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Systemic therapy of inflammatory breast cancer with type 2 diabetes mellitus – Prevention of high risk of radiation-induced progression of tumor tissue cancer

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Abstract

Introduction. *Cancer mortality in diabetic patients has been reported to increase moderately compared to non-diabetic patients.*

The aim of the study aimed to assess the findings and identify radiotherapy's role in the comprehensive care of diabetic IBC patients with various hyperglycemia correction strategies.

Methods. *Patients with diabetes have shown a higher risk of radiation-induced cancer progression for tumor tissue, especially for inflammatory form. For 7 patients, to continue systematic chemotherapy with a scheme change (consecutive anthracyclines-taxanes, 2-week interval) and insulin with individual scheme for hyperglycemia correction on the basis of glycemic control – 1st group, the other (7 patients) – 2nd group, was given radiotherapy to the breast gland and lymphatic drainage ways. 45–50 Grey was prescribed for 25-28 fractions (per 1.8-2.0 Grey), 46–50 Grey in 23-25 fractions were used for zones of regional metastasis and for hyperglycemia correction metformin 2000 mg/day PO divided q8-12hr with meal on the basis of glycemic control.*

Results. *Assessed were the number of patients who qualified for surgery and overall survival for 24 months. 2nd group showed a superior response following resistance to prior systemic treatment. Thus, 5 (71.41%) of the 7 patients exhibited a consistent response – complete or partial regression. There were only 2 individuals (28.61%) who responded to treatment among the patients who maintained chemotherapy.*

Conclusions. *Breast cancer of the aggressive IBC variety requires multidisciplinary treatment from breast surgery, medical, and radiation oncology. Patients with diabetes appear to experience more side effects from radiation therapy than patients without the disease. Hyperglycemia, higher total RT doses, and radiosensitizers are a few techniques that can improve the impact of RT on local-regional management. Local-regional control rates for IBC are increasing with an individual patient strategy. Metformin also improves insulin resistance and has anticancer benefits.*

Keywords: inflammatory breast cancer, radiotherapy, response to treatment, diabetes mellitus, various hyperglycemia correction

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Abbreviatures
IBC – inflammatory breast cancer

INTRODUCTION

Early-stage breast cancer is virtually curable and the prognosis for late-stage treatment is poorly predictable. This applies fully to forms such as Inflammatory Breast Cancer (IBC) [1].

Managing IBC patients is a complex issue that has been the subject of oncology controversy. There are many conservative professionals who consider IBC a contraindication to surgery and focus on chemoradiation therapy [2].

Several papers have revealed a relationship between recurrence-free survival and overall survival growth and the degree of surgical intervention. Radical mastectomy with advanced tissue flap closure of the defect is positioned as the method of choice for surgical management of IBC patients [3].

In many IBC cases, chemotherapy is ineffective or the process progresses against its background. The emergence of resistance to systemic treatment is difficult to predict. It may progress rapidly after the initial chemotherapy block is successful. In other cases, the effects of 6-8 blocks of systemic therapy are not sufficient to transition to surgical invasion. Next, there is an important dilemma in continuing treatment. Most international consensus considers chemotherapy regimen changes or radiation therapy (RT) scheduling issues [4].

Both diabetes, and cancer are known to be prevalent worldwide. Cancer mortality in diabetic patients has been reported to increase moderately compared to non-diabetic patients [5].

For example, women with diabetes have the 27 percent increased risk of developing breast cancer. Insulin resistance, an important feature of diabetes, is associated with reduced incidence and survival of breast cancer [6].

Radiation therapy for breast cancer uses high-energy x-rays, protons to kill cancer cells. Fast-growing cells, such as cancer, are more sensitive this therapy. Radiation therapy can be used to treat breast cancer at almost any stage. Radiation therapy is an effective way to reduce the risk of breast cancer that recurs after surgery. It is also commonly used to relieve symptoms caused by cancer that has spread to other parts of the body (metastatic breast cancer). Inflammatory breast cancer is an invasive cancer that spreads to the lymph vessels in the skin that covers the breast. This type of cancer is usually treated with chemotherapy before the surgery and then radiation therapy to decrease recurrence percent [7].

Patients with diabetes have shown a higher risk of radiation-induced cancer progression for tumor tissue, especially for inflammatory form [8].

Glucocorticoids are the main drug used to treat radiation side effects (RSE), but hormone administration can interfere with the glycemic control and insulin or metformin administration required by diabetics. It also directly affects the treatment of RSE [9].

Studies have shown several functional differences in the oxidative stress and inflammatory cytokines responses in diabetic/normal cancerous patients' candidate for radiotherapy. Also, radiotherapy as a cancer treatment modality is known as a carcinogen due to oxidative damage via generation of reactive oxygen metabolites and also causing inflammation of the tissue by increasing the inflammatory cytokines [10].

Diabetes and radiation therapy cause oxidative stress and an increase in inflammatory cytokines, and the combination of these factors leads to complications in diabetic patients receiving more common radiation therapy side effects compared to non-diabetic patients [11].

Tumor-promoting cytokines are: IL-6, IL-11, TNF-α, IL-1β, IL-23, etc. The effect depends on the type of specific tumor and its stage. In addition, inflammation promotes metastasis, a major mechanism of cancer death [12]. Therefore, long-term exposure to chronic inflammation and oxidative stress increases the progression to malignant transformation in susceptible cells [13].

Many studies report that oxidative stress is an important factor in diabetes and its important role in diabetes, including impaired insulin action and increased incidence of complications [14].

Serious and life-threatening effects on normal tissue function, erythema, pain, ulceration, edema and pneumonia may be due to high levels of ROS and RNS, pro-inflammatory cytokines and prostaglandin [15].

This report describes the principles of depiction of radiation targets and dose escalation. Emphasize new insights into IBC's local and regional management. Provides a critical review of recent literature assessing topical treatment of IBC. And, based on the experience of our organization, we will briefly introduce the future direction of optimal treatment and management of IBC with diabetes mellitus.

Materials and Methods.

This study was approved by the institutional Ethics Committee of the National Cancer Institute of Ukraine (Minutes No. 163 of June 23, 2020).

We performed an analysis of the treatment results of 14 IBC patients with diabetes mellitus, who were treated in National Cancer Institute of Ukraine. The prevalence of the process corresponded to T4b-dN0-2M0, the average age was 53.6 years. In the neoadjuvant mode, patients underwent intra-arterial chemo-

therapy for DC scheme. Tumor growth and/or edema was noted for these 14 patients, which could be described as stabilization (increase up to 20% of the primary volume) or progression of the process (increase over 20% of the primary volume). Standard baseline evaluation included a complete medical history, physical examination, including performance status, and hematology and clinical chemistry assessments. Patients were evaluated weekly during the course of radiation therapy, 3 to 4 weeks after completion of treatment, and then at 3- to 6-month intervals thereafter. To gather information regarding locoregional toxicities, patient charts were reviewed for the development of a treatment break or desquamation (dry or moist) before, during, and after radiation therapy. A treatment break was defined as a pause in treatment, for any number of days, which was secondary to acute radiation-induced skin toxicity. In cases in which a complication could have been the result of metformin and/or radiation toxicity, it was coded as radiation toxicity unless such symptoms predated the radiation therapy.

Statistical analysis was performed using a chi-square or Fisher's exact test when appropriate, with a value of 0.05 or less indicating significance. The computer program software R (version 2.15.1) was used for all statistical testing.

Multidisciplinary team decision is, for 7 patients, to continue systematic chemotherapy with a scheme change (consecutive anthracyclines-taxanes, 2-week interval) and insulin with individual scheme for hyperglycemia correction on the basis of glycemic control – 1st group, the other part (7 patients) – 2nd group, was given radiotherapy to the breast gland and lymphatic drainage ways. 45-50 Grey was prescribed for 25-28 fractions (per 1.8-2.0 Grey), 46–50 Grey in 23-25 fractions were used for zones of regional metastasis and for hyperglycemia correction metformin 2000 mg/day PO divided q8-12hr with meal on the basis of glycemic control. For all macroscopic disease sites, it was advised to raise the radiation dose to 60-70 Grey if the condition persisted. The likelihood of resection was periodically evaluated during the radiotherapy process after the application of 45-50 Grey. On a Clinac 2100 CD linear electron accelerator (Varian Medical Systems) equipped with built-in x-ray portal imaging systems and Millenium 120 multi-lobe diaphragm collimators, 3D conformal CT was performed. Using photon radiation with an energy of 6 MeV, the breast gland was exposed to radiation action. Most frequently, the «field in field» approach was selected, which reduced the areas of highest doses and delivered the dose to «under-irradiated» areas by combining numerous tiny shaped fields (made with the aid of a multi-petal diaphragm collimator) with two tangential fields in the treatment volume. The supraclavicular/subclavian zone's lymph nodes received the majority of their radiation from a single front field. Small «rear» fields were utilized if necessary to ensure that the dose was distributed evenly throughout the specified volume. Before the initial radiation therapy session and once a week after that, 3D conformal radiation therapy patients were required to undergo control CT, a portal imaging system to confirm their location on the treatment table and the accuracy of the radiation.

The effectiveness of the treatment was assessed using the same RECIST standards. Additionally assessed were the number of patients who qualified for surgery and overall survival for 24 months.

Insulin

For a variety of reasons, including its effectiveness and quick beginning of action, insulin therapy is frequently necessary in type 2 diabetes (T2D) patients with cancer. This is especially true in cases of severe hyperglycemia. Second, because insulin regimens are flexible and can be used to treat acute and intermittent hyperglycemia brought on by both chemotherapy drugs – especially if they are cycled – and hyperglycemia, which are frequently used to less the side effects of chemotherapy, to manage cancer-related pain, or as a component of chemotherapy in blood cancers. For treating post-prandial hyperglycemia in cancer patients, short-acting insulin are preferable. When food intake is unpredictable in individuals with nausea, vomiting, and trouble eating, their quick onset of action and the ability to inject after meals are helpful [16].

Effect of Metformin on Breast Cancer

It is widely recognized that diabetes is a major risk factor for breast cancer, controlling the availability of estrogen and the activity of estrogen receptors, hence raising the risk and accelerating the development of breast cancer [17]. Previous studies have shown that diabetic women who use metformin have a decreased incidence of invasive breast cancer [18], than in female users of other hypoglycemic drugs. Then, an increasing number of clinical and fundamental research showed that metformin decreased the occurrence, metastasis, and recurrence rate of breast cancer in women [19]. According to the findings, metformin use decreased by 27 percent, 32 percent, and 48 percent, respectively, the risk of secondary breast cancer occurrences, recurrence, and mortality. Finally, the scientists suggested that metformin's vascular effects could be the mechanism by which it boosted chemotherapy sensitivity and decreased the rate of pulmonary metastasis of primary malignancies [20], whereas the reverse trend was seen in women with normal insulin sensitivity, had an inhibitory effect on the proliferation in the women with higher HOMA index. In this trial, metformin was administered for a comparatively little length of time – 4 weeks

before surgery – and breast cancer progression was influenced by confounders like emotional state and hormone levels. To strengthen this viewpoint, more research is required.

RESULTS

It was discovered that the group of patients who underwent radiation therapy (2nd group) showed a superior response following resistance to prior systemic treatment. Thus, 5 (71.41%) of the 7 patients exhibited a consistent response, which was associated with complete or partial regression. However, there were only 2 individuals (28.61%) who responded to treatment among the patients who maintained chemotherapy – Table 1.

TABLE 1. *Results of treatment of IBC patients who did not respond to previous treatment, according to RECIST criteria*

Response to treatment	radiation therapy, n (%)	chemotherapy (AC+T), n (%)	p
Complete regression	2 (28,6±1,4)	0 (0,0)	> 0,05
Partial regression	3 (42,9±2,6)	2 (28,6±1,4)	0,76
Stabilization	1 (14,3±3,7)	3 (42,9±2,6)	0,59
Progression	1 (14,3±3,7)	2 (28,6±1,4)	0,81
All	7 (100,0)	7 (100,0)	

breast cancer (HR = 2.495, P = 0.047 in early stage; HR = 2.929, P = 0.019 in advanced stage)

In the radiation (2nd group), 5 (71.41%) patients could now undergo surgical intervention, whereas only 3 (42.92%) patients in the chemotherapy continuation group could. At 24 months, there was also a difference in overall survival. Radiation therapy was used to treat IBC patients who were chemotherapy-resistant, and six of them (85.74%) made it through the two-year timeframe. Contrarily, there were 4 such individuals (57.12%) when treatment was prolonged – Table 2.

TABLE 2. *Results of IBC treatment of patients who did not respond to previous treatment, operability and overall survival*

Indicator	radiation therapy, n (%)	chemotherapy (AC+T), n (%)	p
Surgery	5 (71,4±3,2)	3 (42,9±2,6)	0,45
Overall survival (24 months)	6 (85,7±4,2)	4 (57,1±2,4)	0,35

DISCUSSION

Despite an increasing number of patients having both cancer and diabetes, managing their clinical care remains difficult for doctors. One of the main problems is the absence of standards or rules. In actuality, there aren't many data from prospective, better-designed trials, and there aren't many important questions that can be resolved with retrospective, observational studies alone. A few clinical problems that require more understanding include the optimal level of glycemic objectives, the impact of anticancer medications on glucose profile and vascular consequences, drug interactions, and the frequently overlooked nutritional status of patients [21].

According to Zi F et al. and colleagues [22], the majority of clinical investigations have demonstrated that metformin therapy can lower the risk of cancer and increase the survival of cancer patients. The rate at which cancer develops, its unique processes, and its treatment impact may all be influenced by metformin. Membrane transporters are required for metformin to enter cells. Metformin is not advised for usage in cancer patients without diabetes and its effects on breast and prostate cancer are still up for dispute [23].

We expected that patients receiving concurrent metformin and radiation would experience higher locoregional toxicity since preclinical studies have shown that metformin causes radio-sensitization. According to the results of our study, patients who receive radiation and metformin at the same time take treatment pauses more frequently.

CONCLUSIONS

Breast cancer of the aggressive IBC variety requires multidisciplinary treatment from breast surgery, medical, and radiation oncology. Hyperglycemia, higher total radiation therapy doses, and radiosensitizers are a few techniques that can improve the impact of radiation therapy (RT) on local-regional management. Local-regional control rates for IBC are increasing with an individual patient strategy.

Patients with diabetes appear to experience more side effects from radiation therapy than patients without the disease. The role of hypoglycemic medications having protective effects and producing a drop in the difficulties in diabetic patients undergoing radiotherapy should also be examined, as should treatment efforts to less complications with sufficient glycosemia levels. In addition to reducing blood sugar levels, metformin also improves insulin resistance and has anticancer benefits.

Demonstrates the advantages of treating IBC cases that are resistant to chemotherapy with neoadjuvant radiation therapy. For patients with tumors that are stable (with a 20% tumor size increase or less), advancing (with a 20% tumor size increase or more), or demonstrating heightened swelling phenomena, radiation therapy may be suggested as the second stage of IBC patients treatment. The algorithm of treatment for this group of patients cannot be based solely on a small sample of observations, indicating the necessity for additional research.

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