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Chemotherapy and chemoembolization of patients with oncopathology as a risk factor for the development of myocardial dysfunction

Saule Kubekova[1], Natalya Zagorulya[1], Yelena Ryb[2], Niyaz Malayev[3], Aruzhan Abdilda[1]

[1]*Department of Cardiology, Astana Medical University, Astana, Kazakhstan*
[2]*Department of Internal Medicine with a Course of Gastroenterology, Endocrinology and Pulmonology, Astana Medical University, Astana, Kazakhstan*
[3]*Department of General and Thoracic Surgery, National Scientific Medical Center, Astana, Kazakhstan*

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Corresponding author:
Saule Kubekova.
E-mail: dr.kubekova@gmail.com;
ORCID: 0000-0001-5358-3690

Abstract

Considering the aging of the population, the combination of cardiovascular diseases with oncopathology is gaining more relevance. Liver cancer occupies the 6th place in the structure of the incidence of neoplasms and the 3rd place in mortality from all oncological diseases. One of the main methods of treating patients with liver cancer is chemotherapy and chemoembolization, which significantly affect the myocardium, developing cardiotoxicity. Myocardial damage is reflected in the development of heart failure, which subsequently is the main cause of death in cancer patients.

Key words: liver cancer, cardiotoxicity, chemoembolization, treatment, heart failure

Introduction

Oncological diseases occupy the second place among the causes of death not only in the world, but also in the Republic of Kazakhstan, giving way to cardiovascular diseases [1-3]. Currently, the probability of diagnosing cancer during a lifetime is 40% in men and 38% in women [4]. Recent advances in early diagnosis, accurate staging, and more effective therapy have resulted in improved survival rates for cancer patients. Over 25 years (the period 1991-2015), cancer mortality decreased by 26%. This means a reduction in cancer deaths by about 2.4 million over this period [4]. With increasing cancer survival, an increasing proportion of these patients are living with long-term adverse effects and complications of cancer. Chemotherapy - anthracyclines, trastuzumab, cyclophosphamide, 5-fluorouracil, angiogenesis drugs, thyroid kinases, etc. increase the risk of cardiovascular diseases, having a direct toxic effect on the myocardium [5,6].

The purpose of the review: to reveal the problem of myocardial dysfunction in patients with oncopathology receiving chemotherapy and chemoembolization.

Cardiovascular diseases (CVD) remain the main cause of death and disability in developed countries, accounting for 32% of total mortality [7]. Despite the measures taken for prevention and treatment, the overall cardiovascular morbidity (CVM) over the past years of the 21st century in the Republic of Kazakhstan (RK) has increased by 2.5 times, from 6775.6 per 100 thousand population in 2001 to 16982 ,9 in 2020 [8]. For the first time registered CVD in adults (18 years and older) over these years increased from 1841.3 (2001) to 4378.6 (2020) per 100 thousand population, including arterial hypertension (AH) from 614.0 to 2138, 9, coronary heart disease (CHD) from 321.5 to 604.2 and cerebrovascular disease (CVD) from 210.3 to 433.7, respectively. The growth of CVD, along with other factors, is to some extent due to the increase in life expectancy of the population. The vast majority of CVD occurs in the elderly and senile,

but they most often have comorbid diseases. Approximately 80% of older people have three or more diseases [9-11], which significantly increases mortality, so with two or more diseases it reaches 82% [12,13].

The above circumstances become particularly relevant when CVDs are combined with oncopathology [14-17]. Cancer diseases remain the main cause of mortality in patients of all age categories, and their combination with CVD increases the risk of morbidity and mortality [18,19]. As the population ages and life expectancy increases, the number of cancer cases increases [20]. In view of the observed increase in CVD over the past years of the 21st century by 2.5 times, including newly diagnosed major CVDs among adults: AH by 3.48 times, IHD by 1.88 times and cerebrovascular diseases (CVD) by 2.06 times [8]. At the same time, the average life expectancy of the population of the Republic of Kazakhstan in recent years has increased from 68.4 (2010) to 77.1 (2020) by 2.7 years.

Conducted by K.C. Stoltzfuet al. [18] an analysis of 7,529,481 cancer deaths showed that 5.24% were due to heart disease and the CVD mortality rate was 10.61/10,000 person-years, and the standardized rate was 2.24 (95% CI: 2.23–2, 25). The authors noted that the risk of CVD mortality increases with age and increases in cancer survivors over time. Here, it should be noted that the newly diagnosed oncological incidence in the Republic of Kazakhstan has decreased over the past 20 years from 195.9 (2001) per 100 thousand population to 94.2 (2020), and mortality has also significantly decreased from 134.4 to 75.0 respectively. However, advances in the development of new therapies have not only improved the survival of cancer patients, but also increased morbidity and mortality from treatment side effects, in particular due to cardiotoxicity [9,10]. Along with this, observed in practice quite frequent comorbidity of oncopathology with constantly growing CVD, contributed to the development of a new direction in medicine - cardio-oncology [14,17,21]. One of the key issues of cardio-oncology is the study of the effect of chemotherapy drugs on the myocardium.

Currently, chemotherapy remains one of the main methods of cancer treatment [22]. Undoubtedly, the use of new chemotherapy drugs has significantly improved cancer survival rates. However, against this background, the problem of cardiotoxicity, which can be caused by many types of antitumor drugs, becomes even more urgent [23,24]. Thus, the use of drugs such as anthracyclines and kinase inhibitors is associated with the development of chronic heart failure [25,26] and, accordingly, the death of patients [27]. Among the complications of cardiotoxicity during chemotherapy, dilated cardiomyopathy has the most unfavorable prognosis, associated with extremely high two-year mortality, reaching 60% [28,29]. Complications caused by chemotherapy cardiotoxicity negatively affect the quality of life and survival of patients, regardless of the prognosis associated with the underlying disease [30] and, according to leading ACC/AHA experts, the risk of premature mortality from cardiotoxic complications may be higher compared to the risk of death from the tumor process.

Today cardio-oncology is developing at a significant pace, working groups are being formed within such world communities as ACC, AHA, ESC, RCO, developing regulatory documents in this area. There is a sufficient number of studies of cardiotoxicity when using systemic and targeted chemotherapy. Hooning MJ et al. [31], who studied the 10-year risk of developing cardiovascular complications (CVC) in patients who survived after cancer, and later Chowetal [32] found an increase in the risk of cardiovascular death from 1.3 to 3.6 times and up to 18.5 times more complications such as hypertension, diabetes mellitus and dyslipidemia compared with patients of the same

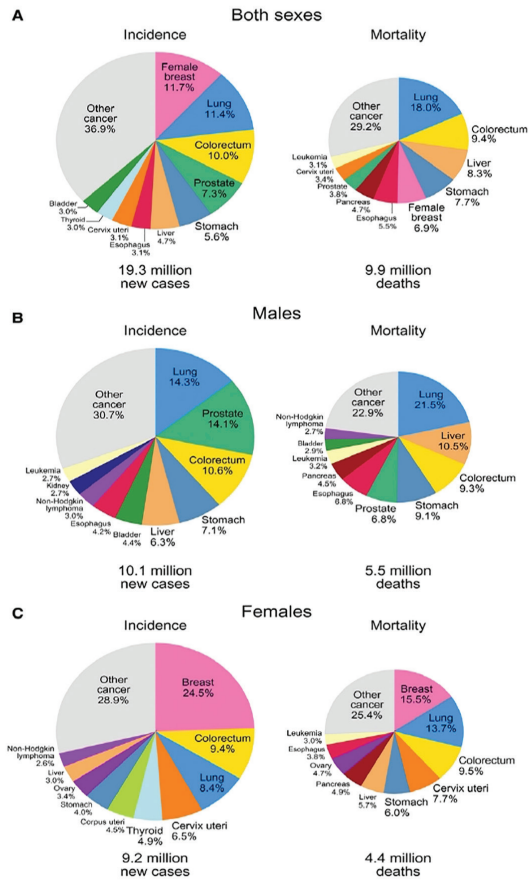

Figure 1 - Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries (https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21660#:~:text=Worldwide%2C%20an%20estimated%2019.3%20million,cancer%2C%20with%20an%20estimated%202.3)

age group who do not have oncological pathology in history. The increased risk of CVD in cancer survivors is probably the result of an aging population combined with the direct and indirect [33] effects of cancer therapy, which extend to multiple systems [34]. According to Koelwyn et al. [35] CVD will become even more common among cancer patients as a result of the continued decline in cancer mortality combined with a rapidly aging population.

With the development of medical technologies, traditional surgical treatment of tumors is becoming less invasive [36]. The treatment of cancer patients is developing at a rapid pace. There is increasing use of minimally invasive techniques such as chemoembolization and radioembolization, used in hypervascular tumors by arterial embolization, such as hepatocellular carcinoma (HCC) [37].

HCC is the 3rd leading cause of death in cancer patients, accounting for more than 550,000 deaths worldwide each year with a 5-year survival rate at all stages of 8.6% [38-40]. The choice of treatment tactics depends on the degree of hepatic dysfunction and the general condition of the patient [41]. Transarterial hepatic artery chemoembolization (TACE) is successfully used in HCC, which is one of the common cancers with high mortality [42] and has become the gold standard of treatment in patients with HCC [43,44]. In traditional chemotherapy (intravenous and oral chemotherapy), the effectiveness of anticancer drugs is limited by the low concentration of the drug in the tumor, while nonspecific systemic toxicity of chemotherapeutic agents is observed, including cardiotoxicity and the development of drug resistance [45]. Delivery of a chemotherapeutic drug to the oncological focus in TACE, excluding systemic effects on

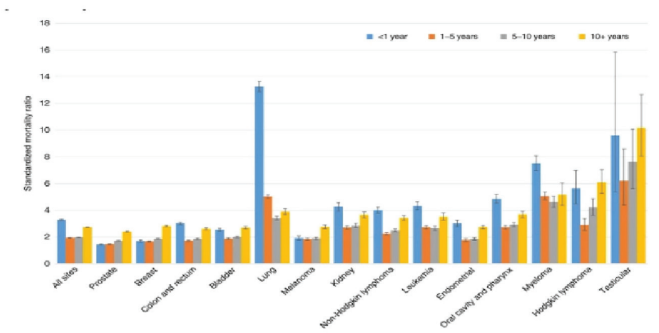

Figure 2 - Standardized mortality ratios (SMRs) of fatal heart disease among cancer patients by cancer subsite (https://www.nature.com/articles/s41467-020-15639-5 (with the author's permission)

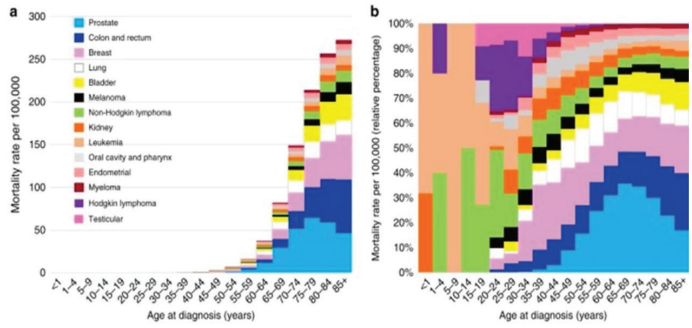

Figure 3 - Age adjusted mortality rates per 100,000 for fatal heart disease by cancer subsite. (https://www.nature.com/articles/s41467-020-15639-5 (with the author's permission))

the body, increases its specific effect on the tumor. Therefore, TACE is a widely used minimally invasive treatment technique that provides increased survival of patients with HCC [46,47]. However, the degree of influence of TACE on cardiotoxicity and, as a consequence, myocardial dysfunction has not been studied. All this has served as a reason to initiate a study on the influence of TACE on functional state of myocardium in patients with liver cancer. Patients with concomitant CVD and complications due to previous conventional chemotherapy are of particular interest in this regard.

Achieving positive results in cancer treatment is an important task for the healthcare system both in the world and in Kazakhstan. Despite the increase in scientific, clinical and biological knowledge about the prevention and treatment of malignant neoplasms, cancer remains one of the leading causes of enormous damage to the health care system [48]. However, behind the mask of malignant neoplasms, CVDs are often hidden, as well as well-known risk factors for their development and/or aggravation (smoking, sedentary lifestyle, heredity, age, etc.). Identified risk factors and early diagnosis of CVD can be corrected by prescribing preventive and therapeutic and rehabilitation measures. Thus, in the OUTCOME and PRADA studies, a positive effect of a prophylactic dose of angiotensin-converting enzyme inhibitors (ACE inhibitors) and b-blockers (BABs) on the myocardium was demonstrated. The primary outcome, the reduction in left ventricular ejection fraction from baseline to the end of the study, was -0.8% in the ACE-I group compared with the placebo group -2.6% (p = 0.026) [49]. It should be emphasized that the tactics of managing and treating cardiotoxicity in cancer are quite well and fully developed in traditional chemotherapy [13,14,17]. Modern innovative methods of administering chemotherapy drugs have not yet become widespread, and there are practically no studies on the management of patients with concomitant CVD and complications [50].

Conclusion

Modern cancer therapy has improved survival rates in patients with cancer, but the cardiotoxicity that develops with chemotherapy is a serious problem. To prevent morbidity and mortality from cardiotoxicity during anticancer therapy, especially in patients with cardiovascular disease, it is important to properly understand the underlying mechanism of myocardial dysfunction.

Questions about the effects of chemoembolization on the myocardium are still open. New studies in this direction will help to study in detail the clinical role of innovative therapies in the development of myocardial dysfunction.

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