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〔Opinion〕

Departure from evidence-restricted medicine

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Abstract

Evidence-Based Medicine (EBM) is at the height of its prosperity in modern clinical medicine. EBM ranks published evidence according to the design of clinical studies and the supremacy of randomized controlled trials (RCTs) has been established. Recently, immune checkpoint inhibitors (ICIs) have attracted attention for lung cancer treatment. Combination therapy with nivolumab, anti-programmed death 1 antibody, and ipilimumab, anti-cytotoxic T-lymphocyte antigen 4 antibody, in non-small-cell lung cancer was approved in the United States and Japan in 2020. This combination therapy is logically expected to be effective for a certain number of patients who previously received chemotherapy or ICI monotherapy. However, because the RCT, which became the basis of approval, was performed in the first-line setting, this combination therapy can be used as first-line treatment only. As ICI combination therapy has the possibility of radical cure, this limitation for use is precisely the issue of critical importance for patients. Taking away a potential treatment opportunity from patients is definitely not the purpose of EBM. This can no longer be referred to as EBM, but should be termed evidence-restricted medicine. We should not be restrained by superficial details of a particular RCT, and it is important to have flexible thinking that enables us to capture the essence of each RCT and utilize the knowledge gained from any evidence.

***Key words*: EBM, RCT, NSCLC, ICI, evidence-restricted medicine**

The term evidence-based medicine (EBM) was first introduced by Gordon Guyatt in 1991[1]. The initial concept of EBM was education for clinicians in the understanding and use of published literature to optimize their clinical practice[2]. Obtaining updated medical information before the development of the internet was very difficult; therefore, most clinicians decided on a treatment strategy based on their own experiences, traditions, and biological common sense. As a result, the medical approach and outcomes were different for each hospital or doctor. To improve this situation, EBM emerged and gradually spread worldwide along with the progress of the internet and large medical databases.

With the passage of time, the weight of attention has swung like a pendulum, and published evidence is regarded as the most important in clinical practice. Clinicians are required to provide standard treatment in conformity with various guidelines that have been created based on EBM. There are many assessment methods, including the Grades of Recommendation Assessment, Development, and Evaluation (GRADE)

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system[3,4]; however, EBM ranks published evidence according to the design of clinical studies[1]. The evaluation is the highest for a meta-analysis of randomized controlled trials (RCTs) followed by each individual RCT, observational study, and case report, and expert opinion is deemed to be at the bottom of the evidence hierarchy[1]. Originally, this was the order of the ease of bias restriction; however, the extraordinary supremacy of RCT has been established. Certainly, RCT has methodological superiority and can answer various clinical questions that are difficult to prove logically. It is absolutely correct that RCTs are useful and valuable. However, RCTs present only a result without the reason. In this sense, an RCT is a temporary salvation until science provides further insight. Moreover, RCTs are not omnipotent. For example, gefitinib, a pioneer of molecularly targeted therapy for non-small-cell lung cancer (NSCLC), is an excellent agent, but the phase III Iressa Survival Evaluation in Lung Cancer (ISEL) Trial, which was an RCT comparing gefitinib with placebo, could not demonstrate the efficacy of gefitinib [5]. Several years later, two case-control studies indicated that gefitinib was effective only for patients with NSCLC with epidermal growth factor receptor (*EGFR*) mutations[6,7].

Recently, immune checkpoint inhibitors (ICIs) have attracted attention for lung cancer treatment. Nivolumab, a fully human anti-programmed death 1 (PD-1) antibody was first approved for the treatment of NSCLC in 2015 in Japan. Subsequently, several anti-PD-1 or programmed death ligand 1 (PD-L1) monoclonal antibodies have been available. In 2020, combination therapy with nivolumab and ipilimumab, a fully human anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, with or without chemotherapy in NSCLC, was approved. An effective immune response requires the cooperation of CD4+ and CD8+ T cells[8]. Anti-CTLA-4 antibody has been demonstrated to relieve the suppression of CD4+ T cells in basic research[9,10]; therefore, it is considered that the overall response rate is increased by combination with nivolumab, which predominantly induces the expansion of CD8+ T cells [9,10]. Since CD4+ T cell dysfunction correlates with low PD-L1 expression on tumor cells, such combination therapy is expected to be effective for a certain number of patients who previously received chemotherapy because of the negative or low expression of PD-L1 or who progressed after anti-PD-1/PD-L1 monotherapy. However, because the RCT, which became the basis of approval, was performed in the first-line setting, this combination therapy can be used as first-line treatment only in the United States (FDA approves nivolumab plus ipilimumab and chemotherapy for first-line treatment of metastatic NSCLC | FDA). In Japan, the first-line limitation is not clearly described in the package insert, but it is specified in the guidelines for implementation of optimal use by the Japanese Ministry of Health, Labor and Welfare that the target patient population is patients with unresectable, advanced, or recurrent NSCLC without a prior history of chemotherapy (in Japanese, https://www.mhlw.go.jp/content/12404000/000687519.pdf). Therefore, second- or later-line use of nivolumab plus ipilimumab might not be covered by national health insurance. As ICI combination therapy has the possibility of radical cure, this limitation for use is precisely the issue of critical importance for patients. Generally, patients with advanced or recurrent NSCLC do not have much time left. Although the RCT, CheckMate 722, for patients with NSCLC, including those with *EGFR* mutation, treated with nivolumab plus ipilimumab as a second- or later-line therapy seems to have already begun, a number of patients will not be able to wait for the result. In practical terms, it is unlikely that the order of treatment definitively influences the curative effect. In fact, nivolumab monotherapy in patients with NSCLC is conversely recommended as a second or subsequent treatment.

If we gather valuable information from each piece of evidence, including RCTs, observational studies, animal research, and expert experience, and choose a treatment considered to be optimal for the patient at hand, restriction by non-essential conditions of key RCTs often interferes with our practice. Taking away a potential treatment opportunity from patients is definitely not the purpose of EBM. This can no longer be referred to as EBM, but should be termed evidence-restricted

medicine. Obviously, medicine should be evidence-based, but the nature of that evidence is debatable[11]. We should not be restrained by superficial details of a particular RCT, and it is important to have flexible thinking that enables us to capture the essence of each RCT and utilize the knowledge gained from any evidence, that is, a departure from evidence-restricted medicine.

Contributors

All authors collected the information and evidence about combination therapy with nivolumab and ipilimumab. TI drafted the manuscript and all authors approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

Ethical approval

Not required.

Data availability

Not applicable.

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Soon after this article was accepted, JN died young suddenly. The other authors heartily pray gods rest his soul.

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