COMMENTARY

Molecular Targeting Agents in Cancer Therapy: Science and Society

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Abstract

The inception of targeted agents has revolutionized the cancer therapy paradigm, both for physicians and patients. A large number of molecular targeted agents for cancer therapy are currently available for clinical use today. Many more are in making, but there are issues that remain to be resolved for the scientific as well as social community before the recommendation of their widespread use in may clinical scenarios can be done, one such issue being cost and cost effectiveness, others being resistance and lack of sustained efficacy. With the current knowledge about available targeted agents, the growing knowledge of intricate molecular pathways and unfolding of wider spectrum of molecular targets that can really matter in the disease control, calls for only the just use of the agents available now, drug companies need to make a serious attempt to reduce the cost of the agents. Research should focus on agents that show sustained responses in preclinical data. More needs to be done in laboratories and by the pharmaceutical industries, before we can truly claim to have entered a new era of targeted therapy in cancer care.

Keywords: Cancer therapy - targeted agents

Asian Pacific J Cancer Prev, **13**, 1705-1708

Introduction

The established availability of Molecular Targeted Agents in the armamentarium of anti cancer drugs has practically revolutionized the options and scope of cancer therapy. Modern molecular techniques are profiling cancers in a way that the concept of cancer care, in may ways, is drifting away from "one size fits all" to "personalized or tailored" medicine. However apart from few distinct clinical situations the targeted agents failed to live up to the mighty talk about them. Some of the agents might have managed to reach the statistical end points, pre-set in the clinical trials, but the small advantage gained does not convincingly justify their across the board use and huge costs.

Both, the scientific community and the society have to brace the impact of the modern era of targeted therapies. With Increasing resource of knowledge and understanding, physicians often have lengthy conversations about the targeted agents and the patients want to know more of what they often believe a ray of hope, light at the end of a dark tunnel , for them. In many ways, cost also remains a big consideration , in countries with proper healthcare system, drug approval authorities and insurance agencies the cost might not even become a point of discussion, but in poor countries , with practically non-existent healthcare system, even discussing " such things" with patients is precarious . Patients must feel helpless and hopeless if they believe that there is some thing that can save their life, but that some thing they can not simply afford!

From the scientific standpoint, it is well known now that the cancer cell growth pathway is complicated, interrelated and multi-factorial (Valentino and Pierre, 2006). Identifying and overcoming one target has often proved fruitless until it is known that the whole pathway, can actually be blocked by doing so, or that the other integrated pathways do not surpass what is achieved by blocking one particular track. Review of the literature suggests that the key factor for efficacy of a Targeted agent is the potential of the "target" in the genesis of the cancer. Some targeted agents might be effective at one site of cancer while less or completely in-effective at the other. Others might loose their efficacy soon after blocking cancer cell growth, by emergence of other cell growth pathways independent of the one blocked.

Many specific targets involved in cancer cell growth are known, many more are in the process of possible discovery. Similarly many agents against the targets are available and so many competitors are in pipeline. Some of available agents are given (Table 1).

Development and Cost of a Molecular Targeted Agent

Development of the modern targeted therapies is often a long and enduring process of research, the time that is taken from identifying a target and actually developing an effective agent against it can span over decades. For

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Table 1. Clinical and Pathologic Characteristics of the 356 CRC Cases in this Study

Targets	Agents	Clinical use
HER 2 Neu (and Her 1, 3, 4 ?)	Trastuzumab, Pertuzumab	Breast cancer,Gastrointestinal Cancers
Tyrosine kinase Inhibitors	Gefitinib, erlotinib Citrozininb , lapatinib , neratinib, sunitinib , sorafenib etc	Lung, renal, Hepatic, neuroendocrine cancers etc
ADP-ribose polymerase (PARP)	BCS210	Triple Negative Breast cancer
CD 20	Rituximab , Oftumamab	B cell malignancies
CD 50	Gemtuzumab	Luekemias
mammalian target of Rapamycin (mToR) phosphoinositide-3 kinase (PI3K)	Evrolimus, Temosirolimus	Renal cell carcionams
vascular endothelial growth factor receptor	Bevacizumab	Lung cancer, brain cancers, Ovarian cancers, breast cancer
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receptor tyrosine kinase RET	Sorafenib, Vandetanib, Motesanib, Sunitinib, and XL-184	Medullary Thyroid Cancer
RAF	Antisense olligonucleotidesorafenib, PLX4032	Multiple
receptor activator of nuclear	factor κB (RANK), Ligand	Bone metastasis from cancers
Philadelphia chromosome	Imatinib, Dasatininb,nirlotinib	Chornin Myelid Leukemia

example, the concept of tumor growth dependence on nourishment provided by neo-vascularization is not new; In fact it is decades old (Folkman, 1971). It might have remained an area of immense interest for researchers in science to find ways to block factors that influence the vascular growth but the 'target' had been elusive until 1980s when a Vascular endothelial growth factor (VEGF) was identified and in 1993 it was shown that a monoclonal antibody against this factor can inhibit cancer cell growth, Bevacizumab (Avastin; Genentech), a humanized variant of this anti-VEGF antibody, as an anticancer agent was then launched in the market in year 2004 (Ferrara et al., 2004)

Rituximab, the most widely used monoclonal antibody and the one that has revoloutionized the therapeutuic paradiagm for managmenet of B cell lymphomas, was conceptualized in mid 1970s, was used for the first time in patients with lymphoma in 1993 and received Its approval by the Food and Drug Administration on November 26, 1997, for the indication of relapsed or refractory, CD-20 positive, B-cell, low-grade or follicular non-Hodgkin's lymphoma. 27 years after it was conceived (Grillo-Lopez et al., 1999; Ronald et al., 2008). Arguably that much of the time spent on research and development of a drug should cost extortionate amount of finance as well.

The cost of development for a new drug according to one estimate may vary from around $500 million to more than $2,000 million, depending on the therapy or the developing firm. The average out-of-pocket cost to develop a new chemical entity has been estimated at $400 million If the opportunity cost of failed development efforts is included, the figure exceeds $800 million (DiMasi et al., 2003). In addition drug companies spend huge sums in one–on-one interaction with doctors. Billions of dollars are spent in marketing interactions with the doctors, including free sampling of drugs, direct gifts to doctors, expensive meals, entertainment, tickets to events and travels to international destinations (Blumenthal, 2004). Pharmaceutical promotion may cause some doctors to prescribe more expensively, less appropriately and more often. One study suggests that Pharmaceutical companies spent $57.5 billion on pharmaceutical promotion in the United States alone in 2004. The same study suggested that many doctors claim they aren't influenced by the information provided by pharmaceutical companies, on the contrary the study shows that they are (Spurling et al., 2010).

Despite the cost of the agents and relative questionable efficacy in many situations the targeted agents have been successful in making a commercial breakthrough. This success for targeted agents has established a paradigm shift in the pharmaceutical industry. The Multibillion dollar revenues earned by some pharmaceutical giants in a short span of time have made this industry an attractive marketplace. The abundance of targets available, coupled with promising revenues has produced many competitors with in the pharmaceutical industry, despite a new agent popping up every now and then, the need surpasses, availability therefore enormous research and development is in place, and the market opportunities incessant (Barbara, 2010). Pharmaceutical companies take on the targeted agent research development and marketing opportunity because there are lucrative profits in sight. Five of monoclonal antibodies are in the top twenty list of best selling global medicinal brands, business only for monoclonal antibodies had grown from $7 billion in 2004 to $35 billion in 2008 and is expected to reach $51 billion by the year 2015 (Maggon, 2007). Interestingly, but, the end user cost of most of the targeted agents is almost always out of proportion for any other chemotherapeutic agent, in many situations the clinical benefit gained is minimal that is why an initial excitement generated by manipulating modest clinical response with a marketing artifice has often met with setbacks such as either withdrawal of approval or the threat of so (Staff Writer, 2010).

The problem of targeted agent in providing absolute efficacy has scientific reason behind it, with the intricate pathways of targeted agents and great inter-woven complexity it is but natural that targeting cancer is one thing but getting the " hit " to work , is another. An example of how interlinked a cancer cell growth pathway can be is given in Figure 1. After initial development, many targets today, have been sub-classified to a greater

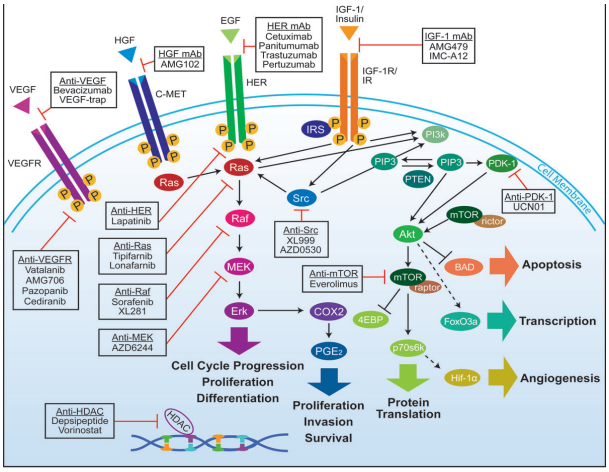

Figure 1. Overview of Interlinked Cellular Signaling Pathways Involved in the Proliferation and Progression of Colorectal Cancer. (reporoduced with permission from Siena et al., Biomarkers Predicting Clinical Outcome of Epidermal Growth Factor Receptor–Targeted Therapy in Metastatic Colorectal Cancer JNCI J Natl Cancer Inst (2009) 101(19): 1308-1324

detail, pathways are now better explored, predictive markers are now identified to define population to benefit from intervention.

Specific Targets

Identification K-Ras mutation for anti EGFR therapy in Colon cancer and EGFR mutations in lung cancers for the use of tyrosine kinase inhibitors such as Gefitinib and erlotinib is commonplace and essential. Furthermore, there exists the possibility of a very small sub-group of patients with-in an entity, to derive the exclusive benefit to an extent that such patients might not only get away with chemotherapy but in-fact achieve even better results, for example, gefitinib an oral tyrosine kinase inhibitor has been shown in an open label phase III trial to work better than carboplatin and paclitaxil when used in advanced adeno-carcinoma of lung in a select population (Mok et al., 2009). Crizotinib, an ATP-competitive inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase has currently been shown to work in lung cancer demonstrating The EML4 (echinoderm microtubule-associated protein-like 4)–ALK (anaplastic lymphoma kinase) fusion-type oncoprotiein, found in about 4 - 5% of all lung cancers (Hallberg and Palmer, 2010).

The canonical example of an effective targeted agent comes, though , from Imatinib a small-molecule tyrosine kinase inhibitor for PDGFR and a potent inhibitor of ABL kinases, including the BCR-ABL fusion protein generated as a result of the t (9;22) chromosomal translocation (Philadelphia chromosome) found in chronic myelogenous leukemia (CML), which also inhibit the receptor tyrosine kinase C-KIT. Imatinib mesylate is a sound and authoritative example of a targeted therapeutic agent, because BCR-ABL is uniquely expressed by leukemic cells and is essential for their survival. It is one of the targeted agents for whom the robust efficacy data lead to their approval even in absence of phase III trials for some indications (van Oosterom et al., 2001). Identifying the great benefit of imatinib mesylate in CML, some donor agencies have arranged for the agent to be provided free of cost to patients in underdeveloped third world countries by implying Glivec patient Assistance Programme. (GPAP). The story of most of many other targeted agents is not as remarkable , especially in metastatic setting of solid tumors where a large number of patients in phase III trials have demonstrated only small survival benefit, as a classic example sorafenib was granted FDA approval for use in hepatocellular carcinoma in november 2007 ,based on the phase III trial SHARP trial which showed 2.8 months improvement in both median survival and time to progression in select group of patients who had advanced hepato-cellular carcinoma (Llovet Ricci et al., 2008). By Contrast in UK the UK's National Institute of Clinical Excellence declined to approve the drug for use within the NHS in England, Wales and Northern Ireland, stating that its effectiveness did not justify its high price, The NHS scotland also refused the approval on same ground (2010).

Discovery of Trastuzumab, a monoclonal antibody directed against the extracellular domain of HER-2 has been seen as a milestone in the management of breast cancer management for women over-expressing her2 neu, an epidermal growth factor receptor belonging to EGFR family. Although extremely useful, there has been questions whether it could be used for a much shorter duration of time 9 weeks, as in a Finnish phase III (Fin Her) trial, Vs for one year, as in NSABP B-31 and NCCTG N9831 and HERA trials, to gain the same benefit of survival (Baselga et al., 2006). A head to head comparison of trials with statistical power to validate the shorter Vs longer duration of need has never been performed and perhaps will never be. This has huge financial implications! B cell lymphoma is one disease in which molecular targets are of great interest and have shown promise. Anti Cd 20 monoclonal chimeric antibody Rituximab has changed B cell lymphoma prognosis like no other in agent in past five decade (Murawski & Pfreundschuh, 2010). The addition of R (Rituximab) is now virtually done with almost all chemotherapeutic regimens for B cell lymphomas and the drug can even be used alone in elderly and frail patients with B cell lymphoid malignancies who are not suitable chemotherapy candidiates. The addition of Rituximab to a common chemotherapy regimen changes the survival benefit figures to approximately 15 % over a period of 10 years.(Coiffier, Thieblemont et al., 2010). From the cost standpoint the treatment with the R- CHOP (cyclophosphomide, vincristine, Doxorubicin, Prednisolone) compared to CHOP alone for average completion of therapy stands at $ 17,225 Vs $ 3358 dollars. Studies however find it to be cost-effective over wide ranges of variables in sensitivity analyses (Hornberger & Best, 2005). Using Rituximab, across the board for B cell lymphomas in an underdeveloped country still seems a distant goal. Factors that will help identify more clearly the patients who are supposed to benefit from a costly intervention, such as addition of Rituximab to the therapeutic recipe, are desperately needed. Identifying patients with high risk of relapse with molecular techniques is awaiting a standard and may help physicians tailor treatment and

select patients.

There are currently more than ten targeted agents in pipeline for management of lymphoma, which one is to become the most cost-effective remains to be seen as success rates for most chemotherapeutic agents in pipeline is 5-8% at best. Amongst the many factors proposed as to be responsible for such a low outcome are a lack of insight into determinants of drug pharmacokinetics and resistance mechanisms; poorly conceived clinical trials; heterogeneous patient populations and lack of use of biomarkers to identify patients most likely to benefit from specific treatments (Rosenwald et al., 2002).

Some of the targeted agents that we use today have an un-equivocal place in the practice of oncology, On the other hand it is clear that most of these agents that we have are in the phase of evolution, and the targets will keep on changing and get further delineated with time. There have been repeated calls for cost considerations for the targeted cancer agents (Ocana et al., 2010). In the interest of science, humanity and research along with business gains, pharmaceutical companies need to pursue further development of agents with solid pre-clinical data, abandon the approach of short term gains on agents without much efficacy, curtail their overhead costs in un-necessary promotions and interaction with doctors and divert the funds to reduce the cost of medication, or subside them for select areas and patients. Project based mergers and revision of patent laws should also be considered to encourage healthy competition, active research and bringing the cost down. Research also needs to focus on traditional chemotherapies, which is the mainstay of cancer treatment, and targets that have been known for long but abandoned and on sensible use of agents already at hand (Cohen, 2008). Physicians need to be judicious in the use of targeted agents, Using the targeted agent may often require the scientific knowledge of the physician to be coupled with art of identifying the proper setting of use. Patients should be informed of survival data, alternative choices and toxcicity profile of the agents in question..

The era of targeting agents is exciting and innovative which is a welcome change for community of medical oncologist's. It is clear, though, that this era is just the beginning of understanding of what appears to be a complex but traceable network of targets involved in cancer cell growth, this era calls for just and appropriate use of the currently available agents and calls for not confusing beginning with the end.

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