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THE BREAST CANCER TREATMENT AS A MARKER OF PROGRESS IN ONCOLOGY

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This review is aimed to discuss the influence of the fundamental investigations in biology and oncology on the clinical strategy and tactics at the example of the breast cancer (BC). The survey of the influence of the theoretical investigations on the clinical methods, their level and results. The analysis of more than 60 years experience of Lviv oncological clinic in treatment nearly 20 000 patients with BC. The history of BC treatment is divided into periods in which different methods of treatment were dominant. We demonstrate the influence of the fundamental investigations on the clinical situation in BC.
Key Words: **breast cancer, diagnostics, treatment, fundamental investigations, perspective.**

The most problems in fundamental and clinical oncology are hidden in the mystery of cancer cell [1, 2]. The cancer cells repeat in some aspects the properties and behavior of normal ones [3]. From this point of view oncology is a part of biology and that's why the achievements in fundamental biology and oncology influence the position of clinical oncology, especially the problems of treatment [4]. On the other hand the needs of clinical oncology demand the adequate answers from the fundamental sciences [1]. The retrospective review of the Noble prize (NP) distinguished fundamental investigations beginning with W.K. Roentgen (NP 1900), A. Becquerel (NP 1903), M. Sklodowska-Curie (NP 1903, 1911) till now (E.H. Blackburn, NP 2009) revealed about 50 researches related to the cancer problems [5].

Recent advances in chemotherapy, hormonotherapy, biological treatment and other kinds of management have significantly improved the prognosis of cancer patients. However prediction of tumor sensitivity to chemotherapy has not reached a high level of confidence and thus inhibits the possibility of individual management and prognosis [6–8].

In this article the main discussion will be pointed to the connection of the breast cancer (BC) treatment problem and basic science achievements. Why have we chosen the BC as a model for the discussion? It is a very convenient object for experimental and clinical research. BC is one of the most widespread localizations of tumor and this problem is valid for the most countries. BC is a hormone dependent and hormone sensitive tumor, in some cases it depends on heredity and has relations to virus etiology [9, 10]. In BC the exact determination of the TNM criteria is possible. In its treatment all known in oncology methods are used: surgery, radiology, chemotherapy, hormonal, biological and immune treatment. That is the reason for the choice of the BC as a favorable example for the treatment response. Each of these methods has its interesting history, which in most cases is closely related to the fundamental investigations [11, 12].

The surgery was the oldest method implied for the BC treatment. The breast surgery dates back to the ancient Egypt, Greece and others. The modern period of BC treatment is related to W. Morton (narcosis, 1846), Y. Lister (antiseptics, 1867), W. Halsted (surgical technics), N. Petrov (antiblastics and ablastics). Till now it is the most effective method of BC treatment that cures the patients. The surgical treatment of BC cancer has changed dramatically over the last several decades [13]. We have to distinguish the surgical oncology and oncological surgery. The surgeon who treats cancer must be familiar with natural history of individual cancer and with the principles and possibilities of surgery and other oncological methods (radiation therapy, chemotherapy, immunotherapy and other new treatment modalities) [13]. To the surgeon belongs the central role in prevention, diagnosis, definitive treatment, palliation and rehabilitation of cancer patient.

To be an expert in performing surgery is not sufficient for treating cancer patients. This problem was discussed in the First Congress of Ukrainian surgeons. The surgical oncology has many aspects: the surgery of primary cancer, surgery of residual disease, surgery of metastatic disease, surgery for palliation, surgery for reconstruction and rehabilitation. The decisions about the necessity of surgery depend on many factors. The volume of surgery and the amount of resected tissue depends on the stage of cancer, biological properties of it, clinical peculiarity of the case and also on the wish of the patient. The surgeon needs to choose between mastectomy and lumpectomy, lymph node removal and sentinel lymph node dissection. A separate surgical problem is breast reconstruction and especially prophylactic mastectomy. To make use of organ-preserving surgery became possible only after introducing of modern diagnostic methods, which allow dealing with early stages of BC. The modern multidisciplinary team of experienced breast surgeons, oncologists, radiation oncologist work closely together to provide a qualified approach to individualized care. The development of surgical

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Abbreviations used: BC – breast cancer; BRCA – breast cancer gene; ER – estrogen receptor; ERDs – estrogen receptor down-regulators; HR – hormone-receptor; PR – progesterone receptor; SERMs – selective estrogen receptor modulators.

techniques is moving in two different directions: increasing the amount of dissection (combined surgery, radical and super radical surgery), and minimizing of the surgery (organ-preserving) [14].

The developments in the radiological methods are due to the research achievements in physics and technical advances. Radiological therapy is one of the possible radical methods of treatment in oncology. In the treatment of the BC it was introduced soon after the discovery of X-rays and is used in the combination with surgery or as a part of complex treatment (surgery, radiology, chemotherapy). The frequency of application of this method depends on the level of technical equipment of the oncological institution.

The basis action of radiation energy on the tumor lies in destruction cells with the possible saving the surrounding tissue.

As well as surgery the radiological treatment is a radical method able to guarantee the recovery. The modern radiological treatment is based on: 1) understanding of the biological action of ionizing radiation, 2) correct use of sources and kinds of radiation, 3) the correct choice of radiological treatment method in skillful prophylaxis of complications. The effect of radiation depends on the histogenesis of the tumor. The development of oncological radiology is closely related to the technological progress in this area.

For a long time the main methods of the cancer management comprised of the radiological treatment and surgery. It was first in the middle of the 20th century that chemotherapy has joined the team, although the idea for it was expressed by P. Ehrlich (NP 1902). In recent years an explosion of life-saving treatment advances against BC is noted. Chemotherapy medicines prevent cancer cells from growing and spreading by destroying the cells or stopping them from dividing [15]. Cancer cells tend to grow and divide very quickly with no order or control. Because they are growing so fast, sometimes cancer cells break away from the original tumor and travel to the other places of the body. Chemotherapy weakens and destroys cancer cells at the original tumor site and throughout the body. Chemotherapy can also unintentionally harm other types of rapidly dividing cells (bone marrow, hair follicles, nails, digestive tract and other) possibly causing the side effects. Chemotherapy is a systemic treatment, which means it affects all body by the bloodstream. It is used in adjuvant, neoadjuvant and paliative regimes. In many cases chemotherapy medicines are given in combination of two or three different remedies. In the early stage of the BC standard chemotherapy regimes lower the risk of cancer recurrence. In adjuvant BC chemotherapy regimes chemotherapy makes the cancer shrink or disappear. Chemotherapy is used to treat all stages of BC, including the BC local recurrence in the breast area and BC that has spread to other parts of body.

Chemotherapy treatment is tailored specially for each patient's situation. The decision for the chemotherapy is based on the cancer's stage, morphology, lymph nodes status, hormone receptor and Her-2 status. The menopausa is also to consider. Chemotherapy for the early stage disease (stage 0, stage I, IIA and IIB) is used after the surgery (adjuvant regime) to get rid of any cancer cells that may be left behind and to reduce the risk of cancer recurrence. The preoperative chemotherapy is used before the surgery to shrink the tumor so less tissue needs to be removed. Chemotherapy is almost always recommended by the presence of the cancer tissue in lymph nodes (N^+), regardless of tumor size or menopausal status.

More aggressive treatment is recommended for premenopausal women with invasive BC. In the advanced cases of BC (stage III and IV) the chemotherapy is used to destroy or damage the cancer cells as much as possible.

The primary of the chemotherapy in the middle of the 20th century was represented by the single medication, nitrogen mustard (embichin). Nowadays nearly 50 medications are applied in the different combinations and regimes. Recommendations for such combinations are based on the fundamental investigations of the normal and cancer cells, their pathophysiological peculiarities and the intracell pathway signals. The novel research data induce the synthesis of the still new classes of anticancer drugs and new principles of their applying are introduced [16, 17].

The new combinations and regimes are continuously under the research worldwide and our clinic is a participant of such multicenter investigations. The new investigations support the evidence that BC cells with the high levels of the polyadenosine diphosphate ADP-ribose polymerase (PARP) are more likely to respond to chemotherapy [18].

The amount of information on BC has doubled in the last 10 years. It is expected to double again in the next 5 year and this is hopeful. It is important to mention the two trends in the treatment options, like individualization and standardization. These interrelations are flexible and depend on the research achievements and clinical results, so-called bed-to-bench approach [19, 20].

In the first half of XX century effective cancer therapy was applied for the patients with surgically treated BC or evolving modality of irradiation. The single available method in case of the disseminated BC was hormonal therapy which involved removing or blocking endocrine substances circulating in the bloodstream and causing cancer cells growth. This process depends on the presence of the hormone receptors. The fate and behavior of BC cell significantly depends on the estrogen and progesterone receptors (ER and PR). From this point all breast tumors are divided into hormone-receptor-positive (HR^+) and hormone-receptor-negative (HR^-) cases. Hormonal therapy is considered as a systemic treatment for HR^+ breast cancers. About 80% of them are ER^+. Almost 65% of ER^+ breast cancers are also PR^+. Nearly 13% cases are ER^+ and PR^- [15, 21].

Reducing the amount of estrogen in the body or blocking the effect of estrogen hormonal therapy can

diminish the growth or shrink advanced stage of ER^+ BC. Hormonal therapy is not effective against HR^- BC.

There are three different types of hormonal therapy medicines: 1) aromatase inhibitors (arimidex, aromasin, femara), 2) selective estrogen receptor modulators (tamoxifen, evista, fareston), 3) estrogen receptors downregulators (faslodex) [22].

Nowadays we despond with tree aromatase inhibitors — arimidex (anastrozole), aromasin (examestane), femara (letrozole). A number of studies have compared aromatase inhibitors with tamoxifen to see which type of medicine was more effective in treating early stage of HR^+ BC in postmenopausal women. Based on the results we can state that an aromatase inhibitor is the best hormonal therapy to start with. When treating early stage HR^+ BC aromatase inhibitors have more benefits and fewer serious side effects than tamoxifen. Switching to an aromatase inhibitor after taking tamoxifen for 2 or 3 years (for a total of 5 years of hormonal therapy) offers more benefits than 5 years of tamoxifen [23].

The hormonal therapy is used to treat any stage of HR^+ BC or to reduce the risk of developing it or having a recurrence. Hormonal therapy can be used before or after other BC treatments.

As estrogens are mostly produced in ovaries, in premenopausal women diagnosed with HR^+ BC the ovarian shutdown is necessary. It may be done using medication (temporary) or by surgically removing the ovaries (permanent shutdown). According to the National Cancer Institute prophylactic ovary removal reduces the number of new BC among high-risk women by 50%. This benefit occurs only if the ovary removal is performed before menopause. The most common ovaries shutdown medicines are zoladex (goserelin) and lupron (leuprolide). Zoladex and lupron are both luteinizing-hormone-relizing hormone (LHRH) antagonist. SERMs (selective estrogen receptor modulators) block the effects of estrogen in the breast tissue. SERMs work by sitting in the estrogen receptors in breast cells. If a SERM is in the estrogen receptor, there is no room for estrogen and it can not attach to the cell. If estrogen is not attached to a breast cell, the cell does not receive estrogen's signals to grow and multiply.

There are three SERMs — tamoxifen (nolvadex), evista (raloxifene), farestone (toremifene). Tamoxifen is the oldest and most-prescribed SERM. For the premenopausal women diagnosed with HR^+ BC the SERM tamoxifen is the hormonal therapy treatment standard [24].

ERDs (estrogen receptor downregulators) keep estrogen from latching on to hormone receptors. Estrogen sends to the breast cells signals through the receptors to grow. Cells with estrogen receptors grow and multiply when estrogen attaches to the receptors. Bur ERDs like faslodex break down those receptors so that estrogen can't latch on. If estrogen is not attached to a breast cell, the cell does not receive estrogen's signals to grow and multiply. ERDs reduce the number of estrogen receptors; they change the shape of breast cell estrogen receptor.

It is not always possible to predict accurately a higher risk of cancer recurrence. For the precise selection of the responders to the adjuvant therapy the researchers concentrated on the genetic aspects of BC. We are able to link certain patterns of genes of more aggressive cancers. Some of this lab tests are already available for practical medicine.

There was proposed some newer classification of BC [25]. The current classification of BC is based on the histological type of BC. A newer classification based on the molecular features may be able to predict prognosis and response to several type of BC treatment better. It suggests 4 basic types of BC considering ER^+ or ER^-, PR^+ or PR^-, as well as HER-2 neu^+ or HER-2 neu^-. The HER-2 neu^+ BC is associated with poor prognosis, while ER^+ with a good one. Consequently, the best prognosis is observed in the ER^+, PR^+, HER-2 neu^- group. The group of ER^- PR^-, HER-2 neu^+ is associated with the worst prognosis thus an especially aggressive therapy is required. High risk usually means the presence of abnormal breast cancer genes BRCA1 or BRCA2 linked to BC, which is strongly related to the family story of BC, ovarian cancer or both and here we face another dramatic aspect in the BC treatment, like prophylactic mastectomy [26].

Looking back to the development of therapeutic schedules we see the increasing of adjuvant methods used as addition to surgery — radiotherapy, chemotherapy, hormonotherapy. A special progress is observed in chemotherapy and hormonotherapy. As a good illustration for this thesis is the review of the changes in BC treatment approach used in Lviv oncological clinics in the 1946–2010 years period. The whole number of observed patients is nearly 20 000 (Table) [8, 27].

The situation and trends presented in the Table correspond to the general state of art in Ukraine and worldwide with the possible time shifting but similar principle approaches. As we see, the surgical treatment is still dominant although the volume of the standard surgery is changing and is in accordance with the temporary scientific data. The increasing number of the adjuvant methods is noted. The special area belongs to chemotherapy and hormonotherapy. The quality and quantity of the radiological treatment depends on the availability of the modern equipment. The target therapy, which uses the principle of the monoclonal antibodies as a new method of the biological therapy is developed.

It should be noted, that the ratio of different treatment methods is changed. Although nowadays surgical approach is still dominant, it is obvious that the future belongs to chemo-hormonotherapy with a specially marked target therapy. Possibly, the biopsy of the primary tumor for morphological characteristics and guarding lymph node for the future tactics determination will remain as a surgical domena. The radiological treatment was considered as a main adjuvant to

Table. Evolution of therapeutic tactics in breast cancer treatment in Lviv oncological clinic

Method	Before 1950	1950-th years	1960-th years	1970-th years	1980-th years	1990-th years	After 2000 year (modern status)
Surgery	Halsted mastectomy		Halsted mastectomy, introduction of TNM-system	Halsted mastectomy, Kholdin-Urban mastectomy	Payty mastectomy and Halsted mastectomy	Payty mastectomy as a rule, Halsted mastectomy as exception, organ-preserving surgery in some cases	Organ-preserving surgery on individual basis, modified mastectomies, lymphadenectomies in individual amount, total mastectomies (Halsted, Madden)
Hormonal therapy	Adnexectomy, ovarion irradiation, testosterone, progesterone, estrogen		Adnexectomy, ovarion irradiation, testosterone, progesterone, prednizolon hypophisis irradiation	Adnexectomy, ovarion irradiation, adrenal glands irradiation, hypophisis irradiation, testosterone, progesterone, prednizolon, antiestrogens, synestrol	Adnexectomy, prednizolon, mamomit, orimiten (aminoglutemid), individualization on the basis of sex-chromatin test	Adnexectomy on the basis of ER- and PR-tests, tamoxifen, toremifen, mamomit, orimiten (aminoglutemid)	Individual hormonotherapy (ER, Payty, PR), hormone-excretion tests, 4 subgroup laminal classification. Adnexectomy, antiestrogen therapy, aromatase inhibitors (aromasin, femara)
Radiological treatment	Hypo- and ortovolt X-ray therapy on RUM-5, RUM-11		Hypo-, meso- and ortovolt X-ray therapy	Hypo-, meso-and ortovolt X-ray therapy on LUCH-1	Hypo-, meso- and ortovolt X-ray therapy, telegammatherapy. CUTCo-400, RUM-7, RUM-17	CUTCo-400, AGAT-S, AGAT-RM	Pre- and postoperative gamma-therapy on basis of individual tactic. Ortovolt X-ray therapy, telegammatherapy. TERAGAM, AGAT-RM, AGAT-S
Chemotherapy		Monotherapy Tio-TEPA, Alkeran	Polychemo-therapy Cooper schedule Tio-TEF, Alkeran	Adjuvant chemotherapy CMF	Polychemotherapy different schedules CMP, CAP, CMF Immunotherapy, Automyelo-transplantation	Polychemotherapy adjuvant and neoadjuvant	Polychemotherapy in adjuvant, neoadjuvant and palliative regimes. Introduction 4 subgroup laminal classification as an individual indications for chemo- and hormonotherapy. Wide use of different polychemotherapeutic schedules. Participations in international trail investigations Target-therapy: trastuzumab, lapatinib. Bisfosfonats

the surgery method for a long time. Now this method is definitely losing if compared with chemo- and hormonotherapy. Rating of the certain treatment method is flexible and dependent on the latest research data.

It is well known that oncology as a science is developed in the different levels: global (for the cancer epidemiology); in population (for cancer genetics); in organism, organon, cell and subcellular structures (for pathogenetic researches). Up-to-date the multilevel complex researches of the metabolic disturbances in chronic non-infectious diseases including oncological problems are performed. In these multidisciplinary investigations the specialists in biology, biochemistry, physiology, ecology and clinical medicine are involved [12, 28].

The nanotechnology as a new direction in BC diagnosis and treatment will appear in the nearest future. Nanoparticles are targeted drugs actually leaving the bloodstream, being concentrated in cancer cells and having a biological effect on tumors. That is a new principle introduced in medicine and oncology. The particle in nanoscale may be from 100 to 10 000 times smaller than human cells. They are similar in size to large bio-molecules such as enzymes and receptors. Those nanoscale devices can interact with biomolecules on the surface of cells and inside of them. Such properties give the potential defect disease and deliver treatment in ways unimagined before now. That is a promising way to diagnose and treat cancer, which can radically change the number of highly effective therapeutic agents [29, 30].

All mentioned above suggests that modern oncologic management requires high level of experience in cancer surgery, chemotherapy, radiation therapy that is not common to most general surgeons. That is why the organization of oncological chairs in the medical institutes (universities) after 1966 by the initiative of prof. A. Hnatyshak (Lviv) was of the great importance for the development of oncology in Ukraine and other countries.

Finally we can state, that the clinical oncology passed a long and successful way during its scientific development:

1) The scientific basis of surgical treatment was established,

2) The influence of radiation on the dividing cells was discovered and the chief principles of radiological therapy were established,

3) The endocrinological oncology was developed and the tumors sensitive to hormones were established,

4) More then 200 medicines with cytolytical effects were synthesized and the theoretical basis for their implication was created,

5) The fundamental studies of cancerogenesis (the discovered pathways of grows regulation and multiplications of normal and malignant cells) allowed to imply the blocking of those ways, that created the basis for target therapy.

All these achievements of clinical oncology would be impossible without the scientific basis, on which the clinical oncology is developed. The introduction of fundamental achievements into the oncological clinic was realized on the model of BC, which appeared to be the best for this aim. Nowadays the BC is treated using all known in oncology methods. That's why we treat the cooperation of theoretical and clinical

oncology through the problems of diagnostics and treatment of BC.

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