Toward Precision Medicine in Gynecology and Obstetrics

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Ikuo Konishi

Abstract

This chapter is an introduction to the contents of this book on precision medicine in gynecology and obstetrics, describing "where are we now, and where should we go" with regard to evidence-based medicine (EBM). At the end of the twentieth century, we faced a drastic change in clinical medicine, i.e., a big wave of EBM which was the application of epidemiology to clinical decision making. Standard treatment under the guidelines based on epidemiologic evidence is very useful in our daily clinical practice. Such treatment is appropriate for more than half of patients, but it may not benefit the remaining patients owing to the heterogeneity of disease. However, recent advances in medical technologies is clearly disclosing the diversity of disease with regard to the differences in genome, epigenome, and expression profiling. Medical treatment has been personalized according to the specific, genomic nature of the patient. Thus, the second big wave of EBM, which is genome-based personalized medicine, started at the beginning of the twenty-first century and is now expanding as "precision medicine". Here we see the current and future perspectives on precision medicine in gynecology and obstetrics, namely, genome evidence-based personalized medicine, clinical practice, and decision making.

Keywords

Evidence-based medicine (EBM) • Clinical epidemiology • Personalized medicine • Genomics • Whole-genome sequencing • Gene-expression profiling Precision medicine

I. Konishi, M.D., Ph.D.
National Kyoto Medical Center, Kyoto, Japan
e-mail: konishi@kuhp.kyoto-u.ac.jp

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1.1 Introduction

Physicians know a priori that there should be one best treatment for the patient who lies down in front of them, and have earnestly been seeking it among the various available modalities. Because physicians also are aware of the heterogeneity of disease among patients, even after the same clinical diagnosis is made, they try to shed light on the specific nature of the disease for a particular patient, using clinical history, physical examination, laboratory tests, histopathology, and imaging. To explore the right treatment strategy for the patient, it is also important to consider the pathophysiology of the patient's disease, study the principles and theories about the disease, and review the empirically employed treatment modalities and previous case reports. Advice from experienced professors and experts are very useful. Collecting all these data, we discuss the patient at a clinical conference, finally decide the most appropriate course for this specific patient, and then explain it to the patient and the family. Under such conditions, both physicians and patients reach a consensus. All of them seem to be happy under such an ideal doctor–patient relationship.

1.2 Evidence (Clinical Epidemiology)-Based Medicine Era Since the 1980s

Since the 1980s, however, the term "evidence-based" has been introduced in clinical decision making, guidelines and policies, and medical education [1]. As early as 1972, Archie Cochrane reported that many practices that had previously been assumed to be effective were not supported by controlled clinical trials [2]. In 1987, David Eddy first used the term "evidence-based" and expanded in his work on clinical practice guidelines and policies [3]. Alvin Feinstein, David Sackett, and others also claimed the importance of clinical epidemiology in decision making by physicians [4]. The term "evidence-based medicine (EBM)" has also been introduced in medical education. In 1990, Gordon Guyatt first used EBM at McMaster University for new medical students [1], and later published it as a new approach to teaching the practice of medicine. Such a big wave of EBM became popular in order to make individual clinical practice more objective by reflecting the evidence and required the application of population-based data to individual patient care. At that time, however, it was also emphasized that practitioners'clinical expertise should be reflected in efficient diagnosis and deep thought about the rights and preferences of individual patients [4]. Thus, during the 1990s, EBM gradually was established as a scientific approach for medical practice and decision making based on clinical epidemiology.

EBM further developed by classifying evidence levels by epidemiological strength, and now requires that only the strongest levels based on data obtained by randomized controlled trials (RCTs), meta-analyses, and systematic reviews can produce the strongest recommendations [5]. Opinions by experienced experts or case studies have been regarded as weaker levels [6]. Then EBM expanded to the design of clinical guidelines and policies that apply to patients and populations and

subsequently spread to decision making that is used at every level of health care. Thus, EBM advocates that decision making should not be based on a clinician's opinion or expert belief that may be limited by gaps in knowledge or by biases, but on the scientific evidence supplemented by all available data. Therefore, publication of clinical guidelines describing the standard treatment along with evidence levels has been greatly needed for daily practice, and for years many physicians have enthusiastically been involved in RCTs to seek the necessary scientific evidence. For the most part, such great efforts have resulted in success for establishment of novel treatments as standard ones. For example, in development of the standard chemotherapy for epithelial ovarian cancer, so many RCTs have been conducted and currently the combination chemotherapy with triweekly paclitaxel and carboplatin (TC) has been standard for first-line treatment [7]. Numerous patients with postoperative or recurrent ovarian cancer participated voluntarily in those RCTs not for themselves but for future patients. Thus, we have to continue our efforts to seek the scientific evidence that will be adopted in clinical guidelines and used for daily decision making in clinical practice.

Nevertheless, there have been many critical opinions of EBM expressed to date [8]. Before the era of EBM, the understanding of basic pathophysiologic mechanisms of disease coupled with clinical experience was of primary importance in medical teaching and clinical medicine. Because some of the original EBM proponents mistakenly touted EBM as a revolutionary new paradigm disregarding the philosophic basis for medicine, EBM was thought to be unscientific [9]. Although the strongest recommendations have been made by use of RCTs and meta-analyses in EBM, studies have failed to show that they are consistently more than "good quality". Similarly designed RCTs frequently disagree with one another, and cohort studies with better quality often disagree with those from RCTs. Actually, EBM may be able to answer clinical questions suited to the evidence but not in questions specific to small patient populations or subjective evaluations. Clinically important details may be hidden, because EBM does not integrate non-statistical forms of medical information such as professional experience and patient-specific factors. Also, EBM may reduce the autonomy of the doctor-patient relationship [10]. At the beginning of the era of EBM, it was clearly declared that EBM is not "cookbook medicine" and should not be applied to restrict options of the patient or doctor, which would be "misuse of EBM" [1]. However, EBM has been hijacked by accountants and managers to cut the cost of health care. Under the clinical guidelines, EBM has been used to prevent physicians from being held hostage and unable to treat a willing patient while waiting for statistical evidence.

Most importantly, it has been recognized that the usefulness of applying EBM to individual patients is limited [8, 11]. Patients are individuals, not groups. Because EBM is based on applying principles of clinical epidemiology to individual patient care, it carries with it many of the assumptions of epidemiological strategy. Individual circumstances and values are varied, and there are a great many uncommon diseases and variants. There is often a lack of studies relevant to the specific patient and intervention under consideration. Although medical research has focused on common clinical situations, there are many rare diseases

and conditions where EBM does not work well. Furthermore, individual patients will respond in their own unique way to a therapy that was not predicted from data by RCTs. In epithelial ovarian cancer, for example, although triweekly TC chemotherapy has been established as standard, i.e., proven to be most effective, the overall rate of obtaining a response is approximately 70% with the remaining 30% being resistant [7]. Among the four histological types, clear cell carcinoma and mucinous carcinoma will usually not respond to TC chemotherapy. Even in patients with serous carcinoma, approximately 20% are resistant even at the first-line treatment. This is a limitation of clinical guidelines based on EBM. For individual patients, therefore, our clinical medicine must resolve disagreements between general rules, empirical data, theories, principles, and patient values. In this setting, recent development of personalized medicine using genome analyses appears to overcome the limitations of an EBM approach for clinical decision making.

1.3 Toward a New Era of Evidence (Genomics)-Based Medicine for Patients

Recent advances in clinical oncology and novel drug discoveries have been playing the major leadership roles in personalized medicine. The final goal of modern medicine is increasing patient specificity so that the right treatment is given to the right patient at the right time. While current cancer studies have largely focused on identification of genomic or epigenomic properties of tumor cells, emerging evidence has clearly demonstrated the heterogeneity between tumors among patients and even in the same patients. In the twenty-first century, the advance of comprehensive genomic analyses using next-generation sequencing (NGS) and gene expression profiling using DNA microarray along with bioinformatics is clearly revealing the diversity of genome, epigenome, and expression profiles of cancer. If the driver oncogene and the main signaling pathway for cancer growth and survival is identified, the specific, molecular-targeted drug is shown to be greatly effective due to the "oncogene addiction" of tumor cells. One representative example is EML4-ALK lung cancer. In 2007, Hiroyuki Mano and his colleagues identified the fusion oncogene *EML4-ALK* in a subset of non-small-cell lung cancer with poor prognosis, and then clearly showed that an ALK kinase inhibitor such as crizotinib was quite effective and dramatically improved the survival of patients with EML4-ALK lung cancer [12]. A RCT was not necessary for approval of the drug in a short period of time by the FDA in 2011. Thus, we are coming into an era where selection of anti-cancer drugs is determined by genomic analysis for the patient rather than by the standards in guidelines.

The natural history of the development of epithelial ovarian cancer was unclear because most patients visit us with advanced disease. Our clinicopathological approach using transvaginal ultrasound disclosed the diversity of natural history of ovarian cancer along with the respective genetic mutations [13]. Therefore, ovarian cancer is not a single disease entity but a heterogeneous group of diseases with

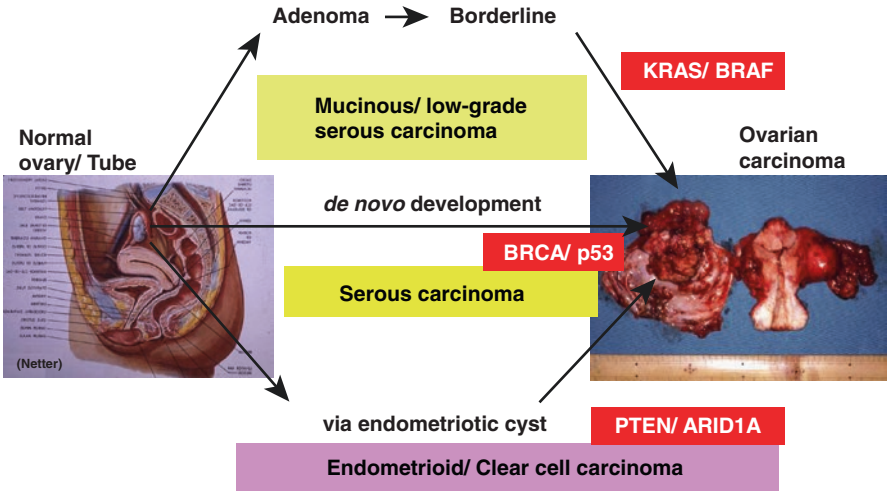

Fig. 1.1 Ovarian cancer is a heterogeneous disease with diverse scenarios

different clinical and molecular scenarios (Fig. 1.1). Regarding clear cell cancer that is resistant to standard chemotherapy, our comprehensive genomic analyses demonstrated that there is a specific gene-expression signature (OCCC signature) [14], in which many anti-oxidative stress genes are upregulated for cell survival via an epigenetic mechanism against the stressful microenvironment of an endometriotic cyst filled with the free iron of menstrual blood [15]. Our analyses also revealed that clear cell cancer is resistant to cisplatin but sensitive to multikinase inhibitors such as sorafenib [16], and the subsequent clinical trial for patients with recurrent clear cell cancer demonstrated its clinical efficacy. Another important step in clinical oncology is immunotherapy using antibodies against immune-checkpoint molecules. We have demonstrated that the immune-checkpoint PD-L1/PD-1 signaling plays an important role in the escape from the host immune system and in peritoneal dissemination in ovarian cancer cells. We then conducted a clinical trial on the safety and efficacy of the anti-PD-1 antibody nivolumab in patients with platinum-resistant, recurrent ovarian cancer, and some patients including those with clear cell cancer showed a remarkable and durable response [17]. Thus, genomic analyses with novel drug development will be able to overcome the resistance to standard chemotherapy.

The Cancer Genome Atlas (TCGA) Network published data from the whole genome sequencing and molecular profiling using NGS and microarray in 2011. For high-grade serous ovarian cancer (HGSC), which comprises the most common histological type in epithelial ovarian cancer and usually responds well to TC chemotherapy, it was shown that HGSC does not have the definitive driver oncogene. Interestingly, however, it was also revealed that there are four subtypes in the gene expression profile, i.e., differentiated, immunoreactive, mesenchymal, and proliferative, and that patients with HGSC with the mesenchymal subtype showed the worst prognosis [18]. Such novel classification is relevant with the difference in the microenvironment of cancer cells. Recent bioinformatics and clinicopathology

approaches have shown that the mesenchymal subtype accompanied by dense fibroblastic stroma is more sensitive to paclitaxel than to other drugs [19]. These findings suggest that the mesenchymal subtype may fit the weekly dose-dense TC regimen, in which a higher dose of paclitaxel than usual is given [20]. Anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, may also improve the survival of HGSC patients with the mesenchymal subtype. Thus, selection of chemotherapeutic and molecular-targeted drugs will be considered under genomic profiling analyses indicating the cancer microenvironment.

The most important factor for poor prognosis of epithelial ovarian cancer is peritoneal dissemination. Therefore, molecular and genomic analyses for the mechanisms in the special metastatic process are mandatory. Through our extensive analyses, we have demonstrated that the hypoxic microenvironment at the beginning of metastasis plays an essential role in downregulation of E-cadherin, upregulation of S100A4, followed by increased RhoA signaling, which is responsible for cancer cell metastasis, motility, and invasion [21]. RhoA inhibitors such as lovastatin have been effective in an animal model for experimental peritoneal dissemination. In addition, we also have observed the epigenetic change of the *S100A4* gene in ovarian cancer cells under a hypoxic environment, which suggests "evolution" of cancer cells during progression [22]. Upregulation of VEGF is also important in the disseminated lesions for angiogenesis and immunosuppression. Therefore, each anti-cancer drug will be directed to each microenvironment and signaling of cancer cells, which continuously evolve via changes in genomics and epigenomics and gene expressions. Accordingly, we must consider now the two-dimensional map model of the cancer genome, which shows both the diversity in carcinogenesis (*X*-axis) and the diversity of evolution in progression (*Y*-axis) (Fig. 1.2). The place

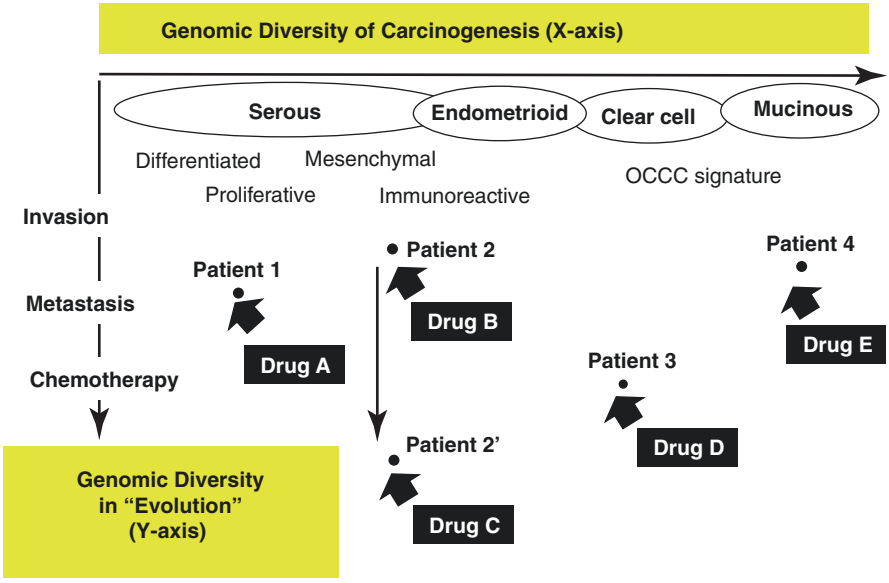

Fig. 1.2 Two-dimension model of cancer genome

of each patient will be identified on the map via genomic analyses, and the right treatment will be given at the right time in the near future.

1.4 Acceleration of "Precision Medicine" for Patients

More recently, the direction of personalized medicine is expanding to "precision medicine". The National Institutes of Health (NIH) in the United States defines precision medicine as an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. Thus, all of us are coming into an ideal world for healthcare and a better doctor-patient relationship. We now must accelerate such movement in clinical medicine for our patients.

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