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REVIEW ARTICLE

Carcinogenic potential of antitumor therapies - is the risk predictable?

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Summary

The growing number of successfully cured cancer patients has created a new field in oncogenesis. The life expectancy of such patients has increased, however this favorable event may create enough time for epigenetic events to occur which can cause a new carcinognic event, i.e. a secondary malignancy. The terms in use are second primary malignancies as well as therapy-related neoplasms in case the treatment of the first neoplasm is a direct cause. Second primary malignancies can be hematological neoplasms or solid tumors, with solid tumors having higher frequency. Hematological malignancies, especially t MDS (therapy-related myelodysplastic syndrome) and t AML (therapy-related acute myeloid leukemia), are causally associated with cytotoxic chemotherapy, while secondary solid tumors are related to radiotherapy.

The pathogenic mechanisms of clonal selection in second malignancies are in connection with induction of fusion oncogenes, induction of genetic instability, selection of resistant cell clones and hereditary predisposition. The most common oncogenic agents are external (antineoplastic systemic treatments including radiation therapy), patient-specific factors (genetic, demographic, hormonal) and tumor-specific factors (tissue radiosensitivity, immunodeficiency).

There are special features in the clinical picture, biological characteristics and evolution of the second neoplasm – different latency period, aggressive course and treatment resistance. Risks, types and characteristics of secondary malignancies are analyzed in specific groups of patients. For example, the peak of t-AML is several years after a primary malignancy and for solid tumors, the risk increases progressively during the observation period.

In this review, the authors outline that the risk of second malignancies is predictable and can be controllable by adequate monitoring of patients as well as by personalized treatment of the first neoplasm.

Key words: *second malignant neoplasm, second primary malignancies, therapy-related neoplasm*

Introduction and background

The achievements in modern oncology and hematology, based on the findings of molecular biology, genetic engineering, and pharmacology, have created prerequisites for improving the duration and quality of life in some neoplastic diseases and even cure in others. Yet, antitumor therapies are accompanied with long-term adverse effects. Reducing mortality of cancer patients and increasing the number of patients who have overcome their disease, as well as enhancing the experience of the specialists in this field, constitute an optimistic view, which, however, could be accompanied by an unfavorable event - the development of a secondary malignant disease.

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According to data from the National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER), cancer patients have a 14% increased risk of a new malignancy compared to the general population [1].

In medical literature, there are terms with similar content. According to the National Cancer Institute (NCI), terms include:

Secondary cancer: Carcinoma metastases with identical histological and biological characteristics but distant from the primary tumor. This also includes cases of malignant transformation of a primary benign formation [2].

Second malignancies: New primary tumor (*de novo*) unrelated to the first malignant disease diagnosed months and years after. It may be of the same or different histological type, from the same or other organ as the primary tumor but is always the result of an independent genetic event. This term overlaps with the commonly used term "second primary malignancies". Predisposing factors in these cases may be hereditary, environmental and iatrogenic.

Only malignancies, for which antineoplastic therapy is the most likely etiologic factor, can be termed "therapy-related neoplasms".

The risk of a second treatment-related malignant disease may be due to the treatment of autoimmune diseases (multiple sclerosis and rheumatoid arthritis) and organ transplantation as a result of pre-existing cytotoxic and immunosuppressive therapy.

History of the problem

The first findings of oncological diseases are dated 4200 years back. Skeletons of Egyptian mummies hold evidence of primary and metastatic bone tumors.

Only at the beginning of the 20th century the first attempts started to treat malignant diseases with cytotoxics [3]. They are associated with the name of Paul Ehrlich, who introduced the term chemotherapy to treat infectious diseases but also attempts to use the first alkylating cytotoxics. By the mid-1960s the leading trend in oncology therapy was surgery. A relationship between myeloma and leukemia was reported for the first time at the end of 1960s [4,5]. At that time, with the enrichment of specialists experience and the increase of the follow-up period of treated cancer patients, evidence of a second malignant disease has gradually emerged.

The first report of malignant tumors after Hodgkin's lymphoma treatment dates from 1972 [6].

The term "Second Malignant Disease" has been introduced in 1992 [7].

In the last 30 years, the number of reports of second malignant tumors has increased substantially.

Frequency of second malignant disease

Second malignancies can be haematological neoplasias and solid tumors, the latter being more common.

Hematologic malignancies, especially t MDS and t AML, are thought to be causally associated with cytotoxic chemotherapy, and secondary solid tumors with radiotherapy.

The significance of this problem is justified by the fact that the WHO classification of myeloid neoplasias in 2016 has a special place for t-MN (therapy-related myeloid neoplasia): t MDS + t AML as a unique clinical syndrome [8].

In adults, 7% of AML cases are associated with treatment. The risk for AML after chemotherapy of the first malignancy is increased 4.7 times compared to the general population [9-11].

t MDS is most common after non-Hodgkin's lymphomas (NHL) - 28%, breast cancer 16%, myeloma 6%, and prostate carcinoma 6% [12].

Of the solid second neoplasias breast carcinoma is first in frequency, followed by bladder carcinoma, thyroid carcinoma and skin cancer [1,13].

Epidemiology

Mostly women are affected by a second malignancy (after breast cancer). A Swedish population-based study found that 10 years after breast cancer therapy 2.15 out of 1000 women developed t AML [12].

In the past 30 years there has been a tendency of increased risk of t AML in NHL, reduced risk for ovarian carcinoma and multiple myeloma, and unchanged risk of breast carcinoma and Hodgkin's lymphoma. The results are related to new treatment trends and changes in cytotoxic regimens [11].

Pathogenetic mechanisms of clonal selection in second malignancy

The genes responsible for carcinogenesis belong to the groups of tumor-suppressor genes, oncogenes, and genes for repairing the DNA. Ninety percent of treatment-associated myeloid neoplasias have an abnormal karyotype, 1/3 of the cases with t-AML have a p53 gene mutation, monosomy 5.7, while complex cytogenetic abnormalities are common.

In 2016, Heuser [12] discussed the following mechanisms of oncogenesis in treatment-related t-AML and t-MDS:

Direct induction of fusion oncogene

Cytotoxic therapy induces oncogenes in a target cell followed by clonal overgrowth of transformed cells.

Topoisomerase 2 (TOP2) normally induces breakdown of the double-stranded DNA during replication and subsequent binding of the two strands after replication. However, TOP2 inhibitors (e.g. etoposide) stabilize this breakage, allowing for the recombination of the terminal unwound DNA regions of two different chromosomes. Such a sensitive region exists in the KMT2A gene, and the KMT2A / MLL fusion genes are one of the most potent in oncogenesis of leukemias, including t-AML.

Induction of genetic instability

Cytotoxic therapy with alkylating agents, often in combination with radiotherapy, induces chromosomal aberrations that lead to instability and later leukemogenic aberrations. This hypothesis explains the long latency period of t-MN and the high incidence of complex cytogenetic aberrations in them [14].

Selection of a pre-existing malignant transformed and resistant cell clone

The frequency of p53 mutation is higher in t-MN compared to *de novo* AML and is quite specific for t-MN. Cells with acquired mutation of p53 accumulate after chemotherapy and give rise to clonal hematopoiesis that evolves into AML after additional genetic mutations.

Hereditary predisposition to several malignancies

In a GAMLSG study [15], two groups of patients with primary malignancy - untreated and treated with cytotoxic agents - were similar in the incidence of secondary AML (3 and 7% respectively in both groups) and similar latency (4 and 5 years). It is considered that in these cases the risk of second malignancy is predetermined by germline mutations of BRCA, TP53 and BCL2 genes. Primary neoplasias predisposing to second neoplasia in this study were prostate cancer, bladder carcinoma and renal cell carcinoma (they were more commonly registered in the second group of patients - GAMLSG). Other tumors associated with a second malignancy (myeloma, retinoblastoma, Wilms' tumor) are also known [15].

Characteristics of the most common oncogenic agents

Oncogenesis is a multifactorial process. The main factors are external, patient-specific and immune dysfunction-related.

1. External factors

Antineoplastic treatment

According to the oncogenic potential, the antineoplastic drugs are divided into high risk (melphalan, etoposide), moderate risk (cyclophosphamide, doxorubicin, cisplatin), low risk (vinca alkaloids) and unknown risk (taxanes). Well studied are the effects of two groups of cytotoxic alkylators and topoisomerase inhibitors [16].

✓ Alkylating cytotoxics - t AML and t MDS occurs 2 years on average after treatment and reaches a maximum frequency between the 5th and 10th year, i.e. they have a long latency period, often with a prior MDS phase. The prognosis is adverse, associated with complex karyotype, unbalanced loss of genetic material, aberrations of 5 and 7 chromosomes. The risk of t AML and t MDS increases with age. These are 70% of the cases of t AML and t MDS [12].

✓ Topoisomerase inhibitors and anthracyclines - they have a short latency period and 2-3 years after treatment with them t AML (often M4-M5) develops and balanced chromosomal translocation of t11q23 - MLL gene is typical. There is usually no MDS phase. Second malignancies caused by topoisomerase inhibitors are better influenced by treatment. These are 30% of the cases of t AML and t MDS [12,16].

There is insufficient data on the relationship of target therapies to second malignancy:

✓ *Vemurafenib (Zelboraf®)*, inhibitor of BRAF serine-threonine kinase, and *dabrafenib (Tafinlar®)*, inhibitor of RAF kinases, which target BRAF protein and are used to treat melanoma, are associated with increased risk of squamous cell skin carcinoma [17].

✓ *Tyrosine kinase inhibitors* - the use of this target therapy has been initiated with CML since 1996 (Imatinib) and patient observation has been ongoing for 20 years. The therapeutic effect is exceptional and, for the time being, no causal link can be established between TKI and a second malignancy [18,19].

✓ *Epigenetic therapy* - agents with hypomethylating and histone-deacetylase inhibitory activity are discussed as potentially carcinogenics [20].

Hormonal therapy also has a proven oncogenic effect.

There is a statistically significant increase in the incidence of endometrial carcinomas in tamoxifen-treated patients with breast carcinoma [21].

The mutagenic effect of radiation therapy is well-known

Low doses of radiation result in single-strand break, followed by breakage of double-stranded DNA molecule and malignant transformation. Another mechanism of radiation damage is directed to the proteins responsible for the repair of the injured structure of DNA. Both dose and radiation are important for the risk of second cancer [22,23].

✓ *Radiotherapy dose* – The incidence of secondary cancers of the breast, lung and sarcomas is proportional to the increase in dose. Paradoxically, following Hodgkin's lymphoma radiotherapy, the risk of thyroid carcinoma is greatest at doses of 20-29 Gy and decreased at doses above 30 Gy. This can be explained by the fact that higher doses destroy the tissue and reduce the possibility of carcinogenesis [22-24].

✓ *Radiation equipment* - there is evidence that changes in the intensity of radiation therapy (IMRT) are associated with a 2-3-fold higher risk of second malignancy compared to conventional radiation therapy, especially in children [25].

Impaired immune regulation is associated with treatment

Current immunotherapy is a new branch in oncological therapy, including monoclonal antibody therapy, chimeric antigen receptor (CAR) therapy, and checkpoint blockade [26]. Data on the occurrence of treatment-related malignancies are scarce. There are no randomized multicenter studies on this issue with results to be trusted.

✓ Opinions are reported on the development of secondary solid tumors causing immunosuppression due to the complexity of monoclonal antibody Rituximab used in the treatment of indolent NHL. Rituximab causes immunosuppression, which could lead to second cancer development [27,28].

✓ In this respect, the immunomodulator lenalidomide has been well studied. A meta-analysis of 7 clinical studies established a causal link between it and second malignancies [29].

✓ The risk of immunosuppressive treatment with azathioprine following organ transplantation is also significantly increased [30].

2. Patient-specific factors

Genetic

The polymorphism of genes encoding enzymes for the transport or metabolism of medicines, as well as genes responsible for repairing the damaged DNA, contributes to the tendency of developing a second neoplasia. Variants of cytochrome P450 and glutathione S transferase predispose to the occurrence of a second malignant disease after radiation-chemotherapy. Changes in the bone marrow microenvironment are an individual factor for MDS/AML development following treatment of myeloma [31].

Genetic features of the erythropoietin-promoter gene are related to decreased erythropoietin production in multiple myeloma patients who develop MDS [32].

Age

It is necessary to reach a certain age for the modifying effect of toxins such as tobacco or alcohol or a hormonal status that creates a predisposition to certain tumors. A well-known fact is the increased breast radiosensitivity in women between 10 and 40 years of age and low sensitivity before puberty [23]. Germline mutations in children may increase the risk of radiation-induced second neoplasia.

Sex

Girls are at increased risk after treatment for lymphoblastic leukemia and Hodgkin's lymphoma (relative risk for second malignancy is 19.9 for girls and 8.4 for boys) [23].

Hormonal factors in oncogenesis

There is lower risk of radiation-induced breast cancer in early menopausal women (sometimes menopause is chemotherapy-induced) [23].

Harmful habits

Smoking: Women with breast cancer treated with radiation therapy and mastectomy have an additional risk of lung carcinoma if they smoke [23].

3. Tumor-specific factors

✓ *Tissue sensitivity to radiotherapy:* According to National Council on Radiation Protection (NCRP), the most common secondary tumors after radiotherapy affect the colon, stomach and lung, and much less the small intestine [23]. Thyroid carcinomas are common in children after radiation therapy.

✓ *Immune deficiency:* Lymphoproliferative disorders, e.g., hairy cell leukemia, are characterized by immune dysregulation and an increased incidence of second neoplasia. This disease is characterized by a V600E activating mutation of serine-threonine kinase BRAF, resulting in neoplastic transformation [33-35].

Prognosis of second primary malignant disease

Haematological diseases are better studied in terms of prognosis. In t-MN, prognosis depends on the cytogenetic risk profile - 50% of patients with t MDS and t AML have unfavorable cytogenetics and the most frequent molecular aberration affects TP53 - 33%. The survival of those patients is less than a year [10-12].

Special features in clinical picture, biological characteristics and evolution

A second malignancy differs from a primary neoplastic disease of the same cellular nature in the following:

✓ Different *latency period;*

✓ *The age* for colorectal, lung, and gastric carcinomas after treatment for Hodgkin's lymphoma is abnormally early;

✓ *Aggressive course:* More rapid progression of t MDS to AML (mean time interval 4-7 months, and in primary MDS 4-11 months, mean 9). The mean survival rate of t AML is lower than *de novo* AML [36,37]. Endometrial carcinomas following tamoxifen treatment have a more aggressive course but are detected in a localized stage with an operative treatment option.

✓ *Resistance to treatment:* The role of the P-glycoprotein (P-gp) product of the MDR1 gene is known [38]. t AML has a poor response to treatment, making the patients immediate candidates for stem cell transplantation.

Second malignancy in specific populations according to the primary tumor and its treatment

✓ *Childhood cancers:* Children have excellent prognosis for survival, but also a relatively well-studied risk of second malignancy . Relative risk is highest after treatment of Hodgkin's lymphoma – 9.7 acute blastic leukemia - 5.7; NHL - 3.2 (CCSS-childhood cancer survivor study) [23]. In ALL, more than 80% of children are considered cured after combined chemoradiotherapy, but there is a risk of second neoplasia, especially in cranial radiotherapy. In children, there is a 20-year cumulative frequency of a second tumor of 3-4%, and with continued follow-up after 30 years - 6%. The peak of t AML is several years after primary malignancy, and for solid tumors the risk increases progressively during the observation period. Secondary CNS tumors (meningeomas, gliomas, lymphomas) associated with radiotherapy are most common! The minimum latent period for secondary CNS neoplasias varies from 9 years for gliomas up to 20 years for meningeomas. Children have rarely pulmonary secondary cancers, perhaps because not all of them reach a critical age for this tumors.

✓ *After prostate carcinoma:* Abdominal and pelvic radiotherapy can contribute to the development of colonic and bladder carcinomas. Thyroid and thymus cancer, carcinomas of skin, lung, NHL have also been reported [23,39].

✓ *After breast cancer treatment:* Contralateral breast carcinoma may develop (especially related to radiotherapy below 40 years of age) [23]. Tamoxifen reduces this risk, but results in 4-fold increased risk of endometrial cancer. Lung carcinoma as second neoplasia, is more often ipsilaterally located after mastectomy and radiotherapy, covering a large area with the supraclavicular, axillary, and/or internal mammary nodal region, and the esophagus. Sarcomas are registered - a 7-fold increased relative risk after treatment for breast carcinoma. They are associated with radiotherapy but angiosarcomas develop on the basis of chronic lymphoedema of upper limb after mastectomy [23]. t AML has a relative risk of up to 17.4% after combined radiation/chemotherapy (especially dose-enhanced regimes with cyclosphamide) [40].

✓ *After testicular tumors:* Men with seminomatous and non-seminomatous tumors diagnosed at around 35 years of age have a cumulative risk of second solid tumors of 36% [23]. Etoposide and cisplatin combined with radiotherapy are hazardous. These tumors have a risk for melanoma, t ALL, t AML, gastric, colon, rectum and pancreatic cancers. There is a causal link of leukemias with previous radiotherapy in large areas, including the mediastinum [23,41].

✓ *After Hodgkin's lymphoma:* In the early localized stage of disease, 90% of the cases are cured. There is a 25-year cumulative incidence of second neoplasia - 19%, with solid tumors in 75-80% of them. Especially susceptible are young patients between 20-30 years of age treated with combined radiation-chemotherapy. The risk decreases after 35 years of age [23]. The most common second neoplasias are breast cancer (15-55-fold increased risk and cumulative frequency 12-35% after 20 years of follow-up); thyroid cancer - particularly

sensitive are children (relative risk 10-35, after 30 years of follow-up the cumulative frequency is 4.4%); lung cancer, gastric cancer (the cumulative frequency is 4.4%, primarily men; colorectal carcinoma (relative risk 1.9-3.2; males); bone tumors (relative risk 6.2 - 31 years and sarcomas [42,43].

✓ *After NHL:* Second neoplasias (sarcomas, breast, lung, colorectal, thyroid, gastric carcinoma) are recorded in 2.5% of patients after standard chemotherapy - CHOP [27,44,45].

Prevention of second malignancy

✓ *Identification of potential biomarkers for patients at risk for second malignancy.*

✓ *Personalization of treatment*, meaning sufficient volume of treatment for optimal effect and maximum survival, with minimal risk of second neoplasia. Aimed at this, attention in recent decades has been paid to stratification of patients in different groups according to the risk of recurrence after standard therapy. This is based on identified prognostic factors for the disease outcome and predictive factors for the effect of particular therapeutic methods. In patients with low prognostic risk it is possible to limit the area of radiation therapy and the volume of chemotherapy, avoiding also cytotoxics with a high carcinogenic potential. For example, in testicular tumors, radiotherapy is limited to paraaortic fields and in lower doses [46]. Another suggestion is the application of new techniques for radiation therapy - partial breast irradiation.

✓ *Dispensary monitoring program specific for the expected second neoplasia terms and diagnostic methods.* It is proposed that such a program should include an assessment of the patient's carcinogenic risk, the expected benefit of screening for second neoplasia, expected life expectancy (special attention in young patients) and patient priorities.

Conclusions

1. There are real data (abbeit not sufficient) on the risk of treatment-related second malignancies.
2. Mainly haematological neoplasias are associated with cytotoxic chemotherapy, and solid tumors with radiotherapy.
3. The risk is predictable and subject to control by adequate monitoring of patients and personalized treatment of the first neoplasia.

Conflict of interests

The authors declare no conflict of interests.

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