually appear within 72 h in about 70 % of cases; the mortality rate is the more rare event (up to 8 %) [24,25]. The risk seems to be related to the rate of 5-FU administration, the presence of preexisting coronary artery disease, and the use of concurrent radiation or other potentially cardiotoxic drugs (e.g., anthracyclines). It is to be noted that most cases arising in patients not known for cardiac disease and preexisting cardiac disease are not predictive of cardiotoxicity. The risk is higher with continuous infusion (both long-term and short-term schedules) compared to bolus regimens. In one series, 8 % receiving a high-dose continuous infusion of FU developed cardiotoxicity [26]. In a second study of 106 patients receiving short-term infusional 5-FU with the FOLFOX regimen, nine developed chest pain during treatment [24]. The onset was during courses one, two, six, and eight in three, four, one, and one patient(s), respectively. Rechallenge is not recommended, and substitution with other agents (e.g., raltitrexed) is suggested. A possible alternative to 5-FU in colorectal neoplasms is in fact represented by raltitrexed (Tomudex®); an inhibitor is thymidylate synthesis (TS). *Raltitrexed*, an analogue of folate, was developed as a direct and specific inhibitor of TS. Clinical studies have shown a similar activity to 5-FU in metastatic colorectal cancer although the treatment had been accompanied by gastrointestinal toxicity concerns, particularly in patients with renal failure. *Raltitrexed is currently indicated for the palliative treatment of advanced colorectal cancer where 5-FU and folinic acid are not tolerated or inappropriate.* In particular, raltitrexed seems to be an option for patients with cardiovascular risk factors. A review by Kelly et al. showed that raltitrexed is associated with a significantly reduced incidence of cardiovascular toxicity in patients with a history of cardiac toxicity or cardiac comorbidities [27]. Some case studies had been published in which patients who had experienced cardiac symptoms when treated with 5-FU had been shifted to raltitrexed without further cardiac symptoms. To such similar conclusions come Avallone and collaborators, reviewing the literature of raltitrexed which suggested a resurrection of the drug specifically for those patients who manifest cardiovascular toxicity during therapy with 5-FU or have a positive cardiovascular history [28]. From a pooled analysis of studies with upfront raltitrexed associated with oxaliplatin and irinotecan (TOMOX and TOMIRI), Barni et al. revealed a substantial clinical equivalence with standard FOLFIRI and FOLFOX with an apparent minor hematological and gastrointestinal toxicity [29]. Capecitabine is an oral fluoropyrimidine that is metabolized to 5-FU. The cardiac toxicity of capecitabine is similar to that reported with infusional 5-FU [30]. Also, patients who previously experienced cardiotoxicity with 5-FU have still a risk of toxicity with capecitabine [31,32]. The incidence of cardiotoxicity with capecitabine ranges from 3 to 9 % [33,34]. The most frequent is angina; arrhythmias, myocardial infarction, and death have also been reported [30,35–39]. It is likely that the mechanism of cardiotoxicity is similar to that seen with FU, with coronary vasospasm being the most hypnotized. In particular in a trial in which 153 patients were treated with capecitabine plus oxaliplatin for advanced colorectal cancer, 10 cases of cardiotoxicity were observed (7 %), 80 % of which occurred during the first cycle of treatment [36]. Angina occurred in 70 % of them, and there was one case each of sudden death, heart failure, and ventricular fibrillation. In a retrospective series of 78 patients treated with capecitabine, 7 (9 %) developed symptoms of chest pain or chest discomfort suggestive of cardiotoxicity [37]: none had documented preexisting heart disease. Abnormalities were present in 60 % of patients

evaluated by ECG, but no elevations of cardiac enzymes were observed. Recurrent symptoms were observed in one of three patients who were rechallenged with a lower dose. In a literature-based review of 53 patients with reported capecitabine cardiotoxicity, the reaction was fatal in 6 (11 %) [39]. Rechallenge led to symptom recurrence in 10 of the 16 patients, and neither dose reduction nor medical prophylaxis influenced the outcome at rechallenge.

Anti-VEGF Agents

Bevacizumab

Bevacizumab is a monoclonal antibody against VEGF that inhibits binding of the normal VEGF ligand to its receptor. *It is approved, other than for the breast, lung, ovarian, and renal cell carcinoma, for the treatment of advanced colorectal cancer in combination with chemotherapy*. Targeting VEGF is associated with typical class effect adverse events as hypertension, thromboembolism, and more rare left ventricular dysfunction. Some events can be fatal as described by a meta-analysis of bevacizumab trials published by Ranpura et al. [4]. The risk of death (2.5 %) was only increased for combinations of bevacizumab with platinum agents or taxanes (RR = 3.49). The primary vascular adverse event reported with bevacizumab is arterial hypertension. The hypothesis for the etiopathogenesis of hypertension is linked with reduced nitric oxide production with a consequent increase in vascular resistance. In a meta-analysis of 12,949 patients treated with bevacizumab for metastatic tumors, the relative risk (RR) of developing significant rise in blood pressure (G3 or 4) was 5.38 (95 % CI 3.63–7.97) for patients treated with bevacizumab [40]. Among patients receiving bevacizumab, the overall incidence of all raised blood pressure events was 24 %, while the incidence of high-grade hypertension was 8 %. The risk was dose dependent, and the risk of G3-4 was higher for those with renal cell carcinoma (RR 13.77, 95 % CI 2.28–83.15) and breast cancer (RR 18.83, 95 % CI 1.23–292.29) who received bevacizumab at 5 mg/kg/week. In two colorectal cancer studies, the RR was 4.87. Data about the correlation of hypertension development with prognosis are controversial. Data about risk of arterial (but not venous) thromboembolic events (ATEs) are also substantial. In a meta-analyses of more than 13,000 patients, the RR of ATEs in patients receiving bevacizumab for advanced cancers was 1.46 (95 % CI 1.11–1.93) with an incidence of 2.6 % (95 % CI 2–3.5) [41]. The highest rate was seen in patients treated for colorectal cancer (3.2 %, 95 % CI 1.9–5.4). In summary, bevacizumab, at the doses labeled for treatment of advanced colorectal cancer, is associated with a small increased risk of ATEs and with a moderately increased risk of hypertension. Heart failure is rarely observed in patients not treated for breast cancer where taxanes are associated with bevacizumab. All these data have to be taken in mind when elderly or hypertensive patients are planned to be treated.

Anti-EGFR Agents

Cetuximab and Panitumumab

Anti-EGFR agents are presently used for the treatment of RAS-wt metastatic colorectal cancer, but they are not known cardiotoxic agents. They, however, are associated with magnesium wasting, probably by a reduced renal absorption, and hypomagnesemia could trigger arrhythmias [42]. Also, anti-EGFR agents are associated with an increased risk of venous but not arterial thrombosis, but the mechanism is presently unknown [43]. Cases of atrial fibrillation not certainly due to cetuximab have been described.

6.2.3 Lung Cancer

Platinum-Based Chemotherapy

Cisplatin

Cisplatin-based chemotherapy is the current standard of care for first-line treatment of advanced non-small cell lung cancer (NSCLC) in fit, good performance status patients. It is used in combination with other agents, rarely alone. Most frequent combinations used are those with gemcitabine, taxanes, or pemetrexed. Carboplatin is a platinum agent with reduced nephrotoxicity and is combined with the same agents listed above, replacing cisplatin when it is contraindicated for preexisting renal insufficiency, neuropathy, or cardiovascular diseases. Cisplatin, in fact, is a known vasculotoxic agent. Cardiac arrhythmias, myocardial infarction, and other ischemic events have also been described, frequently as a consequence of electrolyte disturbance. Cisplatin has also been associated with Raynaud's phenomenon, hypertension, and ischemic cerebral events, frequently observed in long-term survivors of testicular cancer. Patients receiving cisplatin-based chemotherapy are also at increased risk of venous but not arterial thromboembolic events (RR = 1.67, $P = 0.01$ and 1.36, and $P = 0.19$) [44–48]. In those patients with vascular morbidity, elderly or with reduced renal function substitution of cisplatin with carboplatin can be suggested.

Anti-EGFR and Anti-ALK TKIs

Crizotinib, a small molecule anti-ALK inhibitor, is approved for the treatment of ALK-positive advanced NSCLC after one previous treatment. The major event reported in the literature is a sinus bradycardia that is relatively frequent in patients treated with crizotinib with high-grade severity seldom reported [49,50]. In general, patients were asymptomatic, but caution should be used with the concomitant administration of beta blockers in patients treated with crizotinib. In two trials evaluating the efficacy of crizotinib for advanced NSCLC, bradycardia was reported in 12 of 240 patients, and all cases were mild (grade 1 or 2) in severity [49]. In another series of 42 patients receiving treatment with crizotinib for advanced NSCLC, there was a medium decrease of 26 beats per minute (bpm) among all patients; 69 % had at least one episode of sinus bradycardia (heart rate <60 bpm) [50]. Profound sinus bradycardia (heart rate <50 bpm) developed in 31 % of patients. None of the patients who developed bradycardia during treatment was symptomatic or had ECG changes such as QTc interval prolongation.

A QTc interval prolongation was however described with crizotinib, and the drug should be avoided in those patients with congenital long QT syndrome, heart failure, bradyarrhythmias, and electrolyte abnormalities or who are taking other agents known to prolong the QTc interval. Treatment should be temporarily discontinued if severe QTc prolongation develops and definitely discontinued if it reappears or is associated with arrhythmia, heart failure, hypotension, shock, syncope, or torsade de pointes. The suggestion is to perform an ECG at baseline in all patients treated with crizotinib in particular if they have a history of heart failure or cardiac arrhythmias and then regularly check for ECG abnormalities only if the patient develops symptoms (bradycardia) or assumes drugs that are known to cause QTc interval prolongation [51].

6.2.4 Genitourinary Cancers (Renal Cell Carcinoma and Prostate and Bladder Cancer)

Multitarget TKIs Used in Renal Cell Carcinoma

Agents used for the treatment of renal cell carcinoma (RCC) involve the angiogenesis pathway mainly through VEGFR receptor inhibition. Also, further tyrosine kinases associated receptors as PDGF, RET, KIT, and FLT-3 are targeted by a larger spectrum of activity with some drugs. With this in mind, it is expected that arterial hypertension and heart failure, the main cardiovascular effect, even if likely associated with a better outcome (biomarker predictive of efficacy), are the more frequent side effects of agents used for curing advanced RCC and targeting the VEGFR pathway. In the pivotal randomized trial that led to approval of sunitinib for advanced RCC, 21 % of patients experienced a decline in LVEF, but this was symptomatic in only 10 % [52]. All cases were reversible and not associated with an adverse clinical outcome. In a meta-analysis of the published literature that included 6936 patients receiving sunitinib for a variety of oncologic indications and who had regular cardiac function monitoring, the summary incidence of all grades of heart failure was 4.1 % with grade 3 or 4 heart failure of 1.5 % [53]. There were no differences in subgroups of patients receiving sunitinib for RCC versus other cancers. Both hypertension and a history of coronary artery disease are associated with an increased risk of sunitinib cardiotoxicity. Less data on cardiotoxicity are available with sorafenib, but the risk seems to be lower than with sunitinib. In a phase III trial of patients treated for advanced RCC, 2.9 % of patients receiving sorafenib developed cardiac ischemia or infarction compared with 0.4 % of those receiving placebo [54].

In trials of pazopanib, an oral multitarget inhibitor of several cell surface receptors as VEGFR-1, VEGFR-2, VEGFR-3 (PDGFR-alpha and PDGFR-beta), fibroblast growth factor receptor (FGFR-1 and FGFR-3), cKIT, interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms), approved for the upfront treatment of advanced RCC, cardiac dysfunction (decreased LVEF and clinical heart failure) has been observed. In COMPARZ trial [55], a phase III study that compared head-to-head sunitinib with pazopanib as first-line therapy for advanced RCC, symptoms of cardiac dysfunction were rare in both arms (1 %). Instead absolute decrease of ≥15 % of LEVF or >10 % but below the lower normal limit was not rare, but similar in both arms (9 versus 9 % and 7 versus 5 % with pazopanib and sunitinib, respectively).

Sunitinib and sorafenib are associated with a typical increase of blood pressure, a VEGFR class effect. In a meta-analysis of 13 studies (4999 patients treated with sunitinib for RCC or other malignancies), the overall incidence of all-grade hypertension was 22 %, with severe grades in 7 % [56]. Similar results were reported in a systematic review that analyzed the impact of hypertension in patients treated with sorafenib in nine prospective trials [57]. In a meta-analysis of trials with pazopanib [58], it was associated with higher rates of all-grade hypertension than sorafenib or sunitinib (36 versus 23 and 22 %, respectively). However, both this meta-analysis and the phase III trial led by Motzer and coll. showed similar rates of grade 3–4 events.

Sunitinib more than sorafenib is also associated with QTc prolongation [59].

Systemic Therapy Used for Prostate Cancer

LHRH Agents and Antiandrogen (Chemical Castration)

LHRH analogues alone or with antiandrogen represent the initial treatment of castration-sensitive recurrent or metastatic prostate cancer. Other than the well-known vasomotor and endocrine effects due to reduced testosterone levels, potential cardiac effects are observed. The data are contradictory, with some studies suggesting that androgen deprivation therapy (ADT) increases morbidity and/or mortality in particular in men with a cardiac disease [60–63], while others did not found a statistically significant effect [64,65]. An increased risk may be more pronounced in men who have had several (>2) previous cardiovascular disease events, especially during the first 6 months after initiation of ADT [66]. The potential benefits of ADT when it is being considered as part of the multidisciplinary treatment of prostate cancer have to be balanced with the potential cardiovascular harm, in particular in low-risk disease. No randomized trials have prospectively evaluated the risks of cardiovascular disease associated with ADT, but only retrospective data are available. A meta-analysis of eight phase III trials [67] showed that the incidence of cardiovascular death was not significantly different in those assigned to ADT compared with placebo (11.0 versus 11.2 %, relative risk 0.93, $P = 0.41$). There was no increase in risk of cardiovascular death in those who received ADT for a short (≤6 months) or long (3 years or more) duration. Furthermore, the meta-analysis found that in 11 trials with 4805 patients, both cancer-specific mortality and overall mortality were significantly decreased in those assigned to ADT compared with placebo. Another meta-analysis of eight observational studies that included approximately 415,000 men treated with ADT [68] showed that the RR for any type of cardiovascular disease in men treated with an LHRH was 1.38 (95 % CI 1.29–1.48), with similar events observed for surgical or medical castration. Also men with prostate cancer who are on ADT appear to be at increased risk of thromboembolic events (e.g., deep venous thrombosis, pulmonary embolus, arterial embolism). In a Surveillance, Epidemiology, and End Results (SEER) database analysis that included approximately 155,000 men, 38 % of whom received ADT, there was a significantly increased risk of thromboembolic events compared to those not on ADT (15 versus 7 %, HR = 1.56) [69]. Finally, Swedish authors, in an analysis that included approximately 77,000 men with prostate cancer, showed that the risk of thromboembolic events was increased in all men and that the risk was greatest in those who were treated with endocrine therapy [70]. Androgen deprivation therapy may also prolong the QT/QTc interval. Degarelix, an LHRH antagonist, seems associated to a similar risk of cardiovascular events of leuprolide in a prospective trial [71].

New Antiandrogen (Abiraterone and Enzalutamide)

New antiandrogens as abiraterone acetate and enzalutamide are now being used in the earlier castration-resistant stages, before or after chemotherapy. They reduce testosterone effect on prostate cancer cells by reduction of biosynthesis of adrenal precursors (abiraterone) or reducing its interaction with androgen receptors. The most common adverse events related to abiraterone therapy are fluid retention, hypokalemia, hypertension, and cardiac abnormalities due to 17-a hydroxylase inhibition, an enzyme involved in testosterone synthesis in the testis, adrenal glands, and the tumor itself. In the pivotal phase III trial COU-AA-301 that compared abiraterone and placebo in castration-resistant prostate cancer progressing after docetaxel, adverse effects due to elevated mineralocorticoid levels and cardiac disorders (ischemic heart disease, myocardial infarction, supraventricular arrhythmias, ventricular arrhythmias, cardiac failure, and any signs and symptoms

of arrhythmia) were not significantly worse in patients receiving abiraterone than placebo (16 versus 12 %) [72]. In the companion trial in chemotherapy-naïve patients, cardiac disorders of any grade were about 20 % in both arms [73]. In a case series of 51 patients with cardiovascular comorbidities or risk factors, Procopio et al. did not found any evidence of safety alert for patients treated with abiraterone acetate [74]. In enzalutamide phase III trial in pre-docetaxel setting (castrate-resistant prostate cancer), no cardiac concerns were raised [75].

6.2.5 Rare Tumors

Imatinib Used as First-Line Therapy in GIST

Imatinib is a small molecule inhibitor of the Bcr-Abl, Kit, PDGFR, and SRC family of tyrosine kinases, and it *is approved for the treatment of gastrointestinal stromal tumors (GIST)*, which are characterized by mutations in KIT or PDGFR genes. The use of imatinib for GIST but not for chronic myeloid leukemia (another indication of imatinib) is not associated with increased risk of heart failure [76–78]. It seems that Abl inhibition handles cardiac disorders. Usually, cardiac monitoring, baseline and thereafter, is not recommended for all patients on imatinib. NCCN guidelines suggest that patients with cardiac disease or other risk factors for heart failure who are receiving imatinib should be monitored and that any patient with signs or symptoms suggestive of heart failure should be evaluated and treated accordingly [79].

Anti-BRAF Agents (Vemurafenib, Trametinib) Used in BRAF-Mutated Advanced Melanoma

Vemurafenib is an oral BRAF inhibitor approved for treatment of metastatic melanoma with a V600E BRAF mutation. Vemurafenib has been associated with prolongation of the QTc interval. Caution is recommended for use in patients with congenital long QTc syndrome or to those who are assuming drugs known to prolong the QT interval. ECG and electrolytes have to be monitored before treatment and after the start of treatment. For patients commencing vemurafenib therapy for advanced melanoma, ECGs are recommended at day 15, monthly during the first 3 months of treatment, and every 3 months after that or when clinically indicated. If the QTc interval exceeds 500 ms, treatment should be temporarily interrupted, and electrolyte abnormalities evaluated and corrected [80].

Chemotherapy Agents Used Upfront for Metastatic Sarcomas

Single agents that retain activity with more than 20 % of responses in metastatic soft tissue sarcoma are doxorubicin, epirubicin, and ifosfamide. The primary agent used for soft tissue sarcoma is single-agent doxorubicin [81]. The threshold dose for optimal activity appears to be ≥60 mg/m^2 administered every 3 weeks, with lower doses associated with inferior antitumor activity [82]. It was not demonstrated a clinically meaningful dose–response relationship with doxorubicin at doses beyond 75 mg/m^2 per cycle. Doxorubicin is associated with a well-known both acute and chronic cardiotoxicity. Infusional rather than bolus administration reduces the likelihood of cardiotoxicity. Combination chemotherapy, consisting of anthracycline + ifosfamide doublet, increases response rate but not OS, so it indicated only for fit and symptomatic patients when a rapid shrinkage of tumor

mass is needed. To overcome cardiotoxicity, a liposomal formulation of doxorubicin (Caelyx ®) or use of epirubicin are indicated in high-risk patients. Although combination chemotherapies are clearly associated with greater toxicity than single-agent doxorubicin, infusional administration of doxorubicin over 3–4 days through a central venous catheter appears to reduce doxorubicin cardiotoxicity.

6.3 Recommendations

Many cytotoxic drugs and not usually for the treatment of solid tumors in first-line setting are associated with cardiovascular adverse events. In particular hypertension, heart failure, and arrhythmias are the most frequently reported. For this reason, selection of patients when starting treatment is of paramount importance. Strict collaboration with a cardiologist is needed, in particular, to reveal subclinical cardiac disease, a cardiac history, and potentially avoidable drugs with cardiac side effect. A regular check of blood pressure including basal and serial ambulatory room visits and home-based blood pressure assessment with immediate recheck or instauration of an adequate therapy is necessary for patients starting drugs with known hypertensive effect. Periodic monitoring of LEVF through an echo- or MUGA-based assessment for those cancer patients commencing agents known to depress ventricular function is also of paramount importance. Finally, avoiding or checking for drugs with known effect of cardiac rate can reduce the risk of the QTc interval prolongation. It has to be recognized that association with other drugs used in medical oncology as supportive therapies (e.g., antibiotics or antiemetics) have the potential to increase QTc interval and those must be avoided or substituted, if possible, if other agents with similar side effect have to be commenced. It is not possible to give a comprehensive indication to how frequently monitoring for cardiac toxicity. For most drugs, this information is included in the drug's package insert, where frequency and type of monitoring are described (e.g., trastuzumab or crizotinib). Another general recommendation is to avoid, if possible, cardiotoxic drugs in patients with preexisting risk factors. Many tumors are incurable in their advanced stage despite modern therapies that can improve outcome and save deaths, so using potentially equal-effective but less toxic drugs is suggested according to personal clinical judgment and after careful discussion with patients. The Hippocratic injunction *primum non nocere* remains a potent message because each medical and pharmacological have a potential risk of harm.

References

1. Kerkela R, Woulfe KC, Durand JB, Vagnozzi R, Kramer D, Chu TF, Beahm C, Chen MH, Force T. Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. Clin Transl Sci. 2009;2(1):15–25.
2. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. CA Cancer J Clin. 2013;63(4):249–79.
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
4. Ranpura V, Hapani S, Wu S. Treatment-related mortality with bevacizumab in cancer patients: a meta-analysis. JAMA. 2011;305(5):487–94.

5. Schutz FA, Je Y, Richards CJ, Choueiri TK. Meta-analysis of randomized controlled trials for the incidence and risk of treatment-related mortality in patients with cancer treated with vascular endothelial growth factor tyrosine kinase inhibitors. J Clin Oncol. 2012;30(8):871–7.
6. Sivendran S, Liu Z, Portas Jr LJ, Yu M, Hahn N, Sonpavde G, Oh WK, Galsky MD. Treatment-related mortality with vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy in patients with advanced solid tumors: a meta-analysis. Cancer Treat Rev. 2012;38(7):919–25.
7. Zheng R, Han S, Duan C, Chen K, You Z, Jia J, Lin S, Liang L, Liu A, Long H, Wang S. Role of taxane and anthracycline combination regimens in the management of advanced breast cancer: a meta-analysis of randomized trials. Medicine (Baltimore). 2015;94(17):e803.
8. Ryberg M, Nielsen D, Skovsgaard T, et al. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. J Clin Oncol. 1998;16:3502.
9. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010; 10:337.
10. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, Catane R, Kieback DG, Tomczak P, Ackland SP, Orlandi F, Mellars L, Alland L, Tendler C, CAELYX Breast Cancer Study Group. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004; 15(3):440–9.
11. Chan S, Davidson N, Juozaityte E, Erdkamp F, Pluzanska A, Azarnia N, Lee LW. Phase III trial of liposomal doxorubicin and cyclophosphamide compared with epirubicin and cyclophosphamide as first-line therapy for metastatic breast cancer. Ann Oncol. 2004;15(10):1527–34.
12. Gianni L, Munzone E, Capri G, et al. Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol. 1995;13:2688.
13. Gehl J, Boesgaard M, Paaske T, et al. Combined doxorubicin and paclitaxel in advanced breast cancer: effective and cardiotoxic. Ann Oncol. 1996;7:687.
14. Lluch A, Ojeda B, Colomer R, et al. Doxorubicin and paclitaxel in advanced breast carcinoma: importance of prior adjuvant anthracycline therapy. Cancer. 2000;89:2169.
15. Rahman Z, Champlin R, Rondon G, et al. Phase I/II study of dose-intense doxorubicin/paclitaxel/cyclophosphamide with peripheral blood progenitor cells and cytokine support in patients with metastatic breast cancer. Semin Oncol. 1997;24:S17.
16. Giordano SH, Booser DJ, Murray JL, et al. A detailed evaluation of cardiac toxicity: a phase II study of doxorubicin and one- or three-hour-infusion paclitaxel in patients with metastatic breast cancer. Clin Cancer Res. 2002;8:3360.
17. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin-paclitaxel: a safe regimen in terms of cardiac toxicity in metastatic breast carcinoma patients. Results from a European Organization for research and treatment of cancer multicenter trial. Cancer. 2003;97:40.
18. Malhotra V, Dorr VJ, Lyss AP, et al. Neoadjuvant and adjuvant chemotherapy with doxorubicin and docetaxel in locally advanced breast cancer. Clin Breast Cancer. 2004;5:377.
19. Nabholtz JM, Falkson C, Campos D, Szanto J, Martin M, Chan S, Pienkowski T, Zaluski J, Pinter T, Krzakowski M, Vorobiof D, Leonard R, Kennedy I, Azli N, Murawsky M, Riva A, Pouillart P, TAX 306 Study Group. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol. 2003;21(6):968–75. Erratum in: J Clin Oncol. 2003;21(10):2048.
20. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, Gamucci T, Twelves C, Fargeot P, Epelbaum R, Lohrisch C, Piccart MJ. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 multicenter phase III trial. J Clin Oncol. 2002;20(14):3114–21.
21. Seidman A, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20:1215–21.
22. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92.
23. Swain SM, Ewer MS, Cortés J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist. 2013;18:257.

24. Jensen SA, Hasbak P, Mortensen J, Sørensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. J Clin Oncol. 2010;28:5280.
25. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf. 2009;8:191.
26. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol. 1992;10:1795.
27. Kelly C, Bhuva N, Harrison M, Buckley A, Saunders M. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. Eur J Cancer. 2013;49(10):2303–10.
28. Avallone A, Di Gennaro E, Silvestro L, Iaffaioli VR, Budillon A. Targeting thymidylate synthase in colorectal cancer: critical re-evaluation and emerging therapeutic role of raltitrexed. Expert Opin Drug Saf. 2014;13(1):113–29.
29. Barni S, Ghidini A, Coinu A, Borgonovo K, Petrelli F. A systematic review of raltitrexed-based first-line chemotherapy in advanced colorectal cancer. Anticancer Drugs. 2014;25(10):1122–8.
30. Ng M, Cunningham D, Norman AR. The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). Eur J Cancer. 2005;41:1542.
31. Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol. 2002;13:797.
32. Aksoy S, Karaca B, Dinçer M, Yalçin S. Common etiology of capecitabine and fluorouracil-induced coronary vasospasm in a colon cancer patient. Ann Pharmacother. 2005;39:573.
33. Van Cutsem E, Hoff PM, Blum JL, et al. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. Ann Oncol. 2002;13:484.
34. Saif MW, Tomita M, Ledbetter L, Diasio RB. Capecitabine-related cardiotoxicity: recognition and management. J Support Oncol. 2008;6:41.
35. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol. 2001;19:4097.
36. Shields AF, Zalupski MM, Marshall JL, Meropol NJ. Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: a phase II trial. Cancer. 2004;100:531.
37. Bajetta E, Di Bartolomeo M, Mariani L, et al. Randomized multicenter phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. Cancer. 2004;100:279.
38. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol. 2001;19:2282.
39. Manojlovic N, Babic D, Stojanovic S, et al. Capecitabine cardiotoxicity—case reports and literature review. Hepatogastroenterology. 2008;55:1249.
40. An MM, Zou Z, Shen H, Liu P, Chen ML, Cao YB, Jiang YY. Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol. 2010;66(8):813–21.
41. Schutz FA, Je Y, Azzi GR, Nguyen PL, Choueiri TK. Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes. Ann Oncol. 2011;22(6):1404–12.
42. Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Barni S. Risk of anti-EGFR monoclonal antibody-related hypomagnesemia: systematic review and pooled analysis of randomized studies. Expert Opin Drug Saf. 2012;11 Suppl 1:S9–19.
43. Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol. 2012;23(7):1672–9.
44. Lee YG, Lee E, Kim I, Lee KW, Kim TM, Lee SH, Kim DW, Heo DS. Cisplatin-based chemotherapy is a strong risk factor for thromboembolic events in small-cell lung cancer. Cancer Res Treat. 2015;47:670–5.
45. Mellema WW, van der Hoek D, Postmus PE, Smit EF. Retrospective evaluation of thromboembolic events in patients with non-small cell lung cancer treated with platinum-based chemotherapy. Lung Cancer. 2014;86(1):73–7.
46. Seng S, Liu Z, Chiu SK, Proverbs-Singh T, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM, Oh WK, Galsky MD. Risk of venous thromboembolism in patients with cancer treated with cisplatin: a systematic review and meta-analysis. J Clin Oncol. 2012;30(35):4416–26.

47. Proverbs-Singh T, Chiu SK, Liu Z, Seng S, Sonpavde G, Choueiri TK, Tsao CK, Yu M, Hahn NM, Oh WK, Galsky MD. Arterial thromboembolism in cancer patients treated with cisplatin: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(23):1837–40.
48. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, Soff G, Parameswaran R, Hassoun H. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29(25):3466–73.
49. Ou SH, Azada M, Dy J, Stiber JA. Asymptomatic profound sinus bradycardia (heart rate ≤45) in non-small cell lung cancer patients treated with crizotinib. J Thorac Oncol. 2011;6:2135.
50. Ou SH, Tong WP, Azada M, et al. Heart rate decrease during crizotinib treatment and potential correlation to clinical response. Cancer. 2013;119:1969.
51. ▶ http://ec.europa.eu/health/documents/community-register/2012/20121023124213/anx_124213_it.pdf. Accessed 10 Jun 2015.
52. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356:115.
53. Richards CJ, Je Y, Schutz FA, et al. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. J Clin Oncol. 2011;29:3450.
54. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125.
55. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722–31.
56. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol. 2009;48:9.
57. Wu S, Chen JJ, Kudelka A, et al. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008;9:117.
58. Qi WX, Lin F, Sun YJ, Tang LN, He AN, Yao Y, Shen Z. Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis. Cancer Chemother Pharmacol. 2013;71(2):431–9.
59. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). Drug Saf. 2013;36(5):295–316.
60. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA. 2009;302(8):866–73.
61. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst. 2007;99(20):1516–24.
62. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007;110(7):1493–500.
63. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1):39–46. doi:10.1093/jnci/djp404. Epub 2009 Dec 7. Erratum in: J Natl Cancer Inst. 2012;104(19):1518–23.
64. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448–56.
65. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, Paszat LF. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol. 2009;27(21):3452–8.
66. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2015;33(11):1243–51.
67. Nguyen PL, Je Y, Schutz FA, Hoffman KE, Hu JC, Parekh A, Beckman JA, Choueiri TK. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA. 2011;306(21):2359–66.
68. Bosco C, Bosnyak Z, Malmberg A, et al. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol. 2014;68:386–96.
69. Ehdaie B, Atoria CL, Gupta A, et al. Androgen deprivation and thromboembolic events in men with prostate cancer. Cancer. 2012;118:3397.
70. Van Hemelrijck M, Adolfsson J, Garmo H, et al. Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. Lancet Oncol. 2010;11:450.

71. Smith MR, Klotz L, Persson BE, Olesen TK, Wilde AA. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. J Urol. 2010;184(6):2313–9.
72. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman Jr OB, Sternberg CN, Li JH, Kheoh T, Haqq CM, de Bono JS, COU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983–92.
73. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE, COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152–60.
74. Procopio G, Grassi P, Testa I, Verzoni E, Torri V, Salvioni R, Valdagni R, de Braud F. Safety of abiraterone acetate in castration-resistant prostate cancer patients with concomitant cardiovascular risk factors. Am J Clin Oncol. 2013;38:479–82.
75. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS, AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187–97.
76. Verweij J, Casali PG, Kotasek D, et al. Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: analysis of EORTC-ISG-AGITG study 62005. Eur J Cancer. 2007;43:974.
77. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373:1097.
78. Trent JC, Patel SS, Zhang J, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer. 2010;116:184.
79. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 01 May 2015.
80. Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, Xu QC, Tang S, Sridhara R, Jiang X, He K, Roscoe D, McGuinn WD, Helms WS, Russell AM, Miksinski SP, Zirkelbach JF, Earp J, Liu Q, Ibrahim A, Justice R, Pazdur R. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. Clin Cancer Res. 2014;20(19):4994–5000.
81. Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. J Clin Oncol. 1987;5:840.
82. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2001;37:870.
83. Van Cutsem E, Findlay M, Osterwalder B, et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. J Clin Oncol. 2000;18:1337.