

## Era of Targeted Therapy

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Targeted therapy is a treatment for cancer which uses drugs designed to combat specific genes or proteins required for cancer growth and progression. It prevents the survival, growth and spread of cancer cells by targeting the genetic alterations unlike the traditional chemotherapy regimens that target rapidly dividing cells which include cancer cells and certain normal tissues. The primary purpose of this molecularly targeted cancer therapy is to be more precise than traditional chemo-therapy regimens and to reduce toxicity, so there are less adverse side effects for the patients. Combining both these therapies and current practices may improve efficacy of available treatment regimens and may further reduce the risk of relapse and metastatic disease. Targeted therapy remains a treatment of choice for many malignancies however, side effects of the approved drugs are not insignificant.

Cancers have specific types of genetic mutation and advances in genetic profiling of tumors is leading the way for these targeted therapy. The drugs that have been approved for targeted therapy include those that promote cell death by interfering with cellular survival signaling as well as those that interfere with specific targets responsible for maintaining and supporting tumor micro-environment. Targeted therapy directed against cancer cells include antihormonal therapy, tyrosine kinase inhibitors, therapy targeting the Bcr-Abl fusion protein, therapy targeting the epidermal growth factor and therapy targeting HER-2. Targeted therapy directed at the microenvironment include those especially against the secreted vascular endothelial growth factor and therapies activating immune responses are also in use.

The current targeted therapies are either monoclonal antibodies or small molecule drugs. Most monoclonal antibodies cannot penetrate the cell's plasma membrane and are directed against extracellular targets, like the ligand-binding sites of receptors or the ligand itself. Small molecule drugs are typically able to diffuse into cells and thus have the advantageous ability to act on targets localized inside the cell.<sup>1</sup> Thus, Monoclonal antibodies act as an antagonist, prevent the ligand/ receptor interaction as well as activation of its downstream signalling cascade. While small molecule inhibitors enter cells, block receptor signalling and interfere with downstream intracellular molecules. Thus inhibiting a specific function of a multi-functional protein or impeding protein-protein interactions.

The name of a targeted agent provides clues to the type of agent and its cellular target. Monoclonal antibodies end with the stem '-mab'. They have an additional subsystem designating the source of the compound example, '-ximab' for chimeric human-mouse antibodies, '-zumab' for humanized mouse antibodies, and '-mumab' for fully human antibodies. Small molecules end with the stem '-ib' indicating that the agent has protein inhibitory properties. In addition, both monoclonal antibodies and small molecules contain another stem in the middle of the name describing the molecule's target; example monoclonal antibodies include '-ci-' for circulating system target and '-tu-' for a tumor target. Small molecules include '-tin-' for tyrosine kinase inhibitors and '-zom-' for proteasome inhibitors. At the beginning of the generic name there is a prefix that is unique for each agent.<sup>2</sup>

By the year 2014, there were 14 antibodies approved for use in clinical oncology, eight of which were indicated for solid tumors, and six for haematopoietic cancers.<sup>3</sup> Since then a number of antibodies and small molecules have been designed and a whole lot are in the pipeline for clinical trials and approvals. A complete overview of targeted drugs used in clinical practice and clinical trials can be found at: [www.mycancergenome.org](http://www.mycancergenome.org) and [www.clinicaltrials.com](http://www.clinicaltrials.com).

The use of targeted therapy has made a huge impact and markedly changed the outcome for some diseases. It has prolonged survival in patients with certain cancers and provided treatment options for some who may not be candidates for anticancer therapy. Despite the advancement in targeted therapy, cancer still remains as a huge unmet medical need. Multiple factors in addition to the complexity of cancer biology contribute to this unsatisfactory state such as lack of preclinical models to predict anti-cancer drug efficacy, inefficient clinical development and limited single agent activity.<sup>4</sup> Another is the cost factor as these drugs are expensive for the general population. Thus cancer is still one of the leading causes of death worldwide.

Our country Nepal with a population of approximately 30 million has an estimated cancer incidence of 50,000- 70,000 per year. Cancer is identified as a non-communicable disease responsible for 42% of total deaths.<sup>5</sup> In spite of improvements in the diagnosis and treatment and early detection of cancer with the few

armamentarium that the country has, cancer treatment and especially targeted therapies targeting specific genes and proteins are far from reach of the vast majority of patients. Moreover, the financial burden of cancer is a huge setback for patients and family members. We can only hope that someday our country will have a good health care system and diagnostic modalities for cancer detection and treatment.

## References

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