

Personalized Medicine in Cancer

MM RAHMAN

Summary:

Current and emerging biomedical science efforts are driven by determining how to improve clinical outcomes for patients. High-throughput technology has revolutionized the area of translational research, confirming the high complexity and heterogeneity of common diseases, particularly cancer. Therefore, moving from 'classic' single-gene-based molecular investigation to molecular network research might result in discovering clinical implications faster and more efficiently. Molecular characterization of tumour cells enables refinement of classifications for many cancers and can sometimes guide treatment. Malignant diseases are no longer classified only by tumour site and histology but are separated into various homogenous molecular subtypes, distinguished by a presumed key molecular

alteration. Therapies for patients with cancer have changed gradually over the past decade, moving away from the administration of broadly acting cytotoxic drugs towards the use of more-specific therapies that are targeted to each tumour. To facilitate this shift, tests need to be developed to identify those individuals who require therapy and those who are most likely to benefit from certain therapies. In particular, tests that predict the clinical outcome for patients on the basis of the genes expressed by their tumours are likely to increasingly affect patient management, heralding a new era of personalized medicine. In this review a brief discussion on definition and molecular aspects of personalized medicine and its practical application for the management of common solid cancers are highlighted.

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Personalized oncology

The term “personalized medicine” has gained widespread acceptance in the healthcare field and particularly in oncology, where it most often refers to a vision of cancer management in which treatment is tailored to individual patients based on the molecular profile of their tumour.^{1,2} In that sense, the term is neither an accurate reflection of what constitutes a person – the molecular profile of his or her tumour – nor of our capacity to personalize medicine, since for the moment, we can only choose among the existing therapies the one that best matches the tumour characteristics. The rapid advances currently underway in “-omics” research, new high through put molecular analyses and next-generation sequencing, are improving our understanding of cancer biology and have allowed us to develop new agents specifically designed to disrupt the molecular pathways that are critical to disease initiation and tumour-cell proliferation. Here again at best we can hope to identify molecular subgroups of

patients in whom the tumour may be susceptible to therapy. But targeted therapy necessarily implies that there are subgroups of patients whose genetic and biological profiles place them outside the target. Given what we already know about the highly complex mechanisms that drive the disease, the goal of personalised medicine cannot possibly be to develop one treatment for each individual person's cancer.³ Personalized oncology includes the concepts that each individual solid tumor and hematologic malignancy in each person is unique in cause, rate of progression and responsiveness to surgery, chemotherapy and radiation therapy⁴.

In the past, personalized oncology relied on nonspecific clinical signs. However, emerging genomic and proteomic technologies are now allowing for the subclassification of diseases on an individual basis. For example, expanded knowledge of the molecular basis of cancer has shown that significant differences in gene sequence and/or expression patterns can guide therapy for a variety of solid tumors such as breast cancer (*HER2* test-ing), colorectal cancer (*KRAS* and *BRAF* test-ing), lung cancer (*EGF* receptor gene [*EGFR*] testing) and melanoma (*BRAF* testing), as well as for malignant lymphoma and both lymphoid and nonlymphoid leukemias⁵.

Address of Correspondence: Prof. Md. Mizanur Rahman, Professor and Head, Department of Surgical Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka-1212, Bangladesh. E Mail: mizannicrh@gmail.com

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Definition of personalized medicine:

Individualized treatment vs. treatment for a sub-patient group-

Personalized medicine has been defined in many ways. According to the U.S. National Institutes of Health (NIH), personalized medicine is “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease”⁶. The U.S. Food and Drug Administration defined personalized medicine as “the best medical outcomes by choosing treatments that work well with a person’s genomic profile or with certain characteristics in the person’s blood proteins or cell surface proteins”. The President’s Council of Advisors on Science and Technology (PCAST) described personalized medicine as “tailoring of medical treatment to the individual characteristics of each patient”⁷.

It is important to recognize that personalized medicine does not literally mean individuality. The idea of personalized medicine has often been exaggerated, as suggested in a headline in Newsweek (June 10, 2005) “Medicine Tailored Just for You.” In fact, a new treatment regimen is assessed on a group of carefully selected patients but not individuals⁸. As such, PCAST reports that personalized medicine is “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment”⁹. If a new treatment works effectively on a sub-patient group, a preventive intervention can then be furnished to those who will benefit, avoiding adverse drug effects and sparing expense for those who will not.

Why Personalized Medicine?

The wide-ranging impacts and myriad opportunities provided by personalized medicine can be summarized in reference to its four major attributes⁷.

Personalized

Personalized medicine integrates personal genetic or protein profiles to strengthen healthcare at a more personalized level, particularly with the aid of recently emerging “-omic” technologies such as nutritional genomics, pharmacogenomics, proteomics, and metabolomics¹⁰. Personalized medicine targets what has a positive effect on a patient’s disease and then develops safe and effective treatments for that specific

disease. In fact, genetic biomarkers that may be specifically associated with a disease state are the foundation of personalized medicine. Knowledge of a patient’s genetic profile leads to the proper medication or therapy so that physicians can manage a patient’s disease or predisposition towards it using the proper dose or treatment regimen⁶.

Preventative

Personalized medicine pursues not reaction but prevention. With the ability to forecast disease risk or presence before clinical symptoms appear, personalized medicine offers the opportunity to act on the disease through early intervention. In lieu of reacting to advanced stages of a disease, preventive intervention can be life-saving in many cases. For example, females with genetic mutations in the BRCA1 or BRCA2 genes have a higher chance of developing breast cancer compared to those in the general female population¹¹. An accurate test of these breast cancer susceptibility genes can guide surveillance and preventive treatment based on objective risk measurements such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

Predictive

Personalized medicine enables physicians to select optimal therapies and avoid adverse drug reactions. Molecular diagnostic devices using predictive biomarkers provide valuable information regarding genetically defined subgroups of patients who would benefit from a specific therapy. For example, Oncotype DX® (Genomic Health, Redwood City, USA) uses a 16-gene signature to determine whether women with certain types of breast cancer are likely to benefit from chemotherapy^{12,13}.

MammaPrint (Agendia, Amsterdam, the Netherlands) uses a 70-gene expression profile to assess the risk of distant metastasis in patients with early-stage breast cancer. These complex diagnostic tests can be used to classify patients into subgroups to inform physicians whether patients would be treated successfully with hormone therapy alone or may require more aggressive chemotherapy treatment.

Participatory

Personalized medicine would lead to an increase in patient adherence to treatment¹⁴. When personalized

healthcare assures its effectiveness and can minimize adverse treatment effects sparing the expenses, patients will be more likely and willing to comply with their treatments.

Implications of heterogeneity in cancer

Every type of human cancer is comprised of biological subsets that differ in clinical behaviour and response to treatment¹⁵, and there are many important examples of treatment regimens that produce better results in some tumour subtypes than others. Notable examples of tumour subtypes that must be recognized to optimize treatment include oestrogen receptor or HER2 (also known as ERBB2)-positive breast cancer. More recent examples are non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations; colorectal cancer with KRAS mutations¹⁶; or malignant gliomas with hypermethylation of the methyl guanine methyl transferase (*MGMT*) gene¹⁷. In each case, knowledge of the molecular profile of the tumour is necessary to guide selection of therapy for the patient. Expanding knowledge of tumour biology and tumour–host interactions has moved the field of cancer therapeutics in several new directions, including the following: Development of targeted therapies designed to interrupt molecular pathways known to be critical for cell growth and survival; for example, imatinib treatment for chronic myeloid leukaemia and gastrointestinal stromal tumours. Development of single-gene or multigene expression signatures of response or resistance to particular drug treatments (for example, HER2 and oestrogen receptor) to identify patients with breast cancer who are likely to benefit from adjuvant paclitaxel treatment, or ERCC1 expression as a marker of resistance to platinum-based chemotherapy. Development of vaccine therapies and other immunological approaches that are highly specific to each individual tumour¹⁸.

Genomics in personalized medicine

In 2011, the National Cancer Institute of Health, USA, defined “personalized medicine” as a form of healthcare that considers information about a person’s genes, proteins and environment to prevent, diagnose and treat disease. The reason the word “personalized” has been added is that technology has brought us much closer to exquisite precision in disease diagnosis and treatment. In this context, it is clear that genomics will play a pivotal

(though not exclusive) role in the development of personalized medicine¹⁹. While genetics refers to the study of single genes, genomics includes information about the complex interplay between many genomic markers contained not only in genes but also in intergenic regions with environmental and epigenetic variables, although the distinction between the two is more quantitative than qualitative.

Molecular characterization of tumour cells enables refinement of classifications for many cancers and can sometimes guide treatment²⁰. Malignant diseases are no longer classified only by tumour site and histology but are separated into various homogenous molecular subtypes, distinguished by a presumed key molecular alteration. For example, in lung cancer, tumours with mutations in *ALK* (reported in 4% of cases) or *EGFR* (noted in <10% of adenocarcinomas) have specific clinical presentations and targeted treatments. Moreover, the precise sequence of the mutation can predict outcome, and mutation frequencies vary greatly across ethnic groups. Rare cancers can also be fragmented into subtypes. Gastrointestinal stromal tumours comprise at least ten different subtypes, which need distinct treatments for advanced or adjuvant phases²¹. Complexity grows with recognition that heterogeneity can arise within one tumour and patient. Complex branched evolution of mutations is taking place, from primary tumour cells to metastatic cells²².

One important special feature of biology is its diversity, its variation. That is why personalized medicine is significant. Personalized medicine refers to the right treatment for the right individual at the right time in the health-care world and has the potential to diminish the incidence of drug adverse reactions, eliminate invalid therapy, improve the efficacy of treatments, ultimately, achieve optimal health outcomes. During recent years, most people seem to agree that personalized medicine is the trend of the future. Owing to the accomplishment of the Human Genome Project (HGP), personalized medicine is looming in the horizon and modern medicine moves towards a new individualized health-care model with biological–psychological–social–environmental–spiritual characteristics that reflect the thinking of patient-centred care²³.

Since the early 1990s, knowledge of the genetic basis of cancer, coupled with rapid development of new

technologies, has led to an increased understanding of the heterogeneity of cancer and an ability to develop new therapies targeting specific molecular pathways that may be driving a particular tumour's growth. Consequently, the concept of personalized therapy has evolved from selection of a treatment based on the various toxicity profiles of relatively equivalent therapies to selection of a specific treatment based on the genetic and molecular aspects particular to an individual patient's cancer²⁴.

Application of personalized medicine in some common cancers:

Breast Cancer:

The clinical course of breast cancer varies tremendously between patients. While some of this variability is explained by traditional clinico-pathological factors (including patient age, tumor stage, histological grade and estrogen receptor status), molecular profiling studies have defined breast cancer subtypes with distinct clinical outcomes. The genetic heterogeneity seen in breast cancer has important clinical implications.

It has long been recognized that the clinical course of breast cancer varies tremendously between patients. Traditional clinicopathological variables, including tumor stage, grade and estrogen receptor status, have been used for decades by clinicians to help prognosticate and guide treatment of their patients. In the last 30 years or so, a range of molecular biology technologies, including gene expression profiling, have been used to define molecular subgroups of breast cancer with distinct clinical outcomes. These studies have identified recurrent somatic abnormalities, including gene mutations, copy number aberrations and translocations, the most important of which has been the ERBB2 amplification present in 15 to 20% of breast cancers²⁵.

Recent next-generation sequencing studies:

Whole-genome sequencing studies have reported tens of thousands of somatic mutations in different cancers. The degree of genetic heterogeneity within tumors from individual patients in both space and over time is increasingly well characterized²⁶. In one early report using whole-genome sequencing, Shah et al. examined paired, metachronous tumors from a single patient with advanced invasive lobular carcinoma of the breast, and found 19 non-synonymous mutations present in

metastatic tumors that were not evident in the primary tumor diagnosed nine years earlier²⁷.

In the largest breast cancer series reported to date, the METABRIC study group performed an integrated analysis of copy number and gene expression in discovery and validation sets each containing approximately 1,000 primary breast tumors, with long-term clinical follow-up²⁸. Inherited genetic variants (single nucleotide polymorphisms (SNPs) and copy number variants (CNVs)), and acquired somatic CNAs were associated with altered gene expression in approximately 40% of genes. Importantly, analysis of the combined DNA-RNA profiles revealed 10 different sub-groups with distinct clinical outcomes, which reproduced in the validation cohort. These included subgroups not previously identified by first-generation gene expression profiling studies, in particular with seven distinct subtypes of ER positive disease and a separation of triple negative cancers into at least two subtypes²⁹. Indeed, there is increasing evidence that diagnosis of "triple negative" breast cancer does not describe a single biological entity with distinct natural history. Rather, it refers to a wide range of cancers with great genetic diversity, which can be further classified into multiple subtypes³⁰. In one study, the functional heterogeneity observed within the stem-cell-like compartment of triple-negative breast cancers revealed a 31-gene signature which was associated with the development of metastatic disease.

Stephens et al. analyzed the genomes of 100 tumors for copy number alterations and mutations in coding exons of protein-coding genes. The authors found correlations among the number of somatic mutations, the age at which cancer was diagnosed and tumor histological grade. New driver mutations were found in nine cancer genes including: AKT2, ARID1B, CASP8, CDKN1B, AP3K1, MAP3K13, NCOR1, SMARCD1 and TBX³¹. Banerji et al. focused on the use of whole exome sequencing to identify patterns of mutation and translocation from 103 breast cancers from a range of subtypes³². The authors confirmed the presence of PIK3CA, TP53, AKT1, GATA3 and MAP3K1 mutations, but also identified a recurrent MAGI3-AKT3 fusion found most commonly in ER/PR-negative, HER2-negative breast cancers. Functional experiments showed that this fusion gene caused constitutive activation of AKT kinase which was

amenable to therapy with a selective, small-molecular AKT inhibitor^{32,33}.

Scopes of targeted therapy

One of the most well-known examples of a targeted therapy in cancer is trastuzumab for the treatment of breast cancer, which started in 1999. The Her2 protein is overexpressed in 18%–23% of breast cancers and is associated with increased disease recurrence and poor prognosis. Treatment of breast cancer with the Her2-targeted antibody trastuzumab has been directed using fluorescence *in situ* hybridization (fish) to profile amplification of the *ERBB2* gene (which encodes her2), or immunohistochemistry (ihc) to profile her2 protein expression³⁴. In combination with chemotherapy, trastuzumab has improved progression-free and overall survival in patients with both operable early-stage and metastatic breast cancer⁹, representing a significant benefit for 18%–23% of the 20,000 Canadian women diagnosed with breast cancer annually²⁴.

Colorectal Cancer:

Although Colorectal Cancer (CRC) is highly treatable if diagnosed and surgically removed at an early stage, 5-year survival is <10% in patients with unresectable metastatic disease³⁵. Approximately 40–50% of CRC patients develop metastatic disease, and 80–90% of these have unresectable metastases most of which are in the liver. Amongst patients with metastatic disease, 50% present with a synchronous primary tumour and secondary lesion, whereas the rest develop metachronous metastases. Surgical resection represents the only potentially curative therapy for metastatic CRC. Resection of hepatic metastases from CRC has yielded 5-year survival rates ranging from 35 to 55% although these values are strongly dependent upon pre- and postsurgical variables such as the number of lesions, lesion diameter and clear resection margins³⁶. Similarly, 5-year survival rates after resection of lung metastases from CRC ranged from 20% up to 60% in large series³⁷.

It is unfortunate that surgical resection is not suitable for the vast majority of CRC patients with metastatic disease, and the only treatment option to prolong survival is systemic therapy directed at the disseminated metastatic colonies. For several decades, 5-fluorouracil (5-FU)/leucovorin (LV)-based therapy was the mainstay of treatment of metastatic CRC with median survival of about 11 months [16]. In the past decade, the outcome

of patients with metastatic CRC has improved considerably with the advent of combination regimens of oxaliplatin or irinotecan and 5-FU/LV³⁸. The addition of irinotecan to a bolus or infusional regimen of 5-FU in combination with LV in the firstline setting has resulted in a median survival of 15–23 months³⁹. Irrespective of the first-line chemotherapy regimen, an overall survival (OS) exceeding 2 years is currently achieved when patients, especially those presenting with liver metastases, are exposed to all available active cytotoxic drugs against CRC⁴⁰.

Because these compounds act on selective molecules, their efficacy is limited if indiscriminately administered to all patients, but they significantly affect OS and disease-free survival when treatment selection is driven by molecular profiles. Indeed, it has recently been demonstrated that molecular stratification must be adopted to select the most appropriate targeted agent for individual patients. Most of the targeted inhibitors in development or in clinical use are molecules with high affinity for growth factor receptors, such as fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), mast/stem cell growth factor receptor (KIT) and epidermal growth factor receptor (EGFR). The recent introduction of monoclonal antibodies that bind to vascular endothelial growth factor (VEGF) and to EGFR into the combination chemotherapy regimens currently used in metastatic CRC has been shown to be effective and has further widened the treatment options^{41,42}.

Several biomarkers with both prognostic and predictive value have been described over the past decade. In the present review, we focus on the latest progress within the genomic and proteomic fields, with regard to predictive biomarkers for individualized therapy in sporadic CRC.

Genetic macro-classification and response to chemotherapy:

Three major genetic and epigenetic alterations that drive CRC tumorigenesis have been identified: microsatellite instability (MSI), chromosomal instability (CIN) and CpG island methylator phenotype (CIMP). These alterations have mainly been used as markers for defining CRC prognosis, but recent data have demonstrated their correlation with treatment response.

The MSI-positive subgroup accounts for 10–15% of all CRC cases and is characterized by a better prognosis than the microsatellite stable (MSS) group. Conflicting data have been reported for both FOLFOX and 5-FU-based chemotherapy response in MSI-positive patients. Overall, 65–70% of CRCs show a CIN pattern. Mutations of KRAS, P53, SMAD and APC genes are often present in this group of tumours. CIN involves DNA copy number variation (CNV) that has been identified in more than 80% of CRC patients, most of whom are MSS^{43,44}. Changes in DNA copy number determine variations in gene expression that is associated with prognosis and response to adjuvant therapy. Thus, CNV represents a potential predictive marker of response to chemotherapy. CIN is also associated with multidrug resistance and could contribute to the low response rate of CRC patients to taxanes (paclitaxel and docetaxel)⁴⁵.

A large subpopulation of CRC cases, designated as CIN-/MSI- and partially overlapping with the MSI subgroup, contain a high degree of hypermethylation known as CIMP. This post-translational alteration may alter the up- or down regulation of gene expression events that alter the survival of genetically aberrant clones and promote their expansion. Generally CIMP tumours present few P53 mutations, a high rate of BRAF and KRAS mutations, frequent hypermethylation of MLH1 gene and a strong association with MSI-High (MSI-H)⁴⁶. Inconsistent results regarding the correlation between CIMP positivity and CRC responsiveness to 5-FU treatment have been reported. Therefore, more accurate investigations are needed to clarify these results.

For decades, the misleading assumption that all patients with tumours originating from the same primary organ had to be considered and treated as a homogeneous population has profoundly hindered the development of unique therapeutic strategies that can dramatically improve outcome and OS at the individual patient level. The possibility of identifying which patients are most suitable for each chemotherapeutic agent would maximize efficacy and spare unnecessary toxicity. The discovery of the impact of KRAS mutation on the efficacy of antibodies targeting EGFR in metastatic CRC has provided evidence that subgroups of patients may benefit from differential therapy.

The recent development of sophisticated technologies that allow accurate and incisive investigation has led to a better understanding of the molecular alterations on which cancer development and progression are based. Moreover, recent discoveries of alterations in gene and protein expression/activity in tumour cells have generated valuable new hypotheses to explain therapeutic failure and success as well as drug resistance⁴².

Gastric Cancer:

Despite optimization of surgery, radiotherapy, and cytotoxic chemotherapy, survival of advanced gastric cancer is poor. Five years after this multimodal treatment, 40% of Western patients with stage II or III disease are alive. In metastatic stage IV, mean survival is only 10 months. Most promise to improve this poor survival is provided by biologically targeted agents. The concept is exciting. Suppression of deregulated signaling pathways which play a central role in cell proliferation, survival, apoptosis, and angiogenesis may be a highly effective approach against cancer. Over the last decade, several agents targeting key components of important do on-stream signaling have been developed and approved by the Food and Drug Administration (FDA) for a series of cancers. Inhibition of signaling cascades may suppress cancer cell proliferation and survival. However, for most solid tumors, clinical efficacy measured by overall survival benefit is modest⁴⁷.

From Basic Science Discovery to Clinical Practice

The discovery of the epidermal growth factor (EGF) and its receptor (EGFR) in 1962 and 1978, respectively, opened the way for a new era of molecular oncology⁴⁸. However, successful translation of these basic research findings into the clinic has occurred only during the last decade and mostly for only one type of cancer, i.e., breast cancer. The ErbB family consists of four closely related type 1 transmembrane tyrosine kinase receptors: EGFR (or HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4). Each receptor comprises an extracellular domain at which ligand binding occurs, an α -helical transmembrane segment, and an intracellular protein tyrosine kinase domain. Ligand binding to these EGF family receptors phosphorylates and activates a complex intracellular signaling pathways network that controls a range of cellular processes including proliferation, angiogenesis,

cell cycle, survival, and apoptosis⁴⁹. HER2 amplification and overexpression plays a central role in initiation, progression, and metastasis of some common cancers, including breast cancer and gastric cancer. HER2 status has been recognized as an important prognostic factor. Patients with breast cancer or gastric cancer an HER2-positive disease have significantly worse survival than those with HER2-negative tumors^{49,50}.

Thus, this pivotal receptor is a potential therapeutic target. Trastuzumab binding inhibits HER2 signaling pathway activity in tumor cells overexpressing HER2. Phase III trials confirming preclinical and clinical data for the safety and efficacy of trastuzumab independently of robust clinicopathologic factors in both metastatic and adjuvant setting have led to the establishment of this antibody as standard treatment for HER2-positive breast cancer. However, there has been no such evidence for any other cancer.

Changing Treatment of Gastric Cancer

Now, for the first time, positive results of a phase III trial for the efficacy of trastuzumab are reported for gastric cancer. Van Cutsem and colleagues have presented the results of the ToGA study in the 2009 ASCO Annual Meeting, May 29–June 2, in Orlando, FL.⁵¹ In this randomized controlled multicenter trial, 594 patients were randomized 1:1 at sites in Europe, Latin America, and Asia. All these patients had HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent or metastatic). They were randomized to receive trastuzumab (Herceptin) and chemotherapy (5-fluorouracil or capecitabine and cisplatin) for six cycles or chemotherapy alone. Trastuzumab was given until disease progression.

Addition of trastuzumab to chemotherapy improved oncological outcomes. Median overall survival was significantly longer (13.5 months) in the experimental arm (trastuzumab plus chemotherapy) than in the standard arm. Overall response rate was significantly increased by 13% in the trastuzumab arm ($P = 0.0017$). Safety profile and adverse effects data showed that trastuzumab-based regimen was a well-tolerated treatment; there was no difference in symptomatic congestive heart failure between arms, and asymptomatic left ventricular ejection fraction decreases were reported as 4.6% in the experimental arm and 1.1% in the chemotherapy arm.

The rate of 22% for HER2-positive gastric cancer is similar to the HER2-positive breast cancer rate. Second, the investigators correctly decided to use overall survival as primary endpoint and not progression-free survival (PFS). Indeed, the objectivity of PFS to assess response, efficacy, and clinical utility of an experimental targeted agent has become questionable. Cancer heterogeneity is one of the major biological arguments against the use of PFS to measure therapy efficacy. Although several targeted agents have been approved by the FDA based on significant improvement of PFS, more current evidence suggests that some cancer cell populations, initially rare within the tumor, refuse to die under treatment. Therefore, a nonprogressive disease assessment by imaging techniques (no tumor size increase) does not reflect overall response. Sensitive cancer cells are killed, but resistant cells proliferate, developing a uniform tumor consisting of resistant cells. These cancer cells have the ability of metastasis, which results in no overall survival benefit⁴⁷.

Perspectives for Overcoming Resistance:

Resistance to molecular targeting therapy is currently the cause of treatment failure in cancer. Despite trastuzumab-containing treatment a substantial proportion of HER2-positive breast cancer patients either recur in the adjuvant setting or progress after initial response and die of the disease. Similarly, the absolute additional response rate to trastuzumab among HER2-positive advanced gastric cancer in the ToGA study is small: 12.8%. Given that HER2-positive accounts for approximately 25%, only 3.12% of all gastric cancer patients can benefit from trastuzumab treatment.

How could this intrinsic or acquired resistance be overcome? Research strategies are focused on the development of both novel drugs and molecular markers beyond HER2 expression for tailoring the best treatment to individual patients. There are two main directions: first, better understand of Erbb signaling pathways and trastuzumab mechanisms of actions and resistance; second, exploring the role of other signaling pathways including Wnt/bcatenin, TGF- β /SMADs, and other pathways involved in

cancer may lead to understanding of intracellular signaling pathways network in various cancer types. The first, more realistic, approach has already led to clinical applications. Improved insights into the biology of the

ErbB family have led to additional active anti-HER2 therapies. New strategies against HER2 include ErbB tyrosine kinase inhibitors (TKIs), heat shock protein 90 inhibitors, ErbB dimerization inhibitors, and antibody–chemotherapy conjugates. All of these approaches have shown substantial clinical activity in patients who have progressed on trastuzumab treatment.³ TKIs-based targeting of HER2, preventing signal transduction of both the Ras–RAF1 MAPK and PI3K–Akt pathways, led to an increase in apoptosis and a decrease in cellular proliferation^{47,49}.

Multitargeting, Signaling Pathways Network-Based Therapy

Although still in its infancy, the second approach to predict complex signaling pathways interactions, including ErbB signaling, if successful, might revolutionize treatment of gastric cancer, breast cancer, and other solid tumors. Given the current strong evidence that multiple genetic alterations and several signaling pathways are dysregulated in solid cancers, one of the most rational approaches is to inhibit these pathways. Combining targeted agents and considering crosstalk between pathways and bypass of targeted agents as well as predictors of response might lead to highly effective therapies⁵². However, there are many challenges. Cancer heterogeneity is reflected by variation in deregulated pathways among patients with the same tumor, tumor–node–metastasis (TNM) staging, and clinicopathologic factors. At present there is no standard method to identify either which pathways are dysregulated or how they interact in individual patients. The new era of personalized medicine provides major promises. One approach is to integrate personal genomics and clinicopathologic and treatment data into sophisticated in silico models to predict genotype–phenotype map in cancer. Rapid advances in molecular systems biology and future cheaper whole-genome

cancer data scans are innovative exciting developments towards the development of novel response predictors and a new generation of multitargeted agents⁵³. The new era of personalized cancer care is here, but multiple challenges including major funding requirements and reliable data analysis make the translation of personalized research approaches into clinical medical practice difficult.

HER2 status should now be included in diagnostic makeup of patients with advanced gastric cancer. Addition of trastuzumab to chemotherapy improves overall survival and is a new standard treatment for patients with locally advanced, recurrent or metastatic HER2-positive disease. Although this efficacy is likely in the adjuvant setting, an evidence-based decision on trastuzumab use in early gastric cancer requires the completion of new adjuvant phase III trials.

Resistance to current therapies is a major challenge. Lapatinib and other novel antibodies or TKIs tested in clinical trials for HER2-positive breast cancer might also prove effective in trastuzumab-resistant HER2-positive gastric cancer. However, such ErbB-based approaches have less application in HER2-negative disease, which accounts for the majority of patients with gastric cancer or breast cancer. Understanding genotypic–phenotypic cancer diversity and signaling feedback loops as well as developing reliable methods to screen for identifying dysregulated signaling pathways in individual patients is a rational and exciting approach. If successful, such comprehensive approaches using molecular systems biology and future whole-genome cancer data scans may result in the discovery of novel multitargeted therapies tailored to individual patients on the basis of novel predictors of response to combined therapies⁴⁷. Table-1 shows commercially available kits for personalized medicine practice the common available drugs are also mentioned.

Table-I

List of Commercially Available Tests (few) Used for Personalized Medicine in Cancer

Test	Cancer Type	Test Type	Predicts response to
HerceptTest	Breast	Her 2 overexpression	Trastuzumab
KRAS Mutation Kit	CRC	KRAS mutation	Panitumumab; Cetuximab
CYP450 Test	Breast	CYP2D6, CYP2C19 genotype	Tamoxifen
EGFR Amplification Test	CRC	EGFR amplification	Cetuximab, Panitumumab
EGFR Amplification Test	NSCLC	EGFR amplification	Gefitinib, Erlotinib
BCR-ABL Mutation Analysis Test	CML	T3151 mutation	Imatinib
ALK Gene Rearrangement Test	NSCLC	ALK gene arrangement	Erlotinib

CRC-Colorectal cancer, NSCLC- Non-small cell lung cancer, CML- chronic myeloid leukaemia

Future perspective :

Molecular systems approaches allow progress towards understanding how intracellular signal-ing pathways networks operate and how interactions among heterogeneous cancer cells within an individual primary tumor and its associated metastases govern the oncological outcomes. This comprehensive understanding of how a solid tumor functions as a whole biological system, including the primary tumor, its associated metas-tases and their relationships with multiple host variables, such as heritable causal mutations, envi-ronmental exposure and lifestyle, can be achieved by systems approaches, revealing the fundamental importance of systems medicine. Therefore, such sophisticated network-based approaches represent a major hope for the development of novel robust biomarkers and effective biologics.

In the real world, the principles and rules of comparative effectiveness research and the stage of FDA approval should be considered at an early preclinical development stage of designing such molecular systems-based markers and drugs, giv-ing particular emphasis to the integration of clin-ical data. Novel, network-based targets should prove their potential superiority over the current standard cancer diagnostics and therapeutics in clinical trials.

Conclusion:

Personalized medicine is receiving a large amount of growing attention for its tremendous potential with new opportunities. The ultimate promise of personalized medicine depends on the discovery of the personal genetic causes of disease. The remarkable advent of current high-through put technologies in combination with improved knowledge of the molecular basis of malignancy provides a solid base for identifying novel molecular targets. Genomic sequencing and its interpretation will have to be further developed and standardized for routine clinical practice to develop efficient and effective methods for discovering and verifying new biomarkers and enabling personalized medicine technologies. Medical educational institutions should prepare the next generation of physicians to use and interpret personal genetic information appropriately and responsibly. Though for a developing country like Bangladesh it will not be easy to adopt a higher and expensive technology, but for the sake of cancer patients

and better outcome we will have to run in parallel with the developed countries.

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