ISSN: 2577 - 8005

Perspective

Medical & Clinical Research

Cancer Therapy Breakthrough: Drug or Medicine?

Kangla Tsung*

TANLUN Medical Research Inc., Beijing, China

*Corresponding Author
Kangla Tsung, TANLUN Medical Research Inc., Beijing, China

Submitted: 30 Aug 2024; **Accepted**: 12 Sep 2024; **Published**: 21 Sep 2024

Citation: Tsung, K. (2024). Cancer Therapy Breakthrough: Drug or Medicine?. *Med Clin Res, 9*(9), 01-05.

Abstract

We have been hoping for breakthrough in the "war on cancer" for long (decades), and we expect it will come one day with the discovery of a "miracle drug". With time lapsing and repeated showing the same limited effects of new drugs, that expectation is gradually fading. What if the miracle drug does not exist by theory? As this opinion/perspective argues, breakthrough in cancer management does not have to be a drug, it may well come from the science behind using current drugs or treatments. We have been ignoring cancer medicine for long and it is time to bring up our attention to it because it can be demonstrated that using existing means, but with different ways of selecting and using them, we may significantly increase (double or triple) patient survival while significantly decreasing the cost for achieving such goals. If that is not a breakthrough, I don't know what else is. Thus, all we have to do is to find out ways to bring it to cancer clinics everywhere. The first step is to change our concept and acknowledge its significance. That is the purpose of this writing.

Keywords: cancer medicine, cancer drugs, antitumor immunity, individualized therapy

Introduction

Few people still remember the true meaning of the word "Medicine" when it comes to cancer therapy. Most of us take it as equal to "medication" or "drug". Medicine by its original meaning is the science or art to manage disease. It is not the substance that we use to treat disease, but the reasoning behind the selection of the substance and the way to use it. By that definition, cancer management can be simplified to include two parts: individual therapeutic means (drugs or other physical killing of tumor cells) and the design to select and use them. Now days, therapies often come with the way to use them (drug instruction, not the reasoning for selecting them, though). In today's cancer clinic, the selection of therapies is dictated by standardized treatment plan. A clinician does not have to come up with his own reasoning for selecting certain therapies for his patients; it's all according to the "guideline". Therefore, if we want to improve the outcome on the war against cancer, we either develop more effective therapies (drugs, to be more accurate) or improve the existing guidelines. For the past several decades, our main efforts have been focused on finding new drugs almost exclusively without paying attention to changing guidelines. In reality, guideline is dominated by instructions coming with individual drug from the drug developer. The real situation now days are that the "war on cancer" is entirely dependent on finding the drug that gives us miracle.

Have we found that miracle drug? No, we have not. And the more we know about the disease, the less likely it seems that we will find one. It's all because of two reasons. First, cancer by essence is an individualized disease [1], therefore cannot be cured by one fit-all drug. Secondly, the reason behind the first claim is that most, if not all, tumor reductive therapies rely on antitumor immunity to exert their effects [2,3], and the antitumor immunity is highly variable among similar patients of the same cancer, even variable among different times in the same patient, or even variable between different lesions in the same patient at the same time. This individual nature of antitumor immunity determines that different cancer patients respond to the same therapy differently, a fact that is well observed in cancer clinics all the time. Take the recent example of the immune checkpoint inhibition (ICI) therapy (antibody that blocks immune checkpoint molecules), it has been described in social media as miracle drug for cancer. For the past 10 years, many clinical trial findings have been prematurely claimed as bombshell results that are effective against almost any cancer in any patients, only to be nullified later by larger scaled tests. The most recent findings indicate that not only the ICI drugs with the largest annual sale number ever on any drug do not cure all cancers, they may not even beat classic therapies in real world setting [4,5]. When one takes a careful look into each treated cases, one sees the "miracle" this drug can bring: a broad and persistent antitumor action that could last months or even years in some cases, not witnessed by any other antitumor therapies before [6]. On the other hand, one also finds perplexing acceleration of disease and quick death by the drug in substantial portion of cases [7,8]. It is such harmful effects of the drug that cancels its miracle effect and made its indiscriminate use in real-world setting less impressive [9]. Ideally, if we know why this drug can provide

great benefit to some patients while harm others, we could select those who may benefit and avoid those who may be harmed. That requires a full knowledge of the working mechanism of the drug, which may or may not be part of the drug development process as marketing approval does not require such knowledge as long as the drug shows overall benefit in a group of patients in clinical trials [10]. This example shows that even with a potentially miracle drug available, how to use it effectively remains a challenge to the prescribing physicians. Unfortunately, our current system does not encourage that physician to find out because of the limitation by the guideline and by the prohibitive costs to carry out the "credible" analysis through group comparison with statistical significance, a method adopted from drug developers [10].

If that physician did try to find out the reason behind the great benefit and harm with the same drug in different patients, he will find out that cancer is an individualized disease and should be managed with individualized treatment plans [1]. Regardless whether patients are same or different, by logic, individualized treatment is always the best option (Table 1), because one will find that all patients end up taking the same treatment plan if they are the same. Since in reality they are not the same, there is no reason why they are treated with the one-for-a- thousand plan by a standardization guideline/decree. The so-called standardized therapy has fundamentally flawed to begin with. It is likely that such an effort was set up to help inexperienced physicians to manage complicated disease such as cancer by telling them what experienced physicians may choose to do in a case [10]. Unfortunately, such a rigid system ended up inhibiting inexperienced physicians to become independent and inhibiting healthy development of the science behind individualized therapy selection in each individual patient. In other words, the current system of standardized therapy in cancer as a major principle inhibits the healthy development of cancer medicine [10].

Individualized vs standardized therapy, which way?

Mode of therapy	Patients=identical	Patients=different
Standardized therapy	All patients respond equally Benefit equally to therapy	Some patients respond well Benefit not equally to single therapy
Individualized therapy	All patients respond equal Benefit equally to therapy	All patients respond well Benefit equally to different therapy

Table 1: The logical difference between standardized and individualized management in cancer. When all patients are identical, individualized treatment plan would be the same for all of them, thus is the same as standardized treatment plan. In real world setting, all patients are different, thus only individualized treatment plan will gain maximal benefit.

Cancer medicine should be the science and management principles used to treat patients. As patients are different, treatment plans should also be different. There is only one measurement for success: this is to reach the maximal survival under given conditions. If the maximal survival of a case is clinical cure, then any management short of this, regardless of the length of survival, is considered failure. Similarly, if the condition for a case is difficult and the patient can only survive a few months at best, a proper management plan would be to reach that few months without suffering brought by ineffective therapy. Only when individual efficacy can be defined (as outline in Figure 1), can we then have a comparison of management efficacy between cases and among patient-caring hospitals. Cancer medicine is supposed to provide the science and methods to determine the theoretical survival estimate for each patient (Figure 1), and to provide the paths and means to reach that theoretical survival as close as possible. The critical aspect of this medicine is the determination of who at what time receives what therapy with what goal to reach [11]. When this becomes possible, we shall know what to do with each cancer case under the current available means (Figure 2). Improvement on survival shall be made with new drugs become available. According to this criterion, the current status of cancer medicine is significantly lagging behind in both concept and methods. Currently, no clinical decision is made based on the fully individualized basis of a patient, but is based on the characteristics of a group of patients, a group composed of thousands, if not millions, of roughly similar patients. Not only that there must be significant variations in each characteristic among these patients, but also that even between any two randomly selected patients, there could be significant differences that influence therapy effects. For example, the status of antitumor immunity in each patient is determined by the genetics of that patient, therefore is theoretically individualized characteristic not shared by others. As the status of antitumor immunity is the critical factor affecting all tumor reductive therapy [2], there is no reason why patients with different antitumor immunity should be treated with the same therapy. Clearly, had we known this, we would have not set up guidelines to treat different patients with invariable treatment plan. But the significant influence on tumor progression, on establishment of new metastasis and on overall host prognosis by antitumor immunity is known for over 80 years [12]. Especially in the past 40 years, the rapid progresses in the field of tumor immunology have generated thousands of research reports showing and repeating this significance. Yet, the fact is, there is not a single clinical decision made with the status of antitumor immunity in that receiving patient taking into consideration. The impact of each selected therapy on the concomitant antitumor

immunity in that patient is totally unknown and ignored. Even immunotherapy treatment plans do not consider the basic status of antitumor immunity of the receiving patient and the likelihood of benefit or harm from the immunological point of view [6,9].

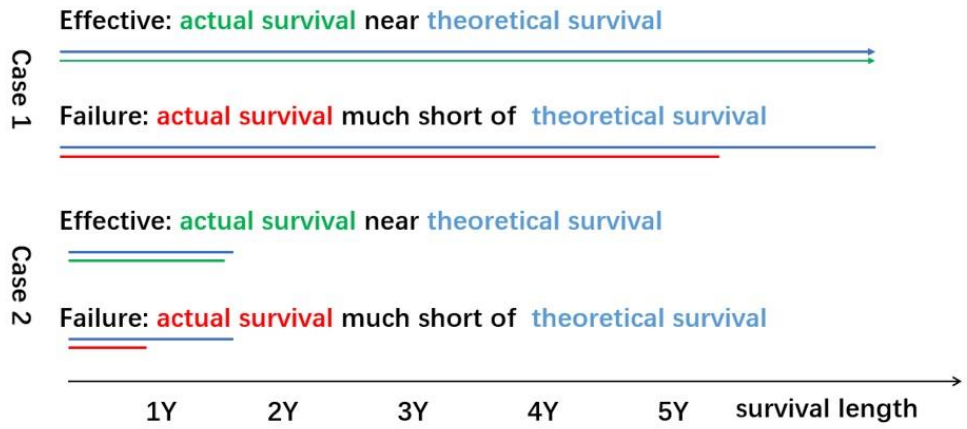

Figure 1: Examples of effectiveness of individualized treatment. Effectiveness is measured not by the absolute length of survival time, but the closeness of actual survival time (green or red bar) to theoretical survival time (blue bar). Note that in Case 1, even the failed outcome has longer survival time than the successful outcome of Case 2.

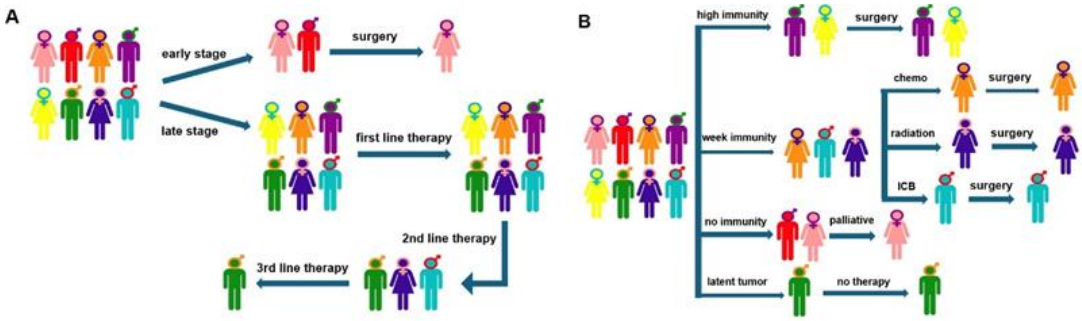

Figure 2: The most critical difference between standardized treatment plan and individualized treatment plan is to determine who at what time receives what therapy with what goal to reach. In a standardized plan (panel A), all "similar" patients are treated with a guideline-depicted plan without further consideration on timing. When they stop gaining benefits from this first-line therapy, they will be moved to receive guideline-depicted 2nd line therapy and then to 3rd line therapy, etc. In contrast, in an individualized plan (panel B), patients are sorted out according to the variable aspects of their disease, for example tumor replication pattern or status of antitumor immunity and treatments are selected based on the different aspects and timing. The sequence of various treatments selected for each patient is based on the specific situation in that patient and is not pre-determined but timely modified to fit the pre-determined goals (for example, activation of antitumor immunity).

There could be several blames to go around on this great gap between research findings in tumor immunology and clinical applications of these findings. The lack of established clinical measurement of antitumor immunity is only part of the blame because if we want to, such methods and tests can be set up quickly (as we have done in the past few years). It is the conceptual ignorance that is the key problem [13,14]. Research scientists who publish their findings based on animal models or even patient data do not have control over patient management, while physicians who manage cancer patients do not understand tumor immunology. Maybe our scientific and medical societies have tried hard to promote the cooperation between these two groups of doctors, but the results are clearly disappointing to say the least. Wouldn't this correction of obvious wrong and true application of 40 years of research finding to cancer clinic be a good breakthrough point?

As a tumor immunologist, I have carried out research in animal tumor models for over 30 years before witnessing this great separation between laboratory and clinic in real-world cancer management. My intuitive opinion is that clinical management is so lagging behind the science in tumor immunology that there must be a lot that we can do to move the findings in research into cancer clinics. I have since shifted my effort towards this direction. After near 10 years of exploration, we have established a set of individualized cancer treatment theory and practice to deal with each cancer case [1]. We have re-examined the three principal pillars of cancer therapy and pointed their limitations [10]. We have provided theory as well as practical methods to improve the current cancer staging system with more accurate assessment on each case [10]. We have also developed highly productive clinical research approaches based on individual cases rather than large

number of patient groups [10]. Our efforts to incorporate the status of antitumor immunity in each treatment selection have clearly yield significant survival benefits for patients. The most accurate assessment of management success would be like the one depicted in Figure 1, which measures the closeness of actual to theoretical survival, not actual survival to average or median survival in a group of patients. But this measurement system has not been accepted by the mainstream, and we will have to rely on the prevailing measurement to demonstrate the efficacy of our individualized management system. On the other hand, if we can reach maximal survival in each case, then the pooled group survival would certainly be superior when compared to the current or historical survival dada of similar patients managed by the guideline system. For that reason, we compiled the survival dada of a group of late stage (stage IIIc-IV or recurred following surgery) cancer cases managed by our individualized therapy and use that to compare to the published data on the similar group of patients in real world managed by standardized therapy [10]. As Figure 3 shows, the Kaplan-Myer survival curve of our 156 patients gives a median survival of 42 months and a 5-year survival rate of 33%.

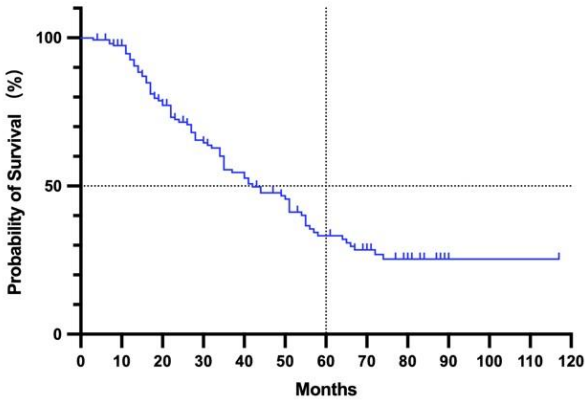

Figure 3: What an individualized treatment plan can achieve in late-stage cancer patients. Kaplan-Meier survival curve of the 156 late-stage lung cancer patients managed by our individualized treatment plan that is specific to each patient in the past 9 years. Characteristics of these patients are described in reference [11].

In comparison, the published survival of the similar patients in the real world managed by guideline-depicted therapy showed a median survival of 3-14 months, mostly 8-11 months and 5-year survival ratio less than 7% [10]. It should be noted that our patients were not enrolled in a clinical trial, excluded for short survival. The only criterion they were included in the analysis is that they accepted our individualized treatment plan and followed through. Some had a dare situation (often lack of antitumor immunity) and survived only few months and others may have better antitumor immunity and obtained clinical cure after successful activation of antitumor immunity. The key point is not the absolute length of survival, but the closeness to the maximal possible survival as illustrated in Figure 1. It is because of this closeness to maximal survival in each individual case that the overall survival of the group would be better when compared to any other groups of patients in which the survival of each individual patient is not close to the maximal possible survival of that patient. According to this thinking, it can be concluded that most of the patients managed by standardized therapy had much shorter survival reachable by our individualized management, thus they must have much shorter survival than the theoretical survival their situation would have allowed under current therapeutic means. It also needs to be noted that our achievement in prolonged survival is obtained with significant reduction of costs, often less than one-half of what would be if treated by standardized plan. The reason for that low-cost management is that when antitumor immunity is activated, it controls tumor progression efficiently and durably compared to the direct effect of tumor killing by tumor reductive therapies. The non-treatment gap between each sequential therapy is generally longer than that dictated by standardized treatment plan according to current guideline.

Our theory and practice have provided an example of what a breakthrough in cancer medicine, but not drugs, may be, i.e., to change the reasoning and ways of selecting current available therapies according to each individual situation for each patient. Had the entire cancer clinics adopt our individualized management theory and practice, the entire cancer survival and cure rate for the most difficult cases would double or triple without inventing new drugs. If that is not a revolution or breakthrough in the war against cancer, I don't know what is. The question is how to reach this adoption goal. The most difficult part is to change cancer medicine and limitations by the medical system we are so used to. One of these limitations is the separation between research and clinical application that are carried out by two very different groups of people. Because the wide gap in knowledge reserve, these people don't work together efficiently, and many years of cross-talking between them have failed. It is in this area that we are facing the most significant challenge, a much bigger one then cancer itself. Yet, we have to spread the breakthrough to every conner where cancer patients are being treated regardless how difficult it may be. One approach currently under development is the use of artificial intelligence to assist clinical diagnosis and treatment deign. As long as such system incorporates the status of antitumor immunity for each patient, the output would be an individualized treatment plan. We anticipate such an effort will be fruitful and are eager to witness its application in a clinical setting.

References

1. Tsung K., Zhanghui, Z.X., Tanlun Research Participants Group. (2023). On the Individualized Cancer Management. Journal of Cancer Research Reviews & Reports, 2023.
2. Guo, H., Tsung. K. (2017). Tumor reductive therapies and antitumor immunity. Oncotarget, 8(33), 55736-55749.
3. Tsung, K., Norton, J.A. (2015). An immunological view of chemotherapy. Immunotherapy, 7(9), 941-943.
4. Haslam, A., Prasad, V. (2019). Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. JAMA Netw Open, 2(5), e192535.
5. Khozin, S., et al. (2019). Real-World Outcomes of Patients with Metastatic Non-Small Cell Lung Cancer Treated with

Programmed Cell Death Protein 1 Inhibitors in the Year Following U.S. Regulatory Approval. Oncologist, 24(5), 648-656.
6. Tsung K, Z.X., Zhang Hui., TANLUN Clinical Research Participant Group. (2023). Supporting Cases for the Depletion Model of Immune Checkpiont Inhibitor Therapy in Cancer. Journal of Cancer Research Reviews & Reports, 5(5), 1-12.
7. Grecea, M., et al. (2020). Managing Hyperprogressive Disease in the Era of Programmed Cell Death Protein 1/Programmed Death-Ligand 1 Blockade: A Case Discussion and Review of the Literature. Oncologist, 25(5), 369-374.
8. Han, X.J., et al. (2020). Hyperprogression: A novel response pattern under immunotherapy. Clin Transl Med, 10(5), e167.
9. Tsung K, Z.X., Zhanghui, Tanlun Research Participants Group. (2022). The Blocking vs Depletion Model of Immune Checkpoint Inhibitor Therapy for Cancer. Journal of Cancer Research Reviews & Reports, 4(2), 4.
10. Tsung , K., Z.X., Zhang Hui., TANLUN Clinical Research Participants. (2022). The truth and dispute in TNM staging, standardized care and evidence-based medicine in cancer management. Medical and Clinical Research, 7(8), 10.
11. Tsung K, Z.X., Zhang Hui., Tanlun Research Participant Group. (2023). On the Individualized Cancer Management. Medical and Clinical Research, 8(10), 1-9.
12. Gross, L. (1943). Intradermal Immunization of C3H Mice against a Sarcoma That Originated in an Animal of the Same Line. Cancer Research, 3(5), 326-333.
13. Dunphy, J.E. (1950). Some observations on the natural behavior of cancer in man. N Engl J Med, 242(5), 167-72,
14. 1Dunphy, J.E. (1953). Changing concepts in the surgery of cancer. N Engl J Med, 249(1), 17-25.