Dynamic Monitoring of Cardio-specific Markers and Markers of Thyroid Gland Function in Cancer Patients – A Pilot Study

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Abstract. Background: With the increased effectiveness of anticancer therapy, much more attention is being paid to the monitoring of the side-effects of chemotherapy, which often constitute a limiting factor in anticancer therapy. In this pilot study, the results of our monitoring of changes in cardio-specific markers and thyroid gland parameters in patients with colorectal carcinoma in the course of adjuvant and palliative chemotherapy are presented. Patients and Methods: A total of 42 patients with colorectal carcinoma were monitored (median age 52 years, range 34-82 years); in these patients a post-operative adjuvant or palliative chemotherapy was applied (de Gramont’s or FOLFIRI regimen). In all of these patients, the cardio-specific markers brain natriuretic peptide (BNP) and troponin I were assessed, as well as markers of thyroid gland function, TSH and FT4. Results: In the course of chemotherapy, more than half of the patients showed laboratory signs of coronary ischemia; in 6 of these (14%) coronary ischemia was manifested with troponin I levels above 0.3 μg/L. Twenty patients (48%) had laboratory signs of heart failure in the course of adjuvant or palliative chemotherapy. A more frequent incidence of elevated cardio-specific enzymes was observed in continual regimens than in bolus application of fluorouracil. Reduced TSH values were observed in the course of chemotherapy in 9 patients (21%), without changes in FT4 values. An increase in TSH values was observed in 4 patients (10%), again without changes in FT4 values. Conclusion: The pilot study demonstrated that in patients undergoing treatment for colorectal carcinoma by adjuvant or palliative chemotherapy on the basis of 5-fluorouracil, it is advisable to check for possible cardiotoxicity and simultaneously to monitor thyroid gland functions. This systematic monitoring may improve the quality of life in cancer patients.

In recent years, more and more attention has been paid to the possibility of targeted monitoring of the effects of anticancer chemotherapy (1). In our previous studies, we dealt with the possibility of controlling the effect of fluoropyrimidines in adjuvant and palliative chemotherapy with tumor markers in patients with colorectal carcinoma. We demonstrated that thymidine kinase is the optimal marker for checking the effects of chemotherapy regimens based on fluorouracil (2). During systematic monitoring of these patients we demonstrated an increased incidence of complications resulting from the side-effects of this therapy. In this pilot study, we present the results of monitoring the changes in cardio-specific markers and parameters of thyroid gland function in patients with colorectal carcinoma in the course of adjuvant and palliative chemotherapy.

BNP is synthesized in the ventricles. The degree of elevation corresponds with the severity of heart failure. Monitoring of BNP levels is important for the diagnosis, evaluation and management of congestive heart failure (4). Troponin I (TnI) is a protein specific to myocardial tissue. An increase in its level in serum is an early, sensitive and specific marker of myocardial injury, including minor myocardial damage (5). The assessment of the thyrotrophic hormone (TSH) and the free fraction FT4 is at present considered to be the basic assessment in thyroidal diagnosis. The aim of this study was to assess the changes of cardio-specific markers in patients treated with chemotherapy and also to evaluate the incidence rate of the pathological values of the thyroid function markers in cancer patients treated with 5-fluorouracil (5-FU) regimens.

Patients and Methods

A total of 42 patients with colorectal carcinoma (median age 52 years, range 34-82 years) to whom a post-operative adjuvant or palliative chemotherapy was being administered (de Gramont’s or
FOLFIRI regimen) were monitored. The representation of individual stages was as follows: Dukes B – 10 patients (24%), Dukes C – 15 patients (36%), Dukes D – 17 patients (40%). In patients with Dukes D an adjuvant chemotherapy was applied for patients with a high-risk prognosis in accordance with UICC criteria which, in patients with Dukes C and Dukes D, is a standard recommendation (3). Blood was sampled from the patients within their routine sampling schedule before starting and after finishing cycles 2 to 4 of chemotherapy, and the serum obtained by centrifugation was stored until assessment at –75°C. In all patients the cardio-specific markers brain natriuretic peptide (BNP) (chemiluminescence, Beckmann) and troponin I (TnI) (chemiluminescence, Beckmann) were assessed. We also assessed markers of thyroid gland function, TSH (IRMA, Beckmann) and fT4 (FPIA, Abbott). The overview of individual markers and their referential values is given in Table I.

### Results

Table II gives an overview of the increased TnI values, as well as BNP values in all patients undergoing anticancer therapy, irrespective of the chemotherapy cycle. It can be seen from Table II that in the course of chemotherapy, more than half of the patients had laboratory signs of coronary ischemia, and in 6 patients (14%) coronary ischemia was manifested with TnI values higher than 0.3 µg/L. Laboratory signs of heart failure occurred during the course of adjuvant or palliative chemotherapy in 20 patients (48%).

Tables III-V give the values of cardio-specific markers before starting and after finishing the individual chemotherapy cycles. The tables show that the incidence of coronary ischemia and temporary heart failure was fairly frequent in the course of the chemotherapy. A more frequent incidence of elevated cardio-specific enzymes was observed in continual regimens than in a bolus application of fluorouracil.

In the course of the anticancer therapy, TSH and FT4 levels were also monitored in all patients. Reduced TSH levels in the course of the chemotherapy were observed in 9 patients (21%), without any changes in FT4 values. Increased TSH levels were observed in 4 patients (10%), again without any changes in FT4 values.

### Discussion

In oncological practice little attention is paid to internal complications suffered by oncological patients. In connection with chemotherapy, cardiotoxicity most commonly occurs with use of cytostatic drugs of the anthracycline group (doxorubicin, epirubicin), and less frequently in anthracenoids (mitoxantrone). Alkylation substances are toxic (cyclophosphamide, ifosphamide), particularly in higher doses, and occasionally this undesirable effect is also observed with cisplatin, vincristine and taxanes (6). Recently cardiotoxicity has also been described as a serious side-effect with 5-fluorouracil. Such side-effects include early manifestations of cardiotoxicity, characterized by an acute coronary syndrome, congestive heart failure or heart rhythm disorder. The frequency of the incidence of heart problems (5-FU related cardiotoxicity) is described in very different ways in the literature, depending on the dose and therapeutic regimen (7). In bolus regimens (e.g. Mayo regimen) the incidence of acute or sub-acute 5-FU cardiotoxicity is given as between 2% and 5%.

In current clinical practice, continuous infusion of 5-FU is the treatment of choice because of its lower toxicity profile and improved efficiency. However, the incidence of cardiotoxicity has increased by up to 7-18% (8). De Gramont’s and FOLFIRI regimen-related cardiotoxicity...
was studied in previous reports to demonstrate its effect on the myocardium, but the true incidence of its cardiotoxicity is still not fully known (9, 10). The problem lies mainly in 5-FU acute toxicity on the myocardium, which is not often diagnosed. The mechanism of this effect has not yet been fully explained. It is presumed that 5-FU causes temporary vascular spasms of coronary vessels and ischemia of a particular part of the myocardium (7, 9). This may subsequently lead to disorders in heart rhythm or to congestive heart failure. Diagnosis is difficult because this is a reversible, temporary condition, which depends on the dosages with which the chemotherapeutic drugs are administered. Sudhof et al. investigated the influence of intravenous application of 5-FU on the diameter of the brachial artery using high resolution ultrasound. Half of the patients showed a contraction of the brachial artery after completion of the 5-FU application. This experiment confirms the fact that the application of 5-FU is usually accompanied by arterial vessel contractions, which is likely to represent the first step in 5-FU-induced cardiotoxicity (11). This finding also corresponds with the results in our group of patients where we observed a slight elevation of TnI in 24 (57%) of the patients (cut-off 0.04 µg/L). When the examined cut-off was 0.3 µg/L, which is already a very significant value for the confirmation of coronary ischemia, 6 (14%) of our patients had a pathological value in the course of chemotherapy. In the anamnesis of all these patients, temporary pains in the chest or palpitations were mentioned. In the course of chemotherapy, we also registered a pathological value for BNP suggesting heart failure in 20 (48%) of our patients. In most cases BNP pathological values correlated with clinical symptoms of developing heart failure which would otherwise be overlooked. Clinical symptoms of heart failure (swelling, breathing problems and others) occurred in these patients in the course of chemotherapy, but they disappeared in most cases after its completion. The results of our study show that acute cardiotoxicity of 5-FU or irinotecan is fairly common and that it requires appropriate attention. A standard examination before the application of chemotherapy, apart from thorough anamnesis and physical examination, should also include ECG. In patients with positive anamnesis of a cardiac disease, echocardiography should also be performed. In the routine clinical practice of oncological centres, access to echocardiography is often difficult. Also the frequency of the examination, which would have to be performed in every instance of heart failure in the course of anti-cancer therapy, would be financially unjustifiable. Therefore, a laboratory assessment of BNP and TnI as markers of heart failure and coronary ischemia seems to provide the best perspective for patients undergoing treatment with 5-FU chemotherapy.

Disorders of thyroid gland function in connection with anticancer treatment are well described, particularly in haematological malignancies, mainly in patients with Hodgkin’s disease where there is an effect of actinotherapy in the area of the mediastinum superius (12). Recently several studies have been published which deal with disorders of the thyroid gland function in patients with lung and breast carcinoma where there is also a connection with radiotherapy (12-14). Our study only states a higher incidence of TSH abnormalities in the monitored group of patients in the course of anticancer therapy. In view of the size of the group, it is impossible to say whether this is a co-occurrence of two independent diseases or a consequence of chemotherapy on thyroid gland function. The pilot study demonstrated that in patients undergoing chemotherapy treatment it is advisable to look for possible cardiotoxicity in any chemotherapy drug and, simultaneously, to monitor the parameters of thyroid gland function. This systematic monitoring will result in an improvement in the quality of life for cancer patients.

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