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Research Article

THE RISK OF TREATMENT OF ARRHYTHMIA IN LUNG CANCER PATIENT UNDERGOING CHEMOTHERAPY

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Abstract

Aggressive cancer therapies cause a number of serious side effects, which are often considered to be a contraindication to further treatment. We would like to show that a personalised approach to patient's disease enables us to successfully continue the anti-cancer treatment. This case report is featuring a 77-year old man with a small cell lung carcinoma, treated with radio- and chemotherapy, which caused serious heart damage. Despite numerous metastases, a DDD- pacemaker was implanted and chemotherapy was reintroduced. The pacemaker helped to extend the patient's life by one year and a prolonged chemotherapy infusion together with cardiological follow-up helped to avoid further cardiac damage.

Introduction

Due to the increasing number of long-term cancer survivors, the ageing of the population, as well as the increased incidence and prevalence of oncologic and cardiovascular diseases, the number of patients presenting oncologic and cardiologic co-morbidities are increasing. Accordingly, there is a rapidly growing need for a comprehensive and proficient management of patients in whom the two co-morbidities exist, and for cancer patients whose clinical history and oncologic treatment put them at higher risk for developing cardiovascular problems, in order to provide the optimal treatment in every situation, and to avoid the possibility that the development of the second disease does not lead to a reduction of therapeutic opportunities for the patients. Cancer chemotherapy has improved over last years and targeted chemotherapeutic drugs have been introduced, but still continued patient exposure to chemotherapeutics has important cardiovascular adverse effects including: left ventricular dysfunction and heart failure, myocardial ischemia, hypertension, arrhythmias, and pulmonary arterial hypertension [1].

Oncologists should be fully aware of cardiovascular risks to prevent adverse cardiovascular effects if possible. Cardiologists should be ready to assist oncology teams in performing cardiological evaluations required for the choice of chemotherapy. It must be underlined that there is growing need for cooperation between these two specilities and for the development of a cardio-oncology [1, 2]. A greater knowledge of cardiac toxicity including bradyacardia reported in this case may help appropriate risk stratification and correct management during treatment and follow-up of patients [3].

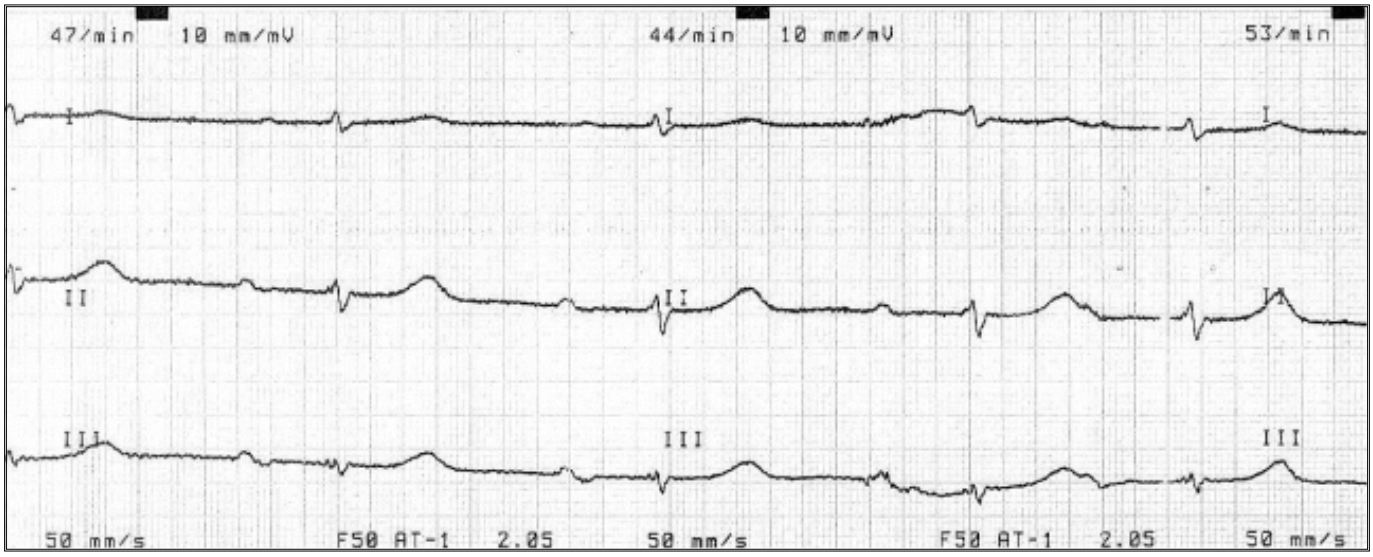

Fig.1 I[st] degree atrio-ventricular block, 350 ms; ECG performed before a chemotherapy course.

Background

Arrhythmias appearing as a result of chemotherapy

Cytotoxic agents and targeted therapies used to treat cancer all affect the cardiovascular system. This cardiotoxicity can develop in a subacute, acute, or chronic manner. Acute or subacute cardiotoxicity is characterized by either the occurrence of abnormalities in ventricular repolarization and electrocardiographic QT-interval changes, by supraventricular and ventricular arrhythmias, or by acute coronary syndromes and pericarditis and/or myocarditis-like syndromes, observed any time from the initiation of therapy up to 2 weeks after termination of treatment. Chronic cardiotoxicity may occurs even more than 1 year after chemotherapy [2]. The antiangiogenic multitarget tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, axitinib, pazopanic and tivozanicb are associated with hypertension and cardiotoxicity [4-7]. In chemotherapy anthracyclines are known to induce cardiomyopathy presenting with congestive heart failure, cyclophosphamide and cytarbine are documented to cause pericarditis, 5-fluorouracil are associated with cardiac ischaemia, taxanes with conduction disturbances and arrhythmias [8]. The mechanisms of cardiotoxicity vary widely among diverse chemotherapeutics, but the cardiomyocyte damaging effect possibly comes either from mitochondrial function disruption or from toxic influence on a local microenvironment [1, 2, 9, 10]. Arrhythmias are generally associated with administration of thalidomide and paclitaxel (bradycardia) or arsenic trioxide (QT- prolongation, torsade de pointes), but other chemotherapeutics could contribute to heart transduction system damage by their ischaemic properties [9, 10]. Hypotension or hypertension, arrhythmias, hear failure, angioedema, left ventricular dysfunction are often reported in patients treated with biological agents such as monoclonal antibodies, and immunotherapy including interleukins, and interferon-α [2]. Cisplatine, which is also known for causing renal failure, possibly induces hyperhydratation, which contributes to the development of arrhythmias [8]. Bradykardia is not a very common side effect of chemotherapy: it appears in only 0.45% of patients receiving chemotherapy and in 0.11% of patients with unspecified stage of small cell lung carcinoma. Most commonly, the patients received carboplatine, cisplatin and docetaxel, however, single reports for those drugs rarely speak about bradycardia, the highest incidence by docetaxel with 0.92% and by carboplatin and cisplatin around 0.6%. Antimicrotubule molecules, such as paclitaxel or vinca alkaloids have been shown to cause not only sinus bradycardia, but also atrioventricular block, ventricular tachycardia, hypotension, congestive heart failure, and finally ischemia [2]. Bradycardia was finally reported as dose-limiting toxicity in dovitinib (TKI258), a potent oral inhibitor of FGF receptor, VEGF receptor (VEGFR), and platelet-derived growth factor receptor tyrosine kinases used in renal cell cancer [11].

Arrhythmias appearing as a result of radiotherapy

Radiation induced heart disease may occur in any structure of the organ. It is most commonly a result of vascular damage and can manifest as acute or late pericarditis, cardiomyopathy, myocardial fibrosis, coronary vascular injury, conduction disturbances or valvular dysfunction [8, 9]. Cardiac radiation tolerance approximates 60Gy with 25% of the heart or less being radiated and drops to 45 Gy when radiation affects 65% or more [12].

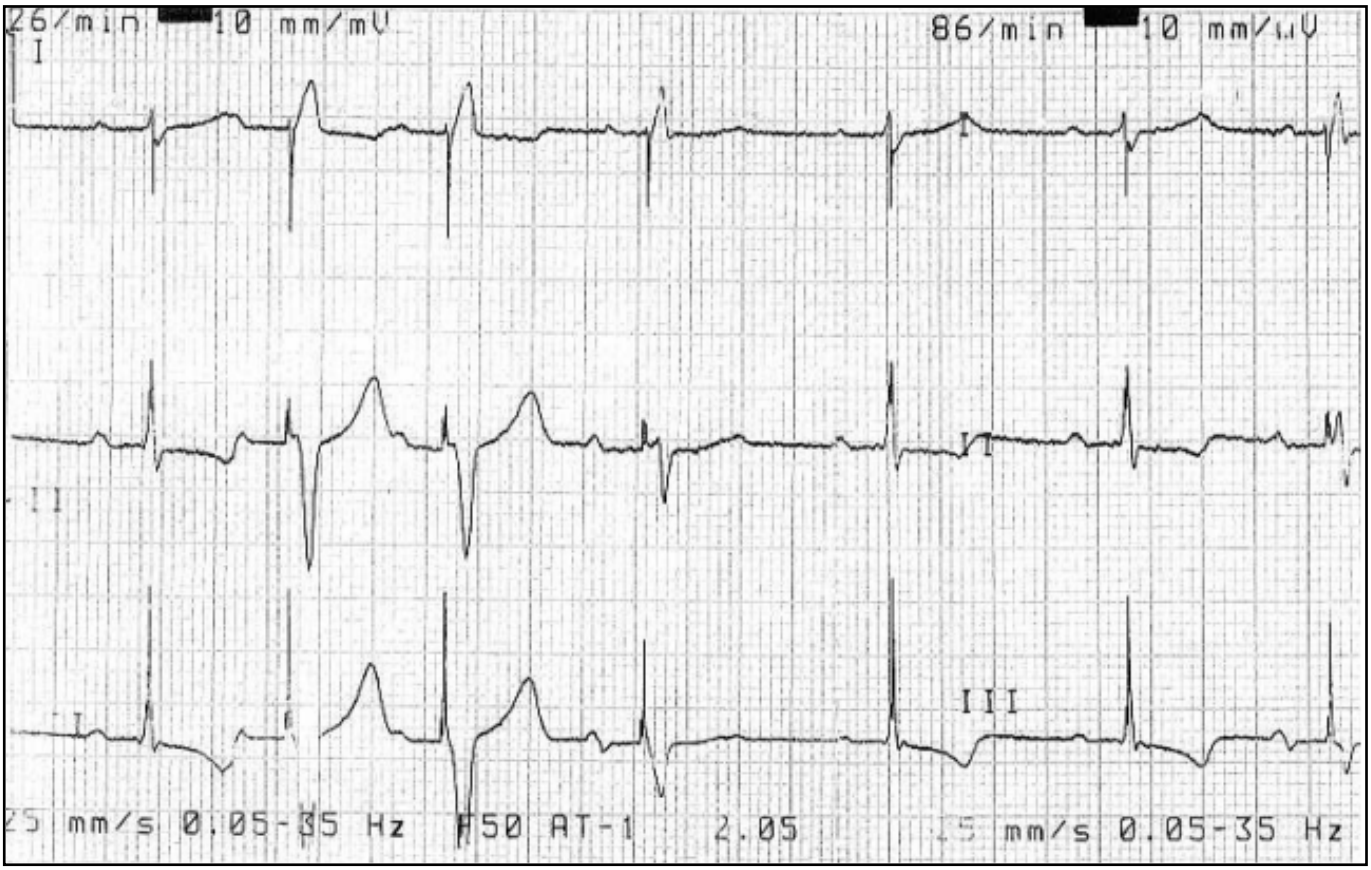

Fig.2 ECG with the incorrect pacemaker function.

Case report

A 77- year-old man without a past history of ischemic or rheumatic heart disease or hypertension was diagnosed with IIIB stage adenocarcinoma of the left lung in March 2007. The diagnosis was verified and changed to small cell lung carcinoma in April 2011. During the next four months after primary diagnosis, he received four courses of PN and radiotherapy at a total dose of 6600cGy to the mediastinum. From March 2008 till June 2010 the patient was experimentally treated with Stimuvax, which is an anti MUC-1 liposomal vaccine, in phase III trials at that time. The study was withheld in December, 2012 and did not meet primary end point of demonstrating a statistically significant improvement in overall survival. Patient safety in the trial was monitored frequently by an independent data monitoring committee and no new or unexpected safety concerns were noted for the study, since Merck reported in 2012 that Phase III Trial of L-BLP25 (Stimuvax) in Patients with Non-Small Cell Lung Cancer Did not Meet Primary Endpoint. The treatment was stopped due to disease progression - appearance of tumors in another lung. An examination conducted in June 2010 revealed a mass in the upper right lobe, in the cavity of the right lung, numerous lymph nodes in the aorto-pulmonary window and an embolic material in the arteries of the lower right lobe. Between October and November 2010 he was given four courses of EP. The patient tolerated chemotherapy poorly, had severe nausea and vomiting and neutropenia. A control CT in October showed a possible progression of the disease. In December the patient was admitted to CSK-WIM in order to undertake further therapeutic decisions. CT of the head, thorax and abdominal cavity was performed. On account of his serious condition, the patient was given a IV cycle of EP. In January the treatment was changed to Docetaxel and an administration of growth factors was scheduled. When the patient appeared for the III scheduled course of Docetaxel, he complained of anorexia, insomnia and constant pain of the whole body. An ECG performed by a cardiologist revealed, besides slight changes in atrial and ventricular stimulation, a fixed I degree block (Fig.1), single episodes of AV block (type II Wenckenbach's periodics), co-present inhibition of sinus node and periods of sinus bradycardia 40/

min, min. frequency ca. 31/min and short episodes of escape junctional rhythm (narrow QRS). In February 2011 the patient underwent a successful DDD pacemaker implantation. Afterwards he received the remaining III and IV course of Docetaxel. Although the patient denied any occurrence of fainting or dizziness, a cardiologist's consultation was scheduled in July, 2011. ECHO showed multiple extra systolic stimulations, slight widening of the right atrium; the left atrium and ventricles were normal. An ECG showed multiple atrial premature depolarizations and a VDD pacemaker stimulation (Fig.2). DDD stimulator was re-programmed and patient's ECG normalised (Fig.3). In April a CAV (Cyclophosphamide, Doxorubicin, Vincristine) chemotherapy course was started. Already during a second course was badly tolerated: the patient presented to the clinic with general weakness, insomnia, lack of defecation for 9 days, pain in the lower lumbar region and abdomen. Fourth grade neutropenia appeared and was difficult to handle also during the third course. A decision of extending the time of chemotherapeutic infusion to 48 hours was undertaken, due to expected better tolerance and weaker cardiotoxic effect. Since then a significant improvement in patient's tolerance for the treatment was noted. A control CT performed in October 2011 showed regression of nodular changes in the mediastinum. In December 2012 the patient received two courses of Topotekan. In January 2012 the patient was admitted to hospital with general weakness and severe dyspnea. He died due to disease progression and related respiratory tract dysfunction with respiratory failure. Death was not result of sudden cardiac event.

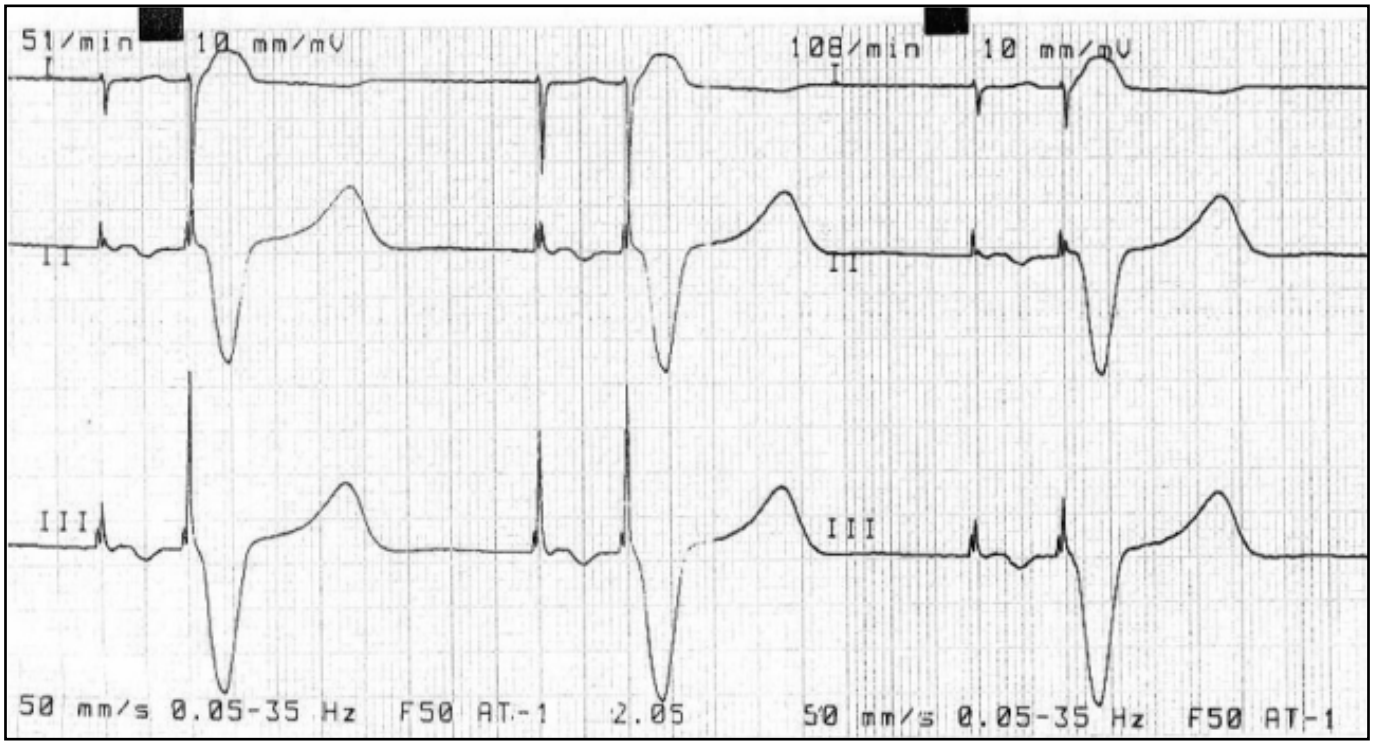

Fig.3 ECG after re-programming of the pacemaker.

Discussion

Cardiac injury is one of the most impairing side effects of anticancer treatment. The extension of the range of available drugs, the use of combination regimens and the association with radiation therapy have improved

Conclusions

More than 4 years have passed from the moment of diagnosis (03.2007) until the moment of death (01.2012), which allows us to conclude, that the pacemaker implantation helped to extend the patient's life by one year. Moreover a prolonged chemotherapy infusion may improve patient's tolerance for a treatment. We believe that patients with an existing pacemaker may be effectively treated with chemotherapy and peacemaker implantation may be an effective treatment method of chemotherapy-related arrhythmia. It is clear that cardiologists and oncologists must work together in an attempt to avoid or prevent adverse cardiovascular effects in patients from certain chemotherapies, especially for those who may be at a higher risk for such effects. Today's oncologists must be fully aware of cardiovascular risks to avoid or prevent adverse cardiovascular effects, and cardiologists must now be ready to assist oncologists by performing evaluations relevant to the choice of therapy. There is a need for cooperation between these two areas and for the development of a novel discipline, which could be termed cardio-oncology or onco- cardiology [8].

life expectancy; however, they have also caused a rising typology of cardiac toxicities, including not only congestive heart failure, but also myocardial ischemia, thromboembolism, hypertension and arrhythmias [3]. Both radio- and chemotherapy are known to cause a wide range of heart function disruptions. Risk factors for radiation-associated heart damage include: dose >30–35 Gy, dose per fraction >2 Gy, large volume of irradiated heart and use of cytotoxic chemotherapy [13]. Cancer patients are at a greater risk of developing arrhythmias, especially manifesting by a prolonged QT interval, than the healthy population. Contributing to this are their older age and often underlying heart problems, sometimes inborn, like congenital long QT syndrome, or acquired, like LV dysfunction, cardiac ischemia, bradycardia and other conduction diseases. Higher incidence is also noted by females and patients with hypothyroidism. Prolonged QT may frequently appear in patients treated by taxanes, cyclophosphamide, epothilones, thalidomide and arsenic trioxide. Some drugs, especially newer ones, may not show their pro-arrhythmic properties during clinical trials, because they would appear only in patients affected with other risk factors, poorly controlled diabetes being one of them. Chemotherapeutic agents, which cause hepatic and renal dysfunction lead to metabolism and drug clearance and disturbed electrolyte levels. Also common chemotherapy side effects, like nausea, emesis, diarrhoea, changes in diuresis and insufficient nutrition lead to electrolyte imbalance and dehydration. Therefore even weak pro-arrhythmic adverse-effects may be disclosed. Multiple medications used in typical cancer therapy also influence the pQT interval: 5-HT inhibitor anti-emetics, antihistamines, anti-depressants, antibiotics, anti-psychotics and methadone, increasing the possibility of arrhythmias [14]. Our patient has undergone a radical irradiation and both cisplatin and etoposide have confirmed cardiotoxiceffect. A similar case was described by Watanabe [15]. A significant improvement in patient's tolerance for chemotherapy after changing the bolus infusion to long-term one is an important observation. According to the recent studies, this method may prove to be very useful in cardio-oncological patients. Several studies analyze the influence of a prolonged chemotherapy infusion, mainly in children. The results are usually promising, showing a statistically significant difference in clinical and subclinical heart failure [16, 17] however, more studies need to be conducted [18, 19]. There is a rapidly growing need for comprehensive and professional management aimed at patients in whom two co-morbidities exist, and at cancer patients whose clinical history and oncologic treatment put them at higher risk for developing cardiovascular problems. This must be accomplished in order to provide optimal treatment in every situation, and to avoid the possibility that the onset of a second disease may lead to a reduction of therapeutic opportunities and negative long-term results. A greater knowledge of this specific cardiac toxicity may help appropriate risk stratification and correct management during treatment and follow-up. The exchange of information among haematologists, oncologists and cardiologists is essential for this purpose [3]. Although QTc measurement is the best way to assess arrhythmic risk, it is imprecise for a variety of reasons [14]. An understanding of onco-cardiology or cardio-oncology is critical for the effective care of cancer patients. All patients being considered for chemotherapy, especially those who have prior cardiac history, should undergo detailed cardiovascular evaluation to optimize the treatment [8]. A decision about a future course of therapy must be undertaken carefully and include numerous factors and perspectives. For a patient, a fear of potentially deadly side effects, deterioration of physical and financial conditions and potential emotional and social concerns will be probably overcome with the stage and seriousness of his illness and a prospect for longer life or symptom relief. Doctor's assessment of risk to benefit ratio may differ and overall benefits of a drug should be considered, together with a common uncertainty by prescribing newer, less documented medications and a reputation of pharmaceutical company. A tempting potential for a therapeutic success against overall patient's safety is certainly a controversial matter. The standard procedure for patients from increased risk groups should include a pre-dose 12- lead ECG, measurement of creatine, calcium, magnesium and potassium levels, which should be all correct before the treatment's initiation, withdrawal of other medications with QT prolongation and an assessment of risk benefit ratio, if a QT prolongation is discovered. During treatment, a regular control of all electrolytes should be maintained. So far, post-clinical monitoring is insufficient; surveillance for arrhythmia-associated therapies is a critical part of the future. Patient's hospitalization with cardiac monitoring would enable doctors to immediately react to QT interval changes by adjusting or stopping the therapy.

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