

Nowadays, All Therapies Are Targeted-Understanding Biology Improves Disease Management

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ABSTRACT

Several decades ago, chemotherapy was the first observed efficient therapy for cancers, particularly for hematological malignancies. It was the time of case reports and short series, when the balance between efficacy and toxicity was evaluated on a patient per patient basis. This was considered as an empiric therapy, just basic clinical research supported by an intuitive and creative medical approach, inherited from medical history. Then, with the emergence of more and more drugs, methodologies and rules for clinical research were implemented with two goals: protect patients and rationalize empiric thinking. It was the time of large cohorts of patients, the time of the p value. Some progress was made as less empiricism and more science facilitated medical decision. With the development of clinical protocols, classifications, prognostic indexes and other relevant tools, including patients in clinical trials became most often the only objective for physicians and other health professionals, with the aim of raising the right questions and creating new protocols.

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INTRODUCTION

Several decades ago, chemotherapy was the first observed efficient therapy for cancers, particularly for hematological malignancies. It was the time of case reports and short series, when the balance between efficacy and toxicity was evaluated on a patient per patient basis. This was considered as an empiric therapy, just basic clinical research supported by an intuitive and creative medical approach, inherited from medical history. Then, with the emergence of more and more drugs, methodologies and rules for clinical research were implemented with two goals: protect patients and rationalize empiric thinking. It was the time of large cohorts of patients, the time of the p value. Some progress was made as less empiricism and more science facilitated medical decision. With the development of clinical protocols, classifications, prognostic indexes and other relevant tools, including patients in clinical trials became most often the only objective for physicians and other health professionals, with the aim of raising the right questions and creating new protocols.

Today, we get into a new period with too many tools, too many drugs, too many targets, leading to personalized medicine plans^[1,2]. Biology has become extremely complex because only a single piece of the puzzle or a single technique, a single result or a single target, are considered. As clinicians we tend to forget the patient, the organ, the tissue where cells are present and interact. By asking right and simple questions, creativity may come back. A targeted therapy is generally viewed as the association of a specific drug designed for a specific biological target. In fact, targeted therapy is just the better use of our knowledge to treat patients. When used appropriately all therapies are targeted. It is time to merge all pieces of the extraordinary biological knowledge to simplify what we need to optimize patient's management.

SOME ILLUSTRATIONS ARE OBVIOUS

Tyrosine kinase inhibitors (ITK)

Tyrosine kinase inhibitors (ITK) are the most cited successful examples of targeted therapies: one disease, one biological target, one specific drug resulting in the best clinical outcome. Since the alternative is the allogeneic transplantation, the comparison in terms of balance between benefit and risk is simple and evident. There are additional targets for ITK, including signaling pathways involved in the chronic myeloid leukemia cancer stem cell survival^[3]. Different immune consequences can be observed, depending of the drug, depending of the patients^[4]. Dasatinib increases the number of circulating large granular lymphocytes, i.e. Natural Killer (NK) and NKT cells^[5]. Which cell response for which type of drug and which type of patients represents the opening way for immune therapy in order to get a better control of residual disease.

CD20 molecule

The case of the CD20 molecule, a cell surface molecule not restricted to tumor cell is another success story. A synergy with chemotherapy and an optimal balance between benefit and risk was observed in B-cell malignancies with rituximab, the first developed anti-CD20 monoclonal antibody (MAb)^[6]. In addition, the partial blockade of B-cells was associated with a clinical benefit in dysimmune diseases, despite they were considered as T-cell mediated disorders. This empiric or intuitive thinking was in fact a good idea because of the good safety and tolerance of the CD20 molecule observed in cancer patients and because of the need for new drugs after the failure of the anti-Tumor Necrosis Factor (TNF) therapy^[7]. Clinical results underlying mechanisms were explained thanks to progresses in biological research.

This success was not the end of the story. Due to the forthcoming rituximab loss of patent, the marketing authorization holder (MAH) built a new scientific and positioning strategy. First, a subcutaneous (SC) form of rituximab (SCR) likely to prolong the use of the molecule by simplifying its administration was developed^[8]. Second, the afucosylated MAb, GA-101 or obinutuzumab, a more active form of anti-CD20 MAb by amplifying Antibody-Dependent Cell Cytotoxicity (ADCC), is close to be marketed^[9]. Therefore, both new anti-CD20 MABs are associated with improved clinical efficacy. The SCR was developed by the MAH as an equivalent drug of its IV formulation. However the MAH omitted the fact that the target organ after SC administration is the lymph node compartment. Had this been taken into account, one could predict a better activity and a better clinical use of the drug. Similarly, GA-101 has a better activity particularly on the lymphoid organs, with increased depletion on B-cell compartment, including B-memory-cells-sharing CD20 molecules. This changes the therapeutic strategy by avoiding the long-term therapy currently applied to rituximab. Wrong clinical targeting would probably be associated with more infections or less protection against standard and atypical infectious agents, with less active vaccination against infectious pathogens^[10]. Taking into account biological and clinical targets is associated with an optimal management of drugs.

Lenalidomide

Lenalidomide is another example that illustrates the need to consider the biological target, present on both the tumor cells and the micro-environment. This was not the case when the clinical development of lenalidomide was initiated^[11,12]. In such conditions, using lenalidomide in Multiple Myeloma (MM) till disease progression

as a maintenance therapy may expose to unexpected clinical consequences. The cautious attitude we adopted was to stop therapy after a limited additional duration, when obtaining an optimal response in MM. Such decision is just logic when biomarkers of interest or biological targets are unknown, and now it is adapted to the follow-up of the residual disease. No unexpected secondary malignancies were observed in our experience. Since « maintenance therapy » is not meaningful « control of the residual disease » should be preferred, representing an example of multi-factorial dynamic targeted therapy.

Interleukin 6

Interleukin 6 (IL6) is a pleiotropic cytokine in both cancers and dysimmune diseases.

In Castelman's disease, it has been shown to be the central factor explaining clinical and biological symptoms. Applying two drugs (siltuximab as a MAb against IL6 and tocilizumab as a MAb against soluble IL6-Receptor) on one key target resulted in a major clinical efficacy with both drugs^[13]. The story is quite different in MM. Siltuximab has been used in different clinical research programs, with no demonstration of major clinical effect such as significant prolongation of progression free survival and/or overall survival. The reason of this failure of clinical benefit is due (1) to a mistargeting of patients, too late in the disease, with clonal evolution and presence of several tumoral growth factors (BAFF, IGF-1, VEGF,...), and (2) to a wrong choice of chemotherapy agents combined with siltuximab, as these drugs also have anti-IL6 effect^[14]. This example is the illustration of a combination of two mistargetings. Now, it is time to perform ibrutinib adequate targeting for this drug, probably by combining anti-IL6 and ibrutinib in patients who overexpress Bruton Tyrosine Kinase (BTK).

Chemotherapy

Chemotherapy is also a targeted therapy, particularly if we use these drugs correctly, combined to newly designed drugs. Their biological targets are well known (cell cycle, DNA repair, epigenetics, metabolism,...)^[15]. For some of these effects, simple biological tests are available, particularly for cell cycle or signal transduction pathways. One could better use these drugs. As an example, high proliferating index (checked by plasma cell labeling index or KI-67 marker) is a simple test that could guide their use^[16].

Immune therapy

Immune therapy represents another aspect of the complexity of targeted therapy. Recently, the knowledge in immunology has substantially progressed. This better knowledge of biological mechanisms should improve the use of the different available tools for an improved clinical efficacy. Such progress has been obtained in different domains, including the tumor cell escape to the immune surveillance and cell-cell communication. Bio-clinical aspects to be considered are simple: target recognition, target accessibility of the effector cells and its biological efficacy, mechanisms of blockade, mechanisms of killing, specificity, consequences of targeting. However, the current complexity of immune therapy is probably due to the race in fundamental research to develop more sophisticated techniques and tools. Immune therapy is now entering a mature phase, an « à la mode » i.e. fashionable therapy supported by drug companies^[17].

Supportive care

Supportive care is also a targeted therapy. Hematopoietic growth

factors are proposed if hemoglobin level is below a certain level depending from other factors such as co-morbidities or iron balance. In addition, the prescription must be evaluated and modulated according to the targeted efficacy. Granulocyte growth factor, platelet receptor agonists have to be similarly managed. Anti-thrombotic agents are also targeted therapies. Among them, low-molecular-weight heparins have an anti-heparanase activity which is not shared by new oral anticoagulants. In MM, heparanase produced by osteoclasts has been shown to perform syndecan-1 shedding from plasma cell surface in the tumor micro-environment and by the way contributing to the accumulation of growth factors in the tumor niche^[18]. Therefore, blocking heparanase may contribute to limit tumor growth, which may represent an additional targeted clinical activity^[19].

CONCLUSION

Progress in biology and technology makes possible to improve clinical efficacy. A new era is emerging, with less empiricism and more science. Efforts have to be made to improve cost-effectiveness of new drugs despite the fact that the direct costs for both developing and approving new drugs largely increased^[20]. Thus, decision is now based on evaluation of different parameters, including an incremental cost-effectiveness ratio (ICER) and the cost per life-year gained (LYG)^[21]. There is a need to create optimal conditions for such new therapeutic age, including dynamic methodologies, bio-clinicians talking and taking care of the patients in the context of real life.

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CONFLICT OF INTERESTS

The author has no conflicts of interest to declare.

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