Acta Poloniae Pharmaceutica – Drug Research, Vol. 65 No. 6 pp. 633–640, 2008 ISSN 0001-6837
Polish Pharmaceutical Society

MOLECULAR UNDERPINNINGS OF THE TARGETED THERAPY FOR CANCER

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Abstract: Cancer is a real challenge for modern medicine. Biologically, it is of a host origin and therefore its eradication appears not so easy as one could expect to do it. Cancer presents itself with many faces as if it would be Janus the deity. The basic knowledge on tumorigenesis at the level of evolutionary science is weak. Additionally, accumulating molecular data are still focused on experimental systems, but more important fact is to determine the molecular pathobiology that could have impact on improvement of control of malignant disease. Poland is among the countries with high cancer morbidity and mortaity. Multidisciplinary approach to detect, control, and treat cancer diseases is the only way to get improved clinical results. Moreover, it is worth pointing out that individual considerations of every patient would offer clinical benefits. Biology of human tumors with the modern armament of molecular and chemical methods would be a help-hand to construct novel drugs. Making a list of crucial pathways worth blocking with their translation into clinical benefits appears to be a great step forward. Chemistry is a real partner to modern medicine due to a technical possibility to have impact on molecules (xenobiotics) that will finally become approved drugs. Combinatorial chemistry offers automated methods for pipeline organic synthesis a large number of chemicals that are further capable of undertaking investigation at a bed. Many chemicals have been used for more than ten years upon treating various cancer patients. New drugs have various origin , i.e., monoclonal antibodies (Herceptin, Erbitux, Avastin) or small molecules (Glivec, Tarceva, Sutent, Nexavar). We do hope that in the future many new drugs will be available for treatment of particular disease in relation to genetic characterization of individual patient's tumor. At the same time, we realize the great need for changes in the financial facets of modern individual treatment, and hoping not to hamper the development of new drugs due to the lack of financial solution how to make new and expensive drugs available to many patients.

Keywords: cancer pathobiology, evolutionary tumorigenesis, cancer progression, targeted therapy

Malignant disease appears a tremendous challenge for medicine

Cancer is a term that gives a huge fear and many threats of the future life in malignant patients. Oncologists are familiar enough with a patient's voice reflecting some kind of a sentence which comes with the pathology report telling the only diagnosis, i.e., cancer. Unfortunately, this scenario is seen very often in all groups of age in civilized society. There are two big challenges still gnawing patients, medical workers, and administration. Namely, social aspects of a malignant disease are reflected by the number of cancer patients noted per annum, and financial proposals to make novel therapy available to them.

The discipline of cancer epidemiology covers the study of cancer patterns in populations and cancer causation. Epidemiologists use various methods to show an incidence of different cancers. Experimental studies are focused on mechanisms resposible for tumorigenesis and further progression. Observational studies comprise descriptive (maps, trends, and correlational-ecologic investigations) and analytic (case-control and cohort) studies. SEER (Surveillance, Epidemiology, and End Results ; web site: www-seer.ims.nci.nih.gov) program provides many data on malignant diseases.

Another source of information is the GLOBCAN series of the International Agency for Research on Cancer which gives data on the relative importance of different cancers worldwide in terms of the absolute numbers and rates of persons developing, living with (five-year prevalence), or dying of cancer in the year 2002. In the beginning, it is useful to give some simple definitions of terms present in epidemiologists' language.

Incidence is the number of new cases occuring, expressed as an absolute number of cases per year or as a rate per 100,000 persons per year. The average risk of developing cancer in one year is used for comparisons among countries or within populations over time.

Mortality is the number of deaths occuring and the mortality rate is the number of deaths per 100,000 persons per year. So mortality appears as

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the product of the incidence and the fatality for a given cancer.

Prevalence describes the number of persons alive at a particular point in time with the disease of interest.

In 2005 the results of global observation on 26 cancers in 2002 were available with such data as 10.9 million new cases, 6.7 million deaths , and 24.6 million persons alive with cancer within three years of diagnosis. The most commonly diagnosed cancers are lung – 1.35 million, breast – 1.15, colorectal – 1 million. On the other hand, the most common causes of death are lung cancer – 1.18 million, stomach cancer – 700,000, and liver cancer – 598,000 deaths. The most prevalent cancer in the world is breast cancer – 4.4 million survivors up to five years (1, 2). Another interesting issue is the level of variations in the risk of different cancers by geographic area.

Many types of cancer vary in incidence by more than an order of magnitude between different populations, and therefore, other risk factors play a key role in this process. Investigations devoted to immigrants show that genetic explanations are no longer enough robust to find out causes of a given cancer. So every type of cancer is rare in some parts of the world (3).

Progress in investigational sphere of cancer is rather costly. The first steps toward the real battle against cancer was made in 1971 when Richard Nixon – then president of the United States – announced an initiative later became known as „war on cancer" (4). In America, projections suggest that 40% of alive persons will be diagnosed with some form of cancer at some point in their lives. And by 2010, the rate will increase to 50%. „War on cancer" needed expenditure of $70 billion to National Cancer Institute. Despite these billions the rate of death from cancer in the US has increased from 163 per 100,000 individuals in 1971 to 194 per 100,000 in 2001 (5). On the other hand, mortalilty rates from heart diseases and strokes have fallen clearly.

Quite different story concers the financial aspects of the modern drugs. Now it is time to open the national debate over the cost of new biologic agents. New drugs hold the promise of improved survival in some cases but longer duration of treatment with these agents is expensive which threatens a significant increase in healthcare costs. In some Western European countries costs of new drugs are transfered to cancer patients. Even for rich countries long-lasting therapy with expensive new biologic drugs has limitations and only 5% of private patients can afford for such a management. Another caveat is expressed as the lack of head-to-head trials between new agents.

Origin of malignant disease

Complex organism is composed of both postmitotic and renewable (mitotic) somatic tissues. Mitosis is a biological process having impact on normal function of tissues at the cellular level. The same process, on the other hand, can start tumorigenesis. Looking at a cancer, it is important to have insight into both internal events going inside a just transforming cell and interaction among transformed cells, and between them and normal cells. Transformed cells acquire certain abnormal properties. These properties usually known as malignant phenotype give ability to form multicellular masses. Cancer is a problem that affects the whole organism. Many molecular events are responsible for tumorigenesis and progression with a fatal result.

A lesion suspected of being cancer must be diagnosed by pathologist! Therefore, it is important to pick up a cellular sample of a suspected lesion. There are several methods of obtaining specimen: surgical biopsy, exfoliative cytology, fine needle aspiration biopsy. Validity of interpretation depends on representative sample, clinical data of the particular patient with additional knowledge of health status. Cooperation between pathologist and clinician is a crucial point to ovecome diagnostic difficulties.

Accumulating clinical and pathologic experience has provided a set of information on different types of malignat tumors. It is possible to summarize the main histologic and cytologic features of cancer. Invasiveness is a process when malignant cells infiltrate surrounding tissues. The following result of this infiltrative growth is destruction of normal tissue. Anaplasia is a kind of growth pattern in which tissue architecture is readily various from normal one. Pleomorphism is the result of heterogenous structure of the tumor and pathologist may recognize various areas in the same tumor. High mitotic rate reflects proliferative nature of a malignant tumor. Diseased tissue sections manifest increased numbers of mitotic figures. Aneuploidy shows abnormal DNA content of the malignant cells. Cancer cells often have irregular and inconstant amounts of DNA (6).

Malignant tumors can originate from almost all types of normal tissues. The origin of a particular tumor is possible to determine when even a small portion of normal cells and tissue pattern is preserved. Consideration of biologic behavior results in the division of tumors into benign and malignant ones. The first group is characterized by mostly local growth with little harm to the whole body of host. The second group contains aggressive malignant tumors which generally result in metastases and death. Benign tumors are usually named by adding

the suffix – oma to the name of a type of cell or tissue. Malignant tumors are divided into two groups: sarcomas of mesenchymal origin, and carcinomas of epithelial origin. At the time of putting the final diagnosis grading and staging are required. The grade is an evaluation of the degree of differentiation of the tumor, and the same, of the degree of malignancy. The stage of the tumor is an evaluation of the extent of the tumor at the time of diagnosis, and usually is not related to its grade (7).

Evolutionary aspects of tumorigenesis

Cancer is characterized by uncontrolled cell growth. Normal cells regulate their divisions into daughter cells. Darwinian tendency relies on reproducing favorably such cells that provide the survival of the body they inhabit. This is one of the fundamental processes of evolution that allow the development of multicellular organisms. On the other hand, it is necessary to keep in mind the notion that evolution works on many levels. Therefore, it is inevitable that mutations in some of the million of cells making up a human body will function incorrectly by changed regulatory genes. In a competition between regulated and unregulated cells, the unregulated ones will multiply faster, and finally win by giving rise of cancer. The possibility of developing cancer appeared 700 million years ago when primitive animals started to exist and reproduce by cell division (8).

It is still debatable whether a tumor develops from one cell or many, and how changes in the biological characteristics of a neoplastic population occur over time. Many investigators have accepted the notion that malignant tumors develop as a clone from a single cell. Cancer researchers have supported the idea that a malignant tumor stems from transformed single cells characterized by chromosome aberrations.

Cytogenetic studies have demonstrated that in many primary tumors all cells show the same abnormal karyotype. Additionaly, even several chromosomal changes are present within a single tumor, marker chromosomes in each cell show that various cells have common ancestor. Other biological markers as isoenzymes of glucose-6-phosphate dehydrogenase present in women (X chromosome bearers) determine that all cells of a given tumor have origin from the same single cell. The same is shown in a pattern of immunoglobulin synthesis in plasma cell tumors which stem from a single precursor (9).

The biological characterization of a tumor reflects its progression. The latter is a result of some kind of regulatory alterations, that embrace a pattern of expression both of genes and proteins, which will be met in further cellular generations. The fundamental process responsible for cancer progression is the increase of proliferative capacity and escape from normal growth control mechanisms. So it is common for tumors as they become more malignant, to show morphological and metabolic alterations interpreted as a loss of differentiation. Two major processes initiate tumorigenesis and further progression by 1. genetic instability in the malignant cells, and 2. the sequential selection of variant subpopulations being the result of above mentioned genetic instability.

The model of clonal evolution in cancer tumor describes the dynamic alterations at the cellular level within growing tumor which further progressed. Carcinogen-induced change in progenitor normal cell produces a diploid tumor cell with growth advantage giving the possibility of clonal expansion. Genetic instability of the primary affected cells leads to production of variants. Most variants die, due to metabolic disadavntages, but sometimes one has an additional selective advantage. The latter cell gives rise to a defined cancer population which dominates. The stepwise sequence in a tumor differs due to environmental pressure on selection and finally results in developing malignancy. Biological characteristics of tumor progression embraces morphological and metabolic loss of differentiation, invasion and formation of metastases, and additionally, resistance to therapy. Human tumors with minimal chromosome changes (acute leukemias) are considered to be early in clonal evolution, and human solid cancer are defined as late in the developmental process (10).

Typical view of cancer entails its development as the result of transformation of a given cell done under the multifactorial conditions. Primary mechanism of the transformation relies on appearance of sequential mutations that activate cancer promoting oncogenes, or inhibiting anti-oncogenes, or trigger genetic instabilities. Currently, there is known one exception of such described development of cancer in which tumor cells, as a whole, behave like infectious agents and move from one host to another.

CTVT (canine transmissible veneral tumor) or Sticker's sarcoma is a histiocytic tumor that is usually transmitted among dogs through coitus, licking, biting, and sniffing. So the tumor grows as a graft initiated by infectious-like factor being in fact a cancer cell. This tumor can only be induced by the implantation of whole CTVT cells, and not by cell extracts or dead cells. Sticker's sarcoma was characterized roughly 130 years ago and was very often used by cancer researchers to study tumor transplan-

tation. Tumor karyotype is aneuploid and has characteristic marker chromosome shown in tumor samples collected in different geographic regions. The diagnostic marker of CTVT is LINE-1 (long-interspersed nuclear element insertion near c-myc).

Sticker's sarcoma is safe for humans. A main reason is tissue graft rejection caused by MHC (major histocompatibility complex) incompatibility. Under normal conditions, the immune system uses cell-surface proteins, i.e., MHC antigens to differentiate self from non-self. The immune system attack against enemy is executed only when alien cells are detected. CTVT has a unique mechanism to avoid immune-mediated destruction of invading Sticker's sarcoma cells by down-regulating the expression of the canine MHC antigens (11-13).

Molecular mechanisms of tumorigenesis and progression

The development of cancer in humans involves a great deal of complicated processes working over many years. During this multistep process, the genome of a given cell acquire mutant alleles of proto-oncogenes, tumor suppressor genes, genes regulating the cell cycle machinery and genes responsible for coding adhesins. Experimental systems of tumorigenesis and further progression have shown that understanding of the complex of neoplastic transformation at the cellular level is associated with a small number of underlying genetic changes. One of the most important events ever happened was the identification of transforming retroviruses. This idea went with experimental achievements of Dr. Rous whose works had supported the notion of transmissible factors responsible for carcinogenesis of a sarcoma of the fowl (14, 15). Viral oncogenes have their counterparts within the human cells which induce transformation after an increase of a given gene copy number. Experimental studies have shown that at least two oncogenes needed to be introduced into the normal cell to begin tumorigenesis (16).

Another very important mechanism is the functional loss of proteins encoded by tumor suppressor genes which have impact on the pattern of neoplastic phenotype. Methylation of nucleotides in the promoter sequences of particular tumor suppressor genes has eliminating function. DNA methylases attach methyl groups to the cytidine residues of cytidine – guanosine sequences in the cell genome. The same biochemical mechanism is frequently observed during tumor progression (17, 18). There are two well known tumor suppressor gene pathways: the retinoblastoma protein, which plays a central part in progression through G1 phase of the cell cycle (19), and the p53 protein pathway, which is altered in almost 50% of all cancers ; in normal cells p53 is responsible for short arresting cell growth to repair DNA or to trigger a program of apoptosis which eliminates damaged cells (20).

Telomers are the protective sequences that constitute the ends of chromosomes. Maintenance of telomers is a crucial issue for the identification of proliferating cells which are defined as the phenotype of cell immortalization. Telomerase is an enzymatic complex responsible for immortalization of normal cells and neoplastic ones as well (21).

Angiogenesis is another complex process responsible for tumorigenesis. When a primary tumor is 1-2 cubic mm , the diffusion cannot offer efficient metabolic exchange, and angiogenic switch is needed for continuation of tumor development. Solid tumors achieve angiogenesis by secreting proangiogenic factors – the most important factors are vascular endothelial growth factor (VEGF) and basic fibroblast growth factor with simultaneous down-regulation of the expression of antiangiogenic proetins as thrombospondin –1. Timely sequence of orchestrating mechanisms assure effective angiogenesis which is highly regulated (22, 23). Attacking tumor angiogenesis appears to be another therapeutic possibilty to control cancer progression. This therapy is indirect and the most beneficial results have been seen when used in combination with chemotherapy or radiotherapy.

The malignant phenotypes are regulated by six devil forces rendering a cancer progression: loss of the growth control, resistance to apoptosis, extended or indefinite replicative lifespan (replicative immortality), ability to attract or create new vessels (angiogenesis), ability to invade the surrounding tissue, and ability to colonize and survive in other organs (metastasis) (24). Despite many years of investigation a cancer progression still appears to be a puzzle. Succession of genetic and epigenetic changes leads to final step of cancer , i.e., dissemination. There are two ways of thinking about this process. The first way assumes that propensity to develop metastases is hidden in the primary tumor, and the second one shows that a metastasis is the result of sequential genetic changes which are responsible for existence of rare pro-metastatic cells at a given time of the whole tumor progression (25, 26).

Epithelial-mesenchymal transitions are vital mechanisms responsible for morphogenesis during embryonic development. On the other hand, the same mechanisms are also implicated in the conversion of early stage tumors into invasive malignancies. A unity of biological processes relies on the

fact that genes discovered for their oncogenic role are often found to be key players in embryogenesis. Epithelial-mesenchymal transition is a process in which epithelial cells lose polarity and cell-cell contacts, and undergo a readily seen remodeling of the cytoskeleton. This mechanism is also very important when damaged tissues are repaired in adults. A hallmark of epithelial-mesenchymal transition is a loss of the E-cadherin expression. This event is consistently observed at sites of developmental embryogenesis and cancer formation. Many investigations have been carried out to find repressors of E-cadherin (27). Repressors of the epithelial-mesenchymal transition seems to be a kind of master controls which play key roles in starting other minor regulatory reactions necessary both for embryogenesis and progression of cancer.

The *eyeless (ey)* mutation of Drosophila was first described in 1915 on the basis of its characteristic phenotype, the partial or complete absence of the compound eyes. The gene *ey* encodes a transcription factor that is an important factor in developing nervous system and in the eye during embryogenesis. Loss-of-function mutations in the gene has been shown to lead to a reduction or absence of eye structures. Targeted expression of the *ey* complementary DNA in various topographic sites has resulted induced ectopic eye structures located on the wings, the legs, and on the antennae (28, 29). Whether a cancer progression has such a master control is unknown and remains to be determined. In 2008 Han et al. (30) discovered the SATB1 gene to be a main regulator (master control) of cancer progression. SATB1 is a nuclear protein that functions as genome organizer essential for proper T cell development. This protein is responsible for architecture and protein distribution surrounding heterochromatin. Even this architecture is called as the SATB1 regulatory network. In breast cancer, SATB1 is expressed by aggressive cancer cells and its expression level has high prognostic significance ($p < 0.0001$), independent of lymph node status. RNA-interference-mediated knockdown of SATB1 in highly aggressive cancer cells altered the expression of more than 1,000 genes. On the other hand, ectopic expression of the SATB1 gene in non-aggressive cells led to gene expression patterns that characterizes aggressive-tumor phenotypes.

The modern technology combining molecular biology with computer sciences offers novel methods of investigating cancer samples to present various gene profile performed by high-throughput analysis. DNA arrays allow the simultaneous analysis of expression levels for thousands of genes in normal and pathological tissues and hold the great promise in molecular dignostics. Biological and clinical diversity of human malignant tumors is poorly characterized by the current classification. Better understanding of the human tumorigenesis should lead to improvements in cancer management. There are still expectations of identification of new target genes and pathways which further could be used at the development of specific anticancer agents. Secondly, DNA arrays will provide a modern tool for malignant tumor classification (31). Metastasis is a harmful process leading to death of patients suffering from cancer. So molecular basis of the process would be highly desired, especially, at the beginning of cancer diagnosis. Cancer management also should be dependent upon the full characterization of the malignant tumor in order to prevent unwanted and toxic therapy.Unfortunately, the metastatic potential of human tumors is encoded in the bulk of a primary tumor (32). DNA array utility in clinic is criticized due to some caveats that should be clarified. Optimal incorporation into clinical practice is not straightforward. Currently, cost –effectivness of this technology is highly difficult to appreciate. Clinical decisions require careful planning and robust evidence (33).

Technology of a single cell allows the investigations of molecular aspects of many regulatory mechanisms with their location in a given cell. This is of paramount importance to detect variabilty of a particular molecular mechanism at the cellular level which potentially indicate the most harmful cells that in fact will be the cause of cancer relapse during course of a malignant disease. Laser capture microdissection (LCM) allows to obtain selected human cell populations from a section of heterogenous tissue. The method entails placing a thin transparent film over a tissue section, visualizing the tissue microscopically, and selectively adhering the cells of interest to the film with a fixed-position. The most important fact is that LCM offers laser precision and can achieve transfer and isolation of single cells with their separation of tumor, normal, and dysplastic cells. This technology gives the modern tool for genetic investigation of single cells (34, 35). Single cell populations analysis has revealed genetic heterogeneity of single disseminated tumor cells. LCM combined with PCR and cytogenetics have offered the new insight into the real nature of a malignant tumor studied in a clinical model of minimal residual cancer present in bone marrow. Moreover, early disseminated cancer cells are genomically very unstable. Among these cells must exist rare cells initiating cancer progression by

appearance of metastatic lesions defined and confimed as distant metastases (36).

Stem cells are defined as cells that have the ability to perpetuate themselves through self-renewal and to generate mature cells of a particular tissue through differentiation. They are rare and must be identified prospectively, and purified carefully in order to study their properties. Although it seems reasonable to propose that each tissue arises from a tissue-specific stem cell. For example, hematopoietic stem cells have been isolated from mice and humans, and have been shown to be responsible for the generation and regeneration of the blood-forming and immune systems. On the other hand, about 60% of the differentiated tissue types in a mammalian body are epithelia. The range of their functions is vast and frequently involves the secretion of bioactive materials and absorption of substances as well as the mechanical integrity of surfaces. How epithelia are formed and maintained is one of the key problems of developmental biology and an area in which many basic questions remain unsolved. Some epithelia, such as the skin or intestine, show rapid cell turnover others, as the liver or pancreas, show a very slow turnover under normal conditions but with special adaptations for regeneration (37).

Understanding the mechanisms that regulate self-renewal of stem cells is a real challenge in scientific community. Self-renewal is crucial to stem cell function, because it is required by many types of stem cells to persist for the lifetime of an animal or a human. Moreover, stem cells from different organs may vary in their developmental potential, all of them must self-renew and regulate the relative balance between self-renewal and differentiation. Understanding the regulation of normal stem cell self-renewal is also fundamental to understanding the regulation of cancer cell proliferation, and in this light, cancer can be considered to be a disease of unregulated self-renewal. For cancer to develop, a population of continuously proliferating (self-renewing) cells must arise. For tumors containing a subpopulation of cancer stem cells, there are at least two ways that the cancer stem cells could have arisen. In the first way, oncogenic mutations may inactivate the constraints on normal stem cell expansion, resulting in cancer stem cells that originated from normal stem cells. In the second one, oncogenic mutations may allow amplifying cells to continue to proliferate without entering a postmitotic differentiated state, and finally creating a pool of self-renewing cells in which further mutations can accumulate. This pool ultimately may give rise to cancer stem cells that originated from a more differentiated cell (38).

Normal stem cells and cancer cells share the ability to self-renew, it seems reasonable to propose that newly arising cancer cells appropriate the machinery for self-renewing cell division that is normally expressed in stem cells. Evidence shows that many pathways that are classically associated with cancer may also regulate normal stem cell development. For example, the prevention of apoptosis by enforced expression of the oncogene *bcl-2* results in increased numbers of hematopoietic stem cells, suggesting that cell death has a role in regulating their homeostasis. Other signaling pathways associated with oncogenesis, such as the Notch, Sonic hedgehog (Shh) and Wnt signaling pathways, may also regulate stem cell self-renewal (39). Cancer stem cells have been found in many cancers as breast, brain, colon, and head and neck. The cells could have impact on tumor growth and maintenance. It is still debatable whether target cancer stem cells may prove more effective than current cancer treatments. Radiotherapy and many chemotherapeutic agents allow to get rid of dividing cells, but it seems that stem cells may have been the culprit of tumor relapse in the future. Therefore, cancer stem cells are frequently considered as very dangerous to maintain cancer in the body, and fatal results of treatment (40).

Targeted therapy

Cancer therapy is a complex managemanet. Unfortunately, currently available methods attack not just cancer cells but the whole organism. So toxicity profile usually attracts special attention of oncologist to balance between clinical benefits and harm. A great vast of new chemical compounds has been investigated upon the occasion of potential utility as novel drugs with anticancer activity. Since 2003, Swiss-based Novartis got the FDA (Food and Drug Administration) approval for imatinib (Glivec) which is used in the treatment of chronic myelogenous leukemia, gastrointestitial stromal tumors, dermatofibrosarcoma protuberans and incidentally in other neoplastic diseases.

Laboratory research has led to an enormous expansion of our understanding of cellular biology and genetics in relation to cancer. Translatory investigations have given the possibilities to use molecular achievements in cancer management. A body of accumulating evidence has provided particular molecules to be considered as master control regulators, at the time of tumorigenesis and progression, with a potential practical utility, and more important, with hope to improve treatment results and not to worsen general toxicity that is so often experienced by can-

cer patients. Now we are at the busy time for creation of new chemicals with potential usage as anticancer agents. Many such substances (Herceptin, Glivec, Tarceva, Sutent, Nexavar, Erbitux, Avastin, MabThera) are used to treat certain tumors.

A plethora of molecules considered to be targets for cancer therapy have been identified. Some of the molecules are well enough characterized as predictive factors of cancer (predictive factor tells us about benefits of clinical usage of a certain drug; prognostic factor tells us about prognosis of overall survival or time to relapse or progression) and their detection give opportunity to treat such a malignant tumor with specific method, e.g., Herceptin is used against breast cancer when HER-2 overexpression is detected. HER-1 (EGFR- epidermal growth factor receptor) and HER-2 are the most frequently detected genes in colorectal cancer, head and neck cancer, and breast cancer, respectively. HER-1 is blocked by monoclonal antibody called Erbitux usually used with chemotherapy in advanced colorectal cancer.

A growing number of molecular factors must be classified under the conditions of practical usage. For instance, the level of expression of HER-1 (EGFR) in colorectal cancer comprises from 25-80% of patients. Monotherapy with Erbitux can offer the response rate not exceeding 10% in advanced colorectal cancer patients. On the other hand, phosphorylated form of HER-1 (biologically active molecule) is detectd at the rate of up to 10%. Therefore, it is necessary to establish the level of biological role of HER-1 in advanced colorectal cancer in relation to a certain patient. Much better results have been obtained when Erbitux was combined with chemotherapy. The clinical benefit manifested as CR (complete response – no signs of disease at all) plus PR (partial response), and SD (stable disease) has been noted in almost 50% of patients. Unfortunately, time to progression after such combined treatment did not exceed six moths (41).

The means of targeted therapy embraces two entities: monoclonal antobodies and small molecules. Monoclonal antibodies against particular targets mainly operate outside a cell. For example, Herceptin blocks HER-2, Erbitux blocks HER-1, Avastin blocks VEGF (vascular endothelial growth factor). Small molecules are much smaller than monoclonal antibodies, and therefore, are able to penetrate into the cells. Their targets are usually protein kinases which play important roles in signaling pathways. Among the receptor-type kinases there is a sub-group known as receptor tyrosine kinases. They are involved in the initiation of cellular activation and signaling in response to extracellular stimuli. The kinase family includes more than 500 genes, and many of them function abnormally in tumor cells (42).

Renal cell cancer affects kidney accounts for up to 3% of all neoplastic diseases. It is highly resistant to standard chemotherapy. Therefore, interleukin-2 and interferon alfa are widely used as the first-line therapy of advanced kidney cancer. Response rates are rather low (5-20%), and median overall survival is approximately 12 months. Early data on sunitinib have clearly shown that this substance is active in patients previously treated with cytokines. Sunitinib is an orally aministerd inhibitor of tyrosine kinases as following: VEGF receptor, PDGF receptor (PDGF-platelet-derived growth factor receptor). The mentioned kinases play key roles in the pathogenesis of clear cell carcinoma of kidney (43).

Motzer et al. (44) showed after completing data of the randomized phase III study that sunitinib offered better results in terms of higher rate of kidney cancer control (79% vs. 55%), and longer progression-free survival (11 months vs. 5 months, respectively) than interferon alpha. Unfortunately, the study did not show longer overall survival for study group, although, there was a trend toward improved survival with sunitinib (no Kaplan-Meier curve present). Further analysis will be reported when more data are completed.

From the historic point of view, there are well known two examples of targeted therapy which are sucessfully used in clinical practice , namely, endocrine therapy either breast cancer or prostate cancer. Breast cancer, especially in elderly, is estrogen-responsive, so blocking this pathway became standard therapeutic choice. And tamoxifen and aromatase inhibitors are used very often to control breast cancer for many years. In case of prostate cancer, since 1940s, androgene blockade has been used as the mainstay to control the advanced disease.

CONCLUSION

There is a great expectation that targeted therapy will have a substantial impact on changing way of treatment of cancer. When more agents are licenced, doctors will have more therapeutic options to select the most appropriate drug or regimen for each patient. One additional point must be fulfilled in relation to targeted therapy, i.e., better characterization of a given malignant disease, to be treated, with predictive factors mostly of molecular nature. Therefore, it is so important to discover new predictive and prognostic factors which are to play key roles at the time of making-decision for a particular

patient. On the other hand, correlations of the potential predictive factors with natural course of the disease could give a real insight into the pathobiology of human tumors. A pattern of more specific data concerning tumor expression of relevant target molecules would provide the rationale to attack the tumor through a number of mechanisms with minimizing the likehood of developing resistance. Of course, another aspect of modern therapy for neoplastic diseases relies on proper management of present toxicities associated with the usage of new drugs, and not to delay such a treatment. Orally administered drugs, mostly small molecules, appear to be more convenient to cancer patients when compared with monoclonal antibodies and standard chemotherapeutics.

There is a surge of oncologic development that offers novel insight into a way how to manage one of the most diffcult phenomenon called malignant disease which is, in fact, a part of the host. So we have hope for further development in many areas of oncologic investigations which are dependent on such disciplines as: molecular evolutionary biology, computer simulations, game theory devoted to cancer, chemistry, biophysics, biomathematics, and nanotechnology.

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