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Conventional Treatment of Cancer Realities and Problems

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Abstract

Statistical data exhibits the fact that cancer decease and the effectiveness of its treatment remain an unsolved problem which is becoming more and more extensive not only in medical but also in social and economic spheres globally. It becomes obvious that conventional medicine in treatment of cancer meets neither the contemporary requirements nor the patients' expectations.

Massive publicity campaign of the target therapy making efforts to substitute the system chemotherapy took place of late years. Huge investments in this new sphere were made in order to meet the high expectations. Clinical experience and medical expertise, on the contrary, do not demonstrate prolonged life expectancy more than a few months however; this takes place with valid side effects and at high cost of the target therapy treatment. Serious and deeper cost-effectiveness analysis leads to a conclusion that most of the agents applied in target therapy do not correspond to conventional range of cost effectiveness.

Significant investments in molecular biology advancement and development of genetics make immense progress and widen the scope of human knowledge in tumor biology. Unfortunately, despite that science progress, oncology follows the beaten track satisfied with prolonged patients' longevity only in terms of a few months and keeping an eye on the illusory effect of the treatment. The current scientific survey aims at summarizing known and less known facts illustrating the opportunities, problems and efficiency of the conventional treatment of cancer. The information presented herein the survey addressing not only professional oncology specialists is also available for a wide reading audience who are interested in current problems of conventional treatment of cancer. We hope the information presented will stimulate a future professional and social debate directed towards change in the contemporary treatment of cancer based on the idea of achieving real progress in solving of a significant medical and social problem.

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Introduction

Achievements and opportunities of the contemporary conventional medicine

In 1995 the "Spontaneous Healing" by Dr. Andrew Well, a Harvard graduate, was published in which he summarized and presented the opportunities of the conventional medicine in an understandable and assessable manner - what medicine successfully cures and what it is unable to do. In his opinion, the areas in which the conventional medicine reached undisputable achievements are: diagnostics of complex medical problems, diagnostics and correction of hormone disturbances, diagnostics and treatment of urgent medical cases, treatment of traumas and orthopedic diseases, reconstructional and cosmetic surgery, treatment of acute bacteriological infections with antibiotics, prevention of infections by immunizations. Areas in which the conventional medicine has limited possibilities include: treatment of the predominant part of chronic degenerative diseases and cancer treatment, diseases caused by viruses, allergic and autoimmune diseases, psychosomatic and mental diseases [1]. Unfortunately, the period following these conclusions did not change the situation and we are still expecting significant changes and progress.

Conventional Cancer Treatment

The spectrum of the conventional cancer treatment includes three basic methods: operations, chemotherapy and radiotherapy. There also are significantly less applicable additional methods such as immunotherapy and hormone therapy. The immunotherapy application is more in the field of the experimental research, while the hormone therapy is primarily applied in breast and prostate cancer treatment. The treatment results are reported by the cancer specialists in the general medical principles based on proofs (evidence based medicine). Practically it is accepted that the results from these treatment methods are not subject to doubts and critics. Cancer specialists are obliged to apply only the accepted standard methods and reject all other treatment methods.

Treatment Efficiency

It is necessary to make here some term explanations.

Cure of cancer disease

This means that among a group of patients treated of some cancer disease there is an equal frequency of mortality as the mortality of a group of healthy people of the same community. In the scientific literature there is no data for a similar mortality frequency owing to which the usage of the term of cure of cancer diseases is misleading. For this reason the term of cure is replaced by a five-year survival with no presence of the disease.

Remission

Remission is a medical term meaning temporary reduction or even disappearance of the symptoms of a given disease resulting from an applied treatment. Depending on the degree of reduction of the subjective or objective signs of disease we differentiate complete and partial response. This term defines the availability or lack of control over the disease resulting from the treatment applied and is a real index of the effect of the treatment carried out but is not a synonym of cure.

Methods for Proving the Efficiency

In practice the following methods are applied:

Anecdotal information or information from an individual case of treatment. Often this information includes different methods of treatment in which the curative effect for each of the treatments cannot be defined making this method only useful as a reference point for future research.

Survival frequency

The five-year survival of the patients is recorded comparing it to that of the control group of similar patients cured by the same treatment in the past. This method or index is not sufficiently trustworthy due to the fact that during the treatment many other facts influence the survival data.

Clinical trials (experience)

The results from the treatment are presented in four categories: complete response (lack of tumor), partial effect (over 50% reduction of the tumor size), stabilization (below 50% reduction of the tumor size), and progressive disease (growth of the tumor). The treatment efficiency is accepted at reduction of the tumor size over 50%. More recently, the lack of disease progression or tumor reduction below 50% is defined by the term stabilization. Logically, disease stabilization is included into the category of remission. A shortcoming of the method is that despite the achieved tumor reduction, this may not have an impact on the survival.

Randomized clinical trials

During these researches two groups are compared, the one of treated patients while the other is a control group. The results are recorded, referring to survival or mortality in both groups. This is the most reliable method of assessment of the treatment efficiency. The statistical data from the application of the different methods of efficiency assessment are the basis for accepting or rejecting a certain method of treatment. All treatment methods adopted by the conventional medicine enforce standards claiming they present the best quality of treatment.

Some data concerning the accuracy of the statistical data, however, need a careful evaluation. We can point out to some of the more significant facts, illustrating the reliability deficiency of the statistical data used in regards with the treatments methods used in the conventional medicine [2-4].

The research proving that the early diagnosis of tumors and early operations contribute to a prolonged survival does not record that the research includes both pre-cancer situations, changed life style and the application of other unconventional treatment methods. It is known that pre-cancer situations very often do not lead to cancer development even without treatment. The inclusion of the pre-cancer cases in the general cancer statistics, on one hand, increases their number while, on the other, reduces the number of deaths. The progress resulting from the treatment concerning the five-year prolonged survival recently recorded in the contemporary diagnostics is not considered to be in line with the increased possibilities of diagnostics to discover tumors significantly earlier.

The comparative studies of patient survival treated with chemotherapy and radiotherapy do not record that all patients do not conclude the full course of treatment while in the control group every death is being recorded. The studies recording the temporary reduction of the tumor volume do not always record survival rate and in the cases when this is done they do not reveal those who died as a cause of the treatment. Owing to the unclear evaluation of the cases with specific cancerous mortality and the one connected to the treatment, the statistical data in recording the cancerous mortality do not reveal real results to evaluate the efficiency and progress of the treatment methods applied. A number of studies concerning cancerous mortality the question is seriously raised for overestimating and underestimating the statistical data in its recording. There is underestimation of the mortality resulting from the treatment when only the death cases are recorded immediately following the treatment omitting the secondary or later complications leading to death. It is often practices the cancerous mortality resulting from the treatment not to be differentiated from the cancer specific mortality and in this case there is a case of overestimating it. There are no serious statistical data concerning the quality of life of those treated by conventional methods.

Efficacy of Surgery Treatment

It is accepted in conventional medicine that for the predominating part of cancer cases the operative method is the main method. It is generally accepted that in the early stage of the disease the operative treatment makes it possible for long remissions. It is widely popular with the public that the results from the treatment entirely depend on the skill of the surgeon to perform a high quality operation. The idea of radicalism and efficiency of operative treatment originates from the concept that tumor disease is a local disease of the respective organ. Unfortunately, irrespective the multitude of scientific proof event today the fact is totally ignored that cancer is a system disease (a disease of the entire organism) and the tumor itself is a symptom of this chronic disease. Similarly to the unsatisfactory results of the contemporary medicine in treating chronically diseases, the removal of the symptom logically does not lead to curing or removing the disease. In the last years based on new scientific data more and more cancer specialists accept that the tumor is not an isolated organ disease, but represents complex interrelations between the tumor and the host, making the integrative approach and reassessment of the existing understanding and practices a serious basis for a quality improvement of diagnostic efficiency and treatment.

Let us again go back to the question of the operative treatment radicalism. It is considered that in the early stage of the disease, with no metastases in the organs, there could be expected optimal results from the operation. The practical problems in these cases are along several directions. The early diagnostics unfortunately still happens in a limited number of the newly registered cases, while in about 60% of the cases the disease is discovered in the advanced stage and results from operative treatment cannot be expected [5]. On the other hand even in the early cases in some patients there is a group of single tumor cells or micro metastases which cannot be discovered by the modern diagnostic methods as well as during the operation and could become the basis for a future progress of the disease in spite of the high quality operation. It is well known that the operation itself is connected with risk factors as distribution of cancer cells in the blood flow, anesthesia complications, infections and suppression of the immune system. The reduced immune reactivity and circulating tumor cells in the blood as a result of the operation are real factors for the distribution of metastases [6,7]. By the help of highly sensitive both molecular and biological, and immunohistochemical methods a team of pathologists from the Institute of Experimental Pathology, Oncology and Radiobiology in Kiev established a presence of tumor cells (micro metastases) in the blood flow and bone marrow respectively in 28.3 and 33.1% in patients clinically diagnosed without metastases [8].

A number of experimental and clinical studies prove that operative treatment stimulates the hematogenic distribution of tumor cells and leads to the increase of metastases growth. Stimulating the tumor growth is explained with the reduction of the control growth factors (endostaine, angiostatine), an increased cancer cell adhesion, stimulation of infections and weakened immune system resulting from the operative treatment [7,9].

Since the beginning of 19th century up to 1978 the standard treatment of breast cancer was its radical removal or the so called radical mastectomy in different modifications. At the same time it was generally accepted that the radical mastectomy was a guarantee for improved survival [7]. Later on the randomized trials prove that in spite of the radical mastectomy by lymph dissection, metastases and mortality from the disease was observed in 30% of patients without lymph metastases and in 75% in those with lymph metastases in a ten year period. For the period of 25 years of follow up studies there are no cured patients on the record [10,11].

Within the interval between 1979 and 1987 researchers from the US National Cancer Institute in a trial covering 237 patients operated with mastectomy or organ preserving operation for an average period of following of 18.4 years established that the survival rate of the mastectomy patients was 58% against 54% from the other group. There is no statistically significant difference in the patients belonging to both groups in the survival rate without the availability of tumor [12]. Subsequently, a number of other studies prove that the conservative surgery holds its own in results compared to the invalidating radical mastectomy [13,14].

Another problem connected with the operative treatment of breast cancer is the hyper diagnostics resulting most often from the screening studies combined with mammography. Using mammography as a method of early diagnostics in about 30% to 40% of the cases are of noninvasive Ductile Carcinoma In Situ (DCIS). Due to the noninvasiveness of these tumors the survival rate of these patients up to the ninth year is 100% independent of the type of operation. This seriously raises the question the application of mastectomy in such cases particularly when patients are younger which is about 92% of the cases following mammography DCIS is discovered. On the other hand diagnosing of more cases of ductile carcinoma in situ significantly improves the statistical data of results from operative treatment and does not always justified surgical activity [14,15].

Similarly to the breast cancer in the cases with prostate cancer introducing the PSA screening lead to an abrupt increase of the number of the early diagnosed stage of the disease. This was followed by increased operative activities with an increase of the number of radical prostatectomy (removal of the prostate gland and the pelvic lymph nodes). In spite of this the mortality from the disease has been insignificantly influenced [16]. In 1995 Iversen P et al. presented their results from a comparative study of two groups of patients: one with a radical prostatectomy while the other of patients not operated on, i.e. watchfully waiting list and observation. It was not observed a statistically significant difference in the survival rate in both groups however these operations have significant side effects the most important of which are impotency and urine incontinence things which violate the quality of life of the patients [17]. In a study involving 695 men with a prostate cancer in the T1-T2 stage, the results are compared with patients operated on and those on the watchfully waiting. The results indicate that operations reduce the relative risk of distant metastases, but do not prolong the survival of the patients [18]. Assessing the results of the radical operations, in most publication the side effects are being left out. In 1996 the magazine Medical Hypothesis published Benjamin D.J. who analyzed results of scientific publications in preceding 35 years evaluating the used proving methods and concludes there were no convincing proofs for the efficiency of cancer surgery. The problem, according to the author, is that it was a matter not of a local but a system disease [3].

The problems described thus far with the tumor surgery and the newest data for activating the metastatic potential resulting from surgery make it necessary to find a vision and approach for applicable methods to reduce tumor dissemination and proliferation activities of the micro metastases following surgery. It is obvious that the adjuvant chemotherapy and radiotherapy cannot resolve the problem, the serious side effects and suppressed immune system are not the only causes for this. According to Michael Baurn and R. Demicheli the new approach should be based on the understanding that tumor and host are a complex system, maintenance of balance in the system being of significant importance. Retaining this balance could be reached by carefully selected therapeutic interventions bearing in mind the influence of the tumor homeostasis, the presence of non-active micro metastases and surgically stimulated metastatic potential. Such a examples in this are the results from the experimental and clinical studies showing that in breast cancer cases the selection of the time of surgery before and after the menstrual cycle and the application of antiangiogenetic medicines could improve the results from surgery [6,7].

The Efficacy of Radiotherapy

Radiotherapy or treatment with ionized radiation is one of the three basic methods in the conventional cancer therapy and its application covers 30% to 40% of the patients with tumors. It is generally accepted that radiotherapy is a proved, efficient and accessible treatment method. It is mainly applied to treat solid tumors primarily combined with the other conventional methods. In

Table 1: Tumor type and cure.

Horiocarcinoma (low risk patients)	90
Burkitt's Lymphoma (Stage I)	90
Acute lymphocyte leukemia	60
Hodgkin lymphoma (stage III and IV)	60
Diffuse histiocite lymphoma	70
Nodular mixed lymphoma	75
Testicle cancer (stage II-III)	70-90
Children's sarcoma (x/radiotherapy & operation)	70-90
Lymphomas in children	75

some cases radiotherapy is used as a palliative treatment to reduce the disease symptoms. The curative effect of the ionized radiation is due to a damage of the genetic material of the tumor cell, which does not allow it to grow and proliferate. Unfortunately, this impact also damages the surrounding healthy tissues and this significantly restricts the treatment results even when using the more modern and new equipment.

The efficacy proof of radiotherapy is exclusively based on the results of separate clinical studies, not on randomized treatment on survival, which makes the reliability of the prolonged survival questionable [19]. In a publication by the Lancet in 1998 a meta-analysis is performed on the results from the treatment of two groups of patients, treated for lung cancer, the one - only by surgery while the other by both surgery and radiotherapy. Follow up period an average of 3, 9 years it was reported an increased mortality in 21% in the group treated by radiotherapy [20]. In the meta-analysis of 28 clinical studies in 2001 of surgery of colorectal tumors, independently or combined with radiotherapy it was established a reduced frequency of the local recidiv in the combined treatment, but insignificant difference in the survival rate of both groups [21]. The review of the results from 36 clinical studies in the NEJM of 1995 indicates there was a 6 percent reduction of mortality in patients with an early breast cancer treated by surgery and by radiotherapy differing from those treated by operations only. At the same time there was established a 24% of mortality increase by other reasons [22]. Gyenes G et al. study heart complications and mortality in patients treated by surgery and high dosage radiotherapy and only by surgery. The results indicated a 30% increase of the cases with a heart insufficiency, a 100% increased mortality due to cardiovascular disease and a 150% increase mortality by an ischemic heart diseases. The difference becomes evident 4-5 years later and continues to increase up to 10-12 years [23]. Analyzing the results from the conventional radiotherapy the fact that it can cause secondary tumors should not be omitted. As a rule these tumors are developed following a latent period of 5-9 years characteristically for leukemia and after more than 10 years in the solid tumors. The risk of developing secondary tumors depends on factors such as the radiation dosage, the place radiotherapy is applied to and age [24].

In a monograph by Curtis R.E. et al. based on data from the National Cancer Institute's Surveillance, Epidemiology and Results (SEER) including more than 2 million of patients treated for cancer during the period of 1973-2000, data is presented for risk of developing secondary tumors for more than 50 tumor types for adults and 18 types for children. For the same period 300,000 women were tracked and treated for breast cancer. Women having received radiotherapy as a part of their treatment and with a survival term of 5-10 years, the risk for developing cancer of the esophagus has increased by 3 times, for the bones 6 times, and for tumor of the soft tissues 3 times. The risk for developing an angiosarcoma of the side where radiotherapy was applied to is over 17 while the 10 year risk for developing a lung cancer is 1.5 [25]. The ionized radiation has also a diagnostic aspect regarding the results of cancer treatment. In the practice it is widely applied mammography as a diagnostic method for early breast cancer diagnosis. The screening programs with mammography are widely promoted as solid means for early diagnostics and respectively as a preconception for cure and prolonged survival. One of the initial studies questioning the role and place of the mammography screening was published in 1992 in the Canadian Medical Association Journal. The results from this national screening study of the breast cancer include about 90,000 women of 40 to 50 years of age. It was concluded that the annually performed mammography are efficient in discovering early tumors without lymph metastases, while for a period of follow-up of 7 years this does not affect the survival of the patients [26].

In 2001 a team from Denmark of the prestigious Cochrane Institute published data reviewing the results from early diagnostics of breast cancer screening which do not establish prolonged survival rate [27]. Later Gotzsche P.C. et al. from the Nordic Cochrane Center in Denmark review and evaluate 7 randomized trials including half a million women and comparing two groups - women with mammographic screening and women without mammography. These trials concluded that the mammographic screening did not indicate significant reduction of mortality but at the same time increased the surgery activities. The authors explain that one from every 2000 women invited for screening during 10 years one of they would be a prolonged life. Additionally 10 healthy women not diagnosed if there was no screening would be treated without being necessary. In conclusion the authors think that it was not clear whether the screening benefits were greater than its damages and the women subjected to screening should be informed about it [28].

In a study by Miller, Anthony B., et al. from Canada including 39405 women of 50-59 years of age for the period of 1980-1985 two groups of women were follow-up - one by mammography and the other by physical examination only. The authors concluded that the mammographic screening did not lead to a reduction of the absolute frequency of the advanced tumors and did not reduce the mortality compared to that in the physically examined women [29].

The lack of prolonged survival is not the only problem connected with the mammography application as means for early diagnosis. The multiple studies indicated a number of risk factors connected to the application such as:

- An excessive pressure on the breast causing pain and discomfort and contributing to the dissemination of tumor cells [30],
- Radio pressure as a risk factor for tumor growth [31],
- A great percentage of false positive results leading to unnecessary operational interventions and psychological stress [32],
- An increased surgical activity [33].

Peter Leando PhD in a publication for the role of mammography in the breast cancer screening (The Role of Mammography in Breast Health an Overdue Paradigm Shift) presents particularly serious data for radiation risk. The radiation dosage from mammography in a single session is nearly 1000 times (1 rad) greater than the X-ray of the lung. The cumulative mammography dosage in screening is 10

rads. With young women this radiation leads to a cumulative risk of tumor growth of 10 percent for a 10 year period. Based on scientific and medical proof the author concludes that:

- Application of mammographic screening in women in premenopause age is unjustifiable;
- Diagnostic mammography can be applied in the age of 50-60;
- Increased attention should be applied controlling the total radiation dosage and the accumulated biological effects;
- Exposure to ionized radiation from all kind of sources should be reduced to a minimum;
- Every patient should be provided with precise information on the basis of which an informed agreement is required;
- The screening programs should include other non invasive methods for early diagnostics as thermography, physical examination and ultrasound examination;
- The more invasive methods as MPT and PET should be studied and adapted [34].

Efficacy of Chemotherapy

According to the data of Cecil's Textbook of Medicine (1988) in part of the cancer cases the chemotherapy can reach long and full remission. With tumors in adults this refers mostly to Hodgkin's and non-Hodgkin's lymphomas and testicle tumors. The table presents the percentage of remissions with tumor in children and adults where the chemotherapy had a curative effect according to Cecil's Textbook of Medicine [35].

Later in 1990 following a 10 year work in the field of cancer statistics the German doctor Ulrich Abel published his book Chemotherapy of Advanced Epithelial Cancer. In this work he reviews and analysis all accessible at that time randomized studies in search of direct proof for chemotherapy results concerning extending treatment survival. The conclusion from the analysis of many years of studies indicates that there are scientific proofs for the fact that chemotherapy with the most tumors do not change a significant prolonged life of the patients [36].

The renounced US doctor and publicist Ralph Moss 1995 published his book Questioning Chemotherapy in which following an in-depth review of the results from the chemotherapy application he concluded that only 2 to 4 percent of tumors were successfully influenced by chemotherapy and that included: the Hodgkin's tumors, acute lymphocyte leukemia, testicle cancer and horiocarcinoma [37]. More recently the Australian Journal Clinical Oncology published a most important article by a team of cancer specialists where the contribution of the cytotoxic chemotherapy was studied in the 5 year survival of adult patients with the usual tumors. The study was based on result analyses of all randomized studies in Australia and the US announcing a statistically important extended five-year survival following application of chemotherapy and the survival data of the Australian and US (SEER) cancer register. The results from this study indicated that total curative and adjuvant chemotherapy contributed to the five-year survival of 2.3% in Australia and 2.1%t in the US. What is more, details from that survival indicated that in most tumors, the lung cancer, the one of the rectum, breast, prostate gland and melanoma as 56.6% of the cases were in Australia in 1998 the five-year survival rate of the patients treated with chemotherapy only was 1.6%. In spite of the introduced new combinations and new chemotherapy medicines in recent years the treatment results had improved not very significantly but at the same time there was no improvement in the toxicity of the treatment. Discussing the question of the correlation between the treatment result and its price, the authors show data indicating that for the period 2000-2001 the expenses for the total price of the medicines had increased by 51%. This was due to the increase by 17% of the prescribed medicines and 29% increase of the medicines ordered. The study concluded that chemotherapy has little contribution to survival and it is necessary a detailed and immediate reassessment of the correlation price-efficiency and the influence of the treatment on the quality of life [38].

In 2006 MERO'Brien et al. published a study targeted towards studying mortality resulting from a 30 day chemotherapy application. For a period of 6 months 1976 patients were included treated by chemotherapy. Within the framework of 30 days 161 died (8.1%) while 124 (77%) of them caused by the progress of the disease, and out of the remaining 37 in 12 (7.5%) mortality was caused by chemotherapy. The information for 25 of the patients is insufficient. The recommendations from this study are that there is a necessity to organize a discussion and define the mortality causes on all levels more precisely [39].

Similarly to radiotherapy, chemotherapy has a cancerous effect which may lead to secondary tumors. A study including 1380 children successfully treated for a Hodgkin's lymphoma 88 secondary tumors were established, compared to 4.4 in the general population. In girls the risk for developing breast cancer in the age of up to 40 is 35%. The leukemia risk appears after the fifth year from the treatment and reaches a level of 2.8 after 14 years. The risk of developing solid tumors reaches 30 percent for 30 years [40].

After 1994 the application of the hormone medicine Tamoxiphen used for treatment and prophylactics of breast tumors was questioned. The usual side effects of this medicine include: cataract, deep venous thrombosis, heart complications, genealogical complications, endometric carcinoma and sarcoma of the uterus, and cysts of the ovaries [41]. One of the first studies on the side effects of Tamoxiphen application was performed by Van Lreuwe et al. from the Netherlands Cancer Institute, Amsterdam. The results of this study indicated that women who took Tamoxiphen for more than two years have 2,3 times greater risk for developing endometric carcinoma [42]. Later a number of other studies confirmed the Tamoxiphen role for development of endometric carcinoma [43-45].

Mignotte H et al. note in their study that the development of endometric carcinoma is directly connected to the duration of treatment and Tamoxiphen dosage. The risk also increases by the application of radiotherapy, and the prognosis for the treatment of this tumor is unfavorable [44]. The negative prognosis for the treatment of these cases of endometric carcinoma is also confirmed by the studies of Bergman L. et al. and Hoogendoorn WE et al. [46].

In 2004 a publication in the Nati Cancer Institute by Leonard GD and Swain SM from the National Cancer Institute, Bethesda based on the results from two randomized studies do not establish increased survival of those treated with Tamoxiphen and recommend its application only in estrogen positive tumors and replace it by aromataze inhibitors [47]. In an attempt to avoid Tamoxiphen's side effects a wide application in practice as adjuvant treatment found

the aromataze inhibitors. Recent comparative studies indicate that aromataze inhibitors have significant advantages both regarding side effects and efficiency [48].

Target Therapy

The unsatisfactory results of standard chemotherapy and its toxicity lead to the development of a new line in treatment of cancer decease. Target therapy or molecular target therapy aims at controlling the growth, cell-division and spreading of tumor cells through influence on them by specific targeted molecules controlling carcinogenesis.

Two categories of targeted cancer therapy are applicable at the process of therapy i.e. therapeutically monoclonal anti bodies targeted at specific antigens localized on the cell surface as trans membrane receptors or extracellular growth factors and small molecules which could penetrate through cell membrane in order to interact with enzyme activity on the purposive protein.

Full-forced development of molecular biology and serious funding of genome researches for epigenome characteristics of tumor cell offered new opportunities for molecular profiling that made it possible for individual genetic changes to allow creation of new type of pharmacological influence designed for target therapy and to make a precise choice of that target agents [49,50].

Defining the individual tumor phenotype gives opportunities for identification of target molecules to allow a selection of specific populations of cancer patients where the treatment success is more likely. For that reason the proponents of target therapy introduced the terminology personalized medicine or précised medicine both is possible to be used to outline the uniqueness and advantages of target therapy. This pretentious terminology of personalized medicine unfortunately cannot cover the scope of personal characteristics and biological transformations of human organism only by using its molecular profile. Even in such cases the diversity of tumor mutation and heterogeneity make it unsubstantiated [51,52].

It is a well known fact that mutation frequency varies from 200 to 300 for lung cancer in every individual cancer patient, and in the cases of breast tumor, esophagus and colon cancer they vary from 50 to 500. With identification of a couple of specific mutations of growth factors, receptors or enzymes the chance for successful treatment grows in 1% to 3%. Along with the number of tumor mutation there are many other problems as tumor heterogeneity, resistance and side effects of treatment as well as the high price of it. As a matter of fact, the concept of target therapy pretending for being a radical change in cancer decease treatment proves unpopular [51-54].

Obviously, the expectations that target therapy would lead to a cure or at least an increase in survival frequency of cancer patients and those of similar chronic deceases i.e. diabetes, hypertonia etc., did not materialize. Two criteria are applied when estimating the results of target therapy treatment, namely Progression-Free Survival (PFS) and Overall Survival (OS). Numerous random researches on the efficiency of target therapy alone or in combination with others have shown that in most of the cases the improvement in PFS and OS is within the scope of 3 to 10 months [55-61].

In a recent study conducted with 302 cancer patients with HER2 negative breast tumors and gremlin BRCA mutation, 205 out of them were included in Orapalib treatment and the remaining 97 were on standard chemotherapy. The average survival period of patients without decease progression within the group of Orapalib 7.0 is 7 months compared to 4.2 months of the control group patients on standard chemotherapy. Treatment toxicity is of 3rd grade found in Orapalib group with 36.6% compared to 50.5% of the control group. The treatment was interrupted due to its high toxicity of 4.9% in the Orapalib group against 7.7% in the control group [62].

The expectations for better results in treatment of advanced metastatic stomach tumors have not been met so far where the chemotherapy has limited opportunities. Based upon a recent study of the prestigious Cochrane Institute and its database, Han Song et al. present a review of their findings on side effects caused by molecular target therapy application alone or in combination with chemotherapy. The research covers 11 random studies carried on 4014 cancer patients, as 3723 were appropriate for the case of study. The authors do not provide convincing evidence for improved treatment results and at the same time indicate a higher risk for side effects from the treatment [63].

The main reason for the gap appearing between the expectations for higher effectiveness of target therapy and the real results of it is caused by heterogeneity of tumor cell and its resistance due to DNA mutations during the course of treatment. Recently a greater attention was paid to intratumor heterogeneity (genomic heterogeneity of patients' tumor) which appears in the early stages of tumor growth and mutating sub-branches induced by the treatment. Molecular analysis done on one part of the tumor does not refer to entire tumor itself which can lead to ineffectiveness of the target therapy and also can increase the risk of tumor growth from different branches of the malignant cell. The attempt for overcoming such problems linked to heterogeneity and resistance of tumor cells in combination with various target agents has not reached success so far. The problem here arises from the fact that the dosage should be decreased due to side effects which impacts negatively the results and serves as basis for cell resistance [52,53,55,64,65].

Research studies carried out by two groups proved that the presence of KRAS mutations before and during target therapy treatment (molecules blocking Epidermic Growth Factor Receptors (EGFR) inevitably leads to a cell resistance where the target therapy has been applied alone. The resistance appears a couple of months after the start of the treatment. Despite the fact that the precise mechanism of resistance has not been found the authors suggest combined application of target therapy [64,65]. Contrary to authors' expectations target therapy side effects are similar to those of standard chemotherapy i.e. skin toxicity, gastrointestinal toxicity, lung disturbances, cardio toxicity, hypertension, complications in blood coagulation, thrombosis and leucopenia, Thyreoideae dysfunction of gl. etc. The combination of target therapy with standard chemotherapy often leads to increased risks of side effects and this is a cause for dosage decrease and interruption of treatment [53,62,66].

When the initial enthusiasm for the advantages offered by the precise medicine and target therapy cooled down, more and more topical became the cost effect of the treatment. Sky rocketing prices were formed not only by the cost of the agent but also by the molecular tests diagnostics for routine genotyping carried prior to treatment, as well as the side effects treatment with combination of various drugs in view of overcoming the resistance. Unfortunately, the increased number of target therapy cost-effectiveness analysis shows inadequately the problem. In most of the cases such cost-effectiveness analysis has been funded by the pharmaceutical industry

which affects their precision. Despite that fact, more serious and deeper cost-effectiveness analysis lead to a conclusion that most of the agents applied in target therapy do not correspond to conventional threshold of cost effectiveness [67,68].

A recent study on reoccurring repetitive failures of modern cancer treatment of solid tumors by Hiroshi Maeda and Mahin Khtami prove the frequency of unsuccessful results reaching 90(± 5)%. The study also includes process effectiveness analysis and problem analysis of target therapy application. The authors, based on modern medical studies progress and achievements, suggest radical changes in cancer treatment concept by rejecting the reduction approach and embracing the systematic approach, at the same time focusing on immune control fully using the defensive mechanism of human organism [53].

Huge investments in molecular biology advancement and development of genetics make immense progress and widen the scope of human knowledge in tumor biology. Unfortunately, despite that science progress, oncology walks the trodden path satisfied with prolonged patients' longevity only in terms of a few months and keeping an eye on the illusory effect of the treatment.

More and more topical becomes the problem with cost-effectiveness of the cancer patients' treatment which has a very serious effect not only in medical but also in social sphere of human life. In the process of new drugs application it is a normal trend that big investments are done in the beginning of the process of treatment and are to be kept at a high cost, however, with time the cost is reduced and covers the expenses, so that return on investment is observed. The outlined trend of cost-effectiveness correction by combined application of agents along with supplementary tests for patients' selection does not under any circumstances lead to financial perspective improvement.

It is worth mentioning that the mass media massive campaign supported by ungrounded scientific publications, created an image of target therapy as a "revolution" in cancer decease treatment [68] which will heavily impact not only health securities system but mainly on cancer patients themselves.

Conclusion

In spite of the constantly increasing financial resources in the field of cancer treatment progress remains elusive. The unsatisfactory results from the conventional methods of treatment when reviewing the scientific studies remain outside the attention of both the medical specialists and the society. Serious studies with negative results regarding the applied conventional methods are being ignored. The scientific studies of cancer treatment to a great degree have badly constructed methodology and realization which makes their reliability questionable.

According to the editor of the British Medical Journal, Richard Smith only 15% of the medical interventions are supported by solid scientific proofs. The reason for this is that only 1% of the articles published in the medical magazines are scientifically supported, partly because many of the treatments were never evaluated [69]. These conclusions refer to a greater extent also for the curative methods applied in cancer treatment. In the scientific studies there is no serious attention paid both to quality of life of the patients and the correlation price versus efficiency. The information provided to patients for the possible curative methods very often is unsatisfactory, and also confusing. The present system and standards of the so called modern cancer treatment therapy do not allow for close collaboration and interrelations between patient and doctor, affecting negatively the treatment results. There are new and expensive medicines promoted to the public as another panacea for cancer treatment without being based on sufficient and reliable proof.

In spite of the scientific proof accumulated supporting the fact that cancer is a system disease, in which the permanent attempts directed solely to the local removal of the tumor are doomed to failure, this approach remains dominant. Outside the conventional medicine there is no enough attention and resources allotted for new contemporary methodology based on integrative and holistic principles. The accumulated present scientific and practical potential of the integrative cancer treatment methods represent a good basis and potential for the future development. We will conclude with quotation of what the great German cancer specialist and pioneer in the field of integrative oncology Josef Issels said: "Cancer treatment will remain a cul-de-sac" due to the fact that it is based on obsolete concepts. The unwritten law in medicine remains valid that the pathogenesis concept, the cause for the disease is necessary to consider in the overall treatment.

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