

The True Face of the Revolution in Oncology Drug Development: A Personal Reflection

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Abstract: The majority of drugs approved for the treatment of malignant disease are traditional cytotoxic agents that, in many cases, have been in use for decades. In the recent past, we have seen the approval of the so-called targeted agents and with this have emerge concepts such as biomarker and optimal biological dose, but which came first and what is actually behind the paradigm shift that is all too evident in modern oncology drug development?

Following critical examination of the issue, it can be argued that many, if not all, cytotoxic chemotherapies are targeted, for example, methotrexate, the folate pathway and the use of neutropenia as a biomarker although not titled as such, in the development of these agents. The most obvious change is the toxicity profile of the new molecular entities and, therefore, the recognition that driving a dose towards a maximally tolerated dose for use in later phase development is inappropriate. Again, it can be argued that this should never have been appropriate, however, the tools necessary to determine the underlying pharmacokinetic/pharmacodynamic (PK/PD) relationships were lacking.

We believe this has brought about the most dramatic change in how oncology drugs are developed, rather than the classification as cytotoxic or targeted. We will argue that it is not practicable to develop a targeted agent using the traditional paradigm, but equally, the same would now be true for cytotoxics.

Key Words: Targeted agents, cytotoxics, pharmacokinetics, pharmacodynamics, biomarkers, oncology.

INTRODUCTION

The cost of drug development has escalated to unsustainable levels and the drug industry is in a position of trying to reduce these costs, whilst developing increasingly effective novel therapies. Paralleled by the recent advances in oncology drug development, new molecules are required to further drive treatment benefit without the need to study thousands of patients or wait for many years. Both scenarios demonstrate the importance of using biomarkers as early markers of efficacy and modelling to predict the probability of success at increasingly early time points. For oncology, there have been some notable early successes; Herceptin® and Gleevec® have benefited thousands of patients and have heralded the dawn of the targeted era and the revolution in oncology drug development. Historically, there have been targeted agents of which methotrexate is an example [1], so what has truly lead to the revolution of oncology drug development? Is it merely the presence in the development world of agents designed with a known molecular mechanism of action? Do these new drugs have a reduced toxicity profile forcing us to rethink dosing to the maximally tolerated dose (MTD), or are the technologies peripheral to the study process, such as mechanistic modelling, forcing the change? The answer lies in the combination of these three questions, but it should be acknowledged that the development of a classical cytotoxic agent, such as doxorubicin, may well be different now compared to its original development path simply because of the evolution in technology.

If one considers the approach to the development of cytotoxics and targeted therapies, clear differences are apparent. Conventional cytotoxic chemotherapies followed an established empirical course; dose escalation followed a fixed or semi-fixed scheme from a starting dose based on a multiple of a preclinical 28-day toxicity dose. Escalation continued until the MTD was defined and this single dose was carried forward into later phase clinical trials. Often toxicity, for example, neutropenia acts as a biomarker (although not labelled as such) of the desired cytotoxic effect in the tumour. The dose and schedule were further refined in post-marketing, often investigator-initiated, studies. Pharmacokinetics was largely descriptive, body surface area dosing a sop to individualised therapy, but without adequate understanding of the covariates that about one third of patients could be under-dosed [2]. The benefit for these molecules was that a reduction in tumour size might be apparent even in phase 1 studies and, hence, signal the possibility of the investigational molecule becoming a commercial drug.

In contrast, the early clinical development of targeted agents is driven by the need to assess the impact on the target which may occur in the absence of clinically definable effect on the tumour or other tissue. Translation to clinical efficacy is more remote (for example, Time to Progressive Disease vs. response rate) and hence more difficult to illicit in phase 1 studies. Dose escalation is more amenable to adaptive study design in which both pharmacokinetics and pharmacodynamics play an increasingly important role. Biological effect, rather than toxicity, determines the subsequent range of doses which might be investigated in phase 2 trials. New considerations have been introduced, such as the degree and duration of target inhibition. Is the maximum inhibition achieved, or the time above a critical value and hence aver-

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age inhibition over 24 hours that is important for ultimate efficacy? How these factors can be determined and what is their influence on go/no-go decisions? Targeted therapy may affect normal cells with toxicity as a consequence. This may be enhanced when combined with chemotherapy. Complete (100 %) inhibition may adversely affect the margin of safety and may not be desirable for efficacy. There remains a need to balance efficacy and toxicity, although the two may no longer be obviously related (cytotoxics and myelosuppression). New challenges in oncology are becoming apparent as chronic oral dosing becomes *de rigueur* and both pharmacokinetic and pharmacodynamic aspects will have a role to play (for example, time dependent kinetics or dynamics).

THE NATURE OF CHANGE

It seems that targeted therapeutics have brought a new facet to drug development, but to what extent is this a consequence of technology rather than the target?

Almost everything has changed in the clinical evaluation of an oncology drug, from target identification to phase 3 registration trials. In discovery, for example, studies of tumour growth delay have been joined by those showing target modulation. Biomarkers of target inhibition developed in this preclinical settings are being translated to the clinic. But to what extent are biomarkers a consequence of targeted therapies and vice versa? A possible answer comes from examining the role of neutropenia in oncology development. Oncologists have been using neutropenia for many years to guide dosing, with the impact of the drug on the neutrophil count being crudely graded by common toxicity criteria system. Recently, a mechanistic chemotherapy-induced myelosuppression model was developed [3] in which myelosuppression could be predicted as a continuous variable dependent on dose. Furthermore, it demonstrated that the parameters determining the time course of haematological toxicity are not a function of a drug, but rather a fundamental property of the patient. This suggests that the mechanistic modelling of haematological toxicity may provide a time course for the antiproliferative effect of each drug which is crucial in the design of combination regimens, as well as optimising the schedule for single agent activity. All of this has not occurred because the investigational agents have changed, rather that technologies have advanced.

LIES, DAMN LIES AND BIOMARKERS

Similar principles to neutropenia apply to biomarkers used in development, such that a more advanced understanding of the nature of the biomarker is required for successful scaling to human studies. Initially, however, it is necessary to understand the purpose of biomarkers. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to therapeutic intervention. Biomarkers can be used to:

- Illustrate a pharmacological effect.
- Identify patients with a particular disease or abnormal condition.
- Stage disease.

- Indicate prognosis.
- Predict a clinical response to an intervention.

Distinct biomarkers for each of the points above can and must be developed if drug development is to be successful.

The ideal biomarker would be truly useful at all stages of drug development and clinical treatment and could be used to:

- Monitor the effect of the drug on the target in a dose-responsive manner.
- Allow for the functional assessment of the critical disease pathway.
- Identify patients who will benefit from treatment.
- Monitor disease bulk and detect early recurrence.
- Act as a surrogate endpoint i.e. be substituted for a late occurring clinical endpoint.

The ideal biomarker:

- Should be fully validated and evaluated.
- Could be widely applicable to the disease irrespective of the treatment.

Biomarkers serve to reduce the uncertainty at each decision point and aid the next stage in the development paradigm (see Fig. (1a)). For novel targets, the mere identification of target modulation is not sufficient to predict benefit to the patient. Once a precedent is set and a link firmly established between the biomarker and patient outcome, the biomarker can be used to evaluate patient benefit, for example, serum glucose in the development of new anti-diabetic agents (see Fig. (1b)). Until that time, biomarkers of target modulation, functional pathway alteration, desired cellular biology and patient benefit are likely to be required. It is the integration of the readout from all of the biomarkers (mechanism, efficacy and toxicity) which shows promise in adding this new agent to the oncologist's armamentarium.

It is in the development of biomarkers that technology may have escaped the bounds of current reality. The need to expeditiously identify biomarkers to justify the identification of a valid target, and subsequently, a drug often takes on a life of its own. There is an unspoken notion that the more elaborate the process of biomarker identification, the greater its value, however, there is an element of smoke and mirrors to this approach. The identification of a series of markers through microarray analysis *per se* will not result in anything that is applicable without the proper integration with the biology. Time too, is an important consideration. The process of identification, validation and qualification of a biomarker is laborious and often lags behind the development of any new chemical entity. The pressure to advance a molecule to clinical development is great, but the utility of that marker in the decision making process must be clearly understood.

If ultimately, a biomarker of target modulation is found and a dose or range of doses defined in clinical studies, the next stage in development is the quantification of efficacy. Indeed, this is true for conventional cytotoxics, but unlike the

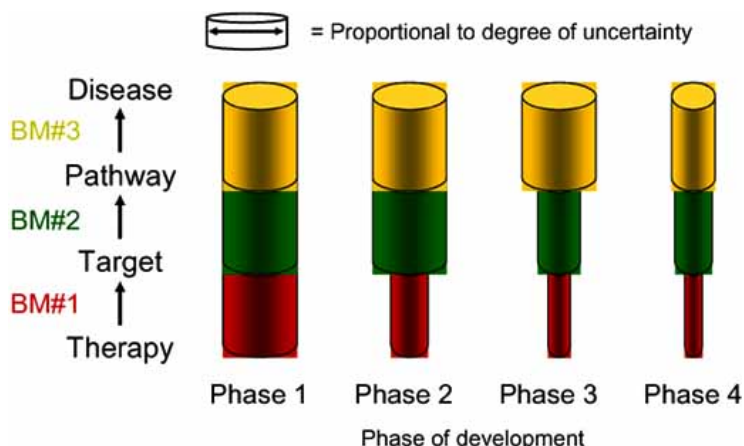


Fig. (1a). The sequential application of different biomarkers at each stage I development serves to reduce the uncertainty of success at each of the next stages of development. This serves also to build a link between the initial biomarker of molecular efficacy (BM#1) and the clinical outcome for patients.

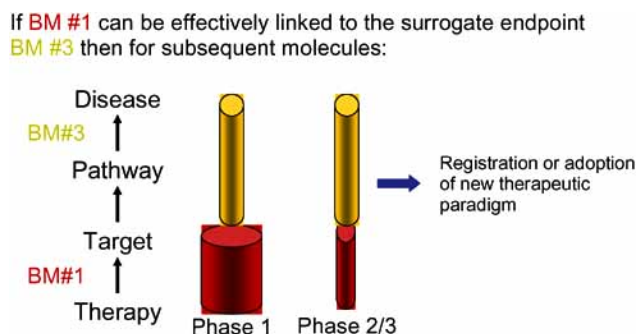


Fig. (1b). The benefit derived from being able to link the effect on an early biomarker with the desired outcome. Uncertainty is effectively reduced using only a biomarker in early development (BM#1) and the registration path is thereby shortened.

development of yesteryear, there is a push to identify subgroups of individuals who have a greater chance of responding to therapy. The intent is that, by identifying individuals using an efficacy marker, a greater proportion of individuals will derive benefit. However, the ability to successfully achieve this goal is dependent on understanding of the biology underlying the molecular pathophysiology of the disease which in many cases is not clear. The initial success of Gleevec® may be attributed to the well-established biology of CML and the role of bcr-abl kinase. The target in this case effectively defines the disease it was designed to treat. The difficulties experienced by Iressa® stem from the fact that, neither the epidemiology of the target, nor the role of the EGF receptor in the pathophysiology of lung cancer was defined in advance to the clinical development. Only in the post-marketing investigation of Iressa®, are the important factors contributing to efficacy being determined. It is impossible to predict how many of the current targeted molecules in clinical development will meet the same fate, but in an environment where the preclinical tools are artificially designed, based on the desired outcome without adequate appreciation of the disease-based pathophysiology, success is likely to be limited. Positive results from preclinical studies are heralded as proof of concept, however, a negative outcome is either ignored or complex explanations, which may

not be representative of the situation in life, are sought. In order to achieve success, we must look carefully at current processes to establish the validity of a target and the promise of an agent against that target. This could be realistic given time and experience, however, hundreds of agents are currently in development and the number of targets is much smaller, therefore, many pharma companies and academic institutions are addressing the same targets. The value from this shotgun approach will only be realised if the reasons for success, and more importantly, failure of an individual agent or target are understood and are shared openly. Important questions such as, did the molecule fail? was the target not appropriate? was target modulation effective and was the right patient population examined? must be addressed if progress is to be made.

WHAT POPULATION?

This last point, the right population, is the one that is under increasingly close scrutiny, but how does one can define that population? Again, the role of biomarkers in this area is significant, but risky, if they are designed on the basis of artificial preclinical experiments discussed above. The literature contains many references to molecular signatures which may indicate an appropriate population, but how relevant is this to the real world? In order to be of use and widely appli-

cable, this signature must be of greater value than stratification based upon conventional clinical or histopathological means and must be validated prior to use in clinical studies. Often this is not the case as employing complicated semi-validated analysis of this type may define a slightly better population than by using conventional means. Is it, therefore, worth the effort? With the pressure to progress a molecule through clinical development, there is often not the time, or necessarily the will, to wait for the validation and this question to be addressed. The result is a complex study with little or no useful information identified to help the treating physicians. The other aspect frequently forgotten is that, by subdividing the population in this way, it may result in an improved outcome for those patients who have received conventional chemotherapy treatment. A comparison to historical control data in which no subdivision of the population was performed, or is possible retrospectively, is fundamentally flawed. Randomised trials in this setting are essential and the value of the randomised phase 2 learning experience for the future direction of the molecule is enormous. Increasingly, this is being realised and, in applying the learning from the Iressa® experience, can only be of benefit to the whole community. The key to biomarkers in this setting is a thoughtful development in parallel with that of the drug. The adage “more haste less speed” is particularly relevant. The introduction of disease-based models, which have applicability across platforms, may be a key to successful therapies. Mechanistic models of angiogenesis, for example, have been developed and have the utility across different angiogenic strategies [4]. Other models of tumour growth and effects of treatment on preclinical tumour models have also been used successfully [5]. Integration of this type of mechanistic model, with models of disease, toxicity and changes in efficacy biomarkers, are yet to be seen prospectively in clinical studies. The use of these models, however, is imminent and will, if implemented properly, yield tremendous benefit.

IS ONE TARGET ENOUGH?

The above discussion primarily focuses on molecules against a single target, but there is a question as to whether a single target is the optimum way forward. Cancer involves many different mechanisms and the ability to perturb more than one is obviously attractive. Many of the agents currently undergoing clinical evaluation are permissive in their target, for example, sorafenib and sunitinib, highlighting some potential challenges. Toxicity may be more significant and there is limited flexibility in the ability to control modulation at each of the different targets. Nonetheless, many are pursuing this multi-targeted approach but how much this is a proactive choice, versus a consequence of the lack of specificity of a molecule designed against a single target, is difficult to say. A parallel can be drawn to the cytotoxic therapies in which the intended target was not the only mechanism of action of the drug. Combinations of agents, whether targeted or conventional chemotherapy, seems to be the best way to seek a meaningful therapeutic benefit, and efforts are underway to selecting combinations which result in synergy in preclinical models in the hope that these will translate to the clinic. Combinations of molecules with single target activity may offer the ability to control the effect at each of the targets more predictably, but how realistic is this given what has

been learnt so far in the targeted era? It is amusing to ponder that part of the drive away from chemotherapy, besides toxicity, is that targets for chemotherapies are many and varied and yet we are heralding the ability to hit a multitude of targets unpredictably with a single drug. Has oncology development gone full circle?

HISTORY REPEATS ITSELF

Although the era of targeted therapy is new, can we learn from history? There are a few examples of targets, and their respective molecules, which have been the subject of extensive research for a number of years. Arguably, the most thoroughly explored is P-glycoprotein (P-gp). The discovery of P-gp in the 1970s and its role in cancer cell resistance was greeted, in hindsight, with a naive belief that inhibiting this protein would result in a much improved treatment outcome. Yet, 30 years on, and we are still waiting. P-gp shares many of the features with the new generation of targeted agents required for the development. P-gp is up-regulated in many tumour types and its functional presence is associated with a poorer prognosis which can be mimicked preclinically. A biomarker of P-gp activity exists (rhodamine efflux in tumour or NK cells) and this can be used in the clinic to evaluate activity. Issues over single target versus multi-targeted approaches with the later identified MRPs also being inhibited have been encountered. A number of inhibitors of P-gp have been identified but success has proven elusive. Failure has been due to a number of factors, including, not inhibiting the target in the patients (for example, quinidine), toxicity of the agent (for example, cyclosporine) and to inhibiting the target for too long or inhibiting metabolic enzymes (CYP3A4), resulting in toxicity that compromised the efficacy of the co-administered chemotherapy (for example, PSC833, tariquidar, [6]). Hence, the value of P-gp inhibition in treating cancer cannot be properly assessed, given the increased toxicity which limited the ability to assess the efficacy associated with this target. From a therapeutic point of view, the exploration of this target has not benefited the patient. However, resulting from both the clinical experience of a number of molecules, and a better understanding of the biology of the target, a possible way forward is evident. Clearly, efficacy at the target at non-toxic doses must be shown before efficacy in a patient population enriched for P-gp over-expression in combination with full dose chemotherapy can be demonstrated. Such a study is being performed by ECOG in elderly patients with de novo AML treated with the P-gp inhibitor Zosuquidar.3HCl and full dose daunorubicin [7]. Recruitment is complete and without many of the toxicity issues that have dogged other agents. This has been achieved because the balance between toxicity and efficacy was adequately explored in early clinical trials by the application of extensive PK/PD modelling [7, 8]. The treatment outcome for patients, together with the effectiveness of inhibiting this target will be determined upon completion of the study. Therefore history has taught us not to be impetuous, but to explore the biology, understand it in relation to the disease under investigation, have a clear appreciation for the factors that influence efficacy and toxicity, either alone or in combination, and to address the balance appropriately. The development of any agent is a stepwise process, and much like a skyscraper, without the appropriate foundations and building

blocks, however pretty the promise of a final building, it will collapse.

FUTURE DIRECTION

It is evident that the selection of the target is not responsible for the revolution in oncology drug development, but rather it is the plethora of data and our ability to analyse such data that has forced us to rethink the way in which oncology drug development is undertaken. In an era where it is possible to collect thousands of data points at any one point in time for a multitude of parameters, and yet because we can collect them does not make it correct to do so. We must first understand the value of such an approach and secondly understand the limitations of these data and how to interpret them for the future benefit of patients. Every effort must be given to understand the nature of the signal to noise ratio, the nature of the variability and, therefore, the uncertainty which will enable us to manipulate this to the advantage of the patient. The age of “right drug to the right patient for the right disease” will not be realised until we have this understanding. Now data are separated in silos, but this fractionation of data will prohibit progressive development. To unleash the benefit of years of molecular research to patients, a more integrated approach to oncology drug development is required. The true face of the revolution, the ability to integrate and manipulate data from many sources, and to act on the output in proactive, rather than reactive, manner must be advanced. In silico techniques, integration of disease-based models with mechanistic pathway and PK/PD models must

be prominent at an early stage to ensure that clinical development is confirmatory and not merely learning. For the benefit of patients, we say “up the revolution!!”

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