

Targeted Therapy: A New Horizon in Cancer Management

OP Gupta[†], R Joshi[‡], TB Lathia^{*}

[†]Professor, [‡]Lecturer, ^{*}Resident;
Dept. of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram-442 102,
Maharashtra

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Cancer research has always remained an enigma. Last fifty years saw advent of various chemotherapeutic regimens, alongwith path breaking research into the mechanisms of cancer cell growth. All well established chemotherapeutic drugs were based on a variety of cellular mechanisms, such as alkylation, DNA duplication, folate inhibition, or on microtubule assembly-disassembly. Mechanisms of cancer cell growth have focused on even further micro approach, into growth factors, growth factor receptors, tyrosine kinases, and inositol mechanisms. The later mechanisms based on molecular biology and genetics had so far been limited to the basic science research, is now emerging to come to the application stage. There have been initial hopes and disappointments on this front, but surely an attempt has been made to change the way we look at anti-cancer therapy.

Traditional chemotherapy can be visualized to an armored infantry, which in a battle field would attempt to overcome the enemy, but would also destroy numerous innocent bystanders. Traditional chemotherapy hence inflicts major collateral damage on healthy cells.¹ Targeted therapy tries to act like as sniper, or a laser-guided missile system, which would destroy a high value target, but spare the healthy viable cells. In this light it becomes important to identify the high value target of each neoplasm, also known as the "Achilles heel" of the tumor.²

Chronic myeloid leukemia was the first neoplasm to give a readily identifiable Achilles heel, in the form of bcr-abl gene. It has been long known that chromosomal anomaly in the form of Philadelphia chromosome, or genetic rearrangement otherwise results in generation of a bcr-abl gene, which produces abnormal protein kinases responsible for myeloproliferation in CML. Theoretically if these specific tyrosine kinases were inhibited, it could have been an effective target in CML therapy. In 1988 2-phenylaminopyrimidine compounds were identified, which had variable levels of tyrosine kinase inhibitory activity.³ In 1996 Druker and coworkers reported a selective abl- tyrosine kinase inhibitor, which prevented bcr-abl positive cells from growing. In 1997-99 various laboratories confirmed the findings. Hence a new drug, imatinib (formerly ST1571) was developed as a specific inhibitor of the PDGF receptor.³

The clinical response of this first targeted therapy was dramatic. The Phase I trial, among patients of CML, who had either not responded or did not tolerate interferon alpha, 98% showed normal counts within four weeks of initiation of therapy (300 mg PO

daily). Subsequent phase II trials in over 1000 patients established the safety of this new drug, and complete hematological response in 95% patients in chronic stable CML. Complete hematological response was 34% and 7% respectively in accelerated and blast phase, respectively. Imatinib was FDA approved for treatment of CML in May 2001, and for gastrointestinal stromal tumors in February 2002.³

Flood gates for targeted therapy opened. The next targets were epidermal growth factor receptors (EGFR), and vascular endothelial growth factor (VEGF) targeted therapy. Laboratories had already churned out many designer molecules, and clinical trials were in progress. The breast cancer research focused on the HER2 gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.⁴ Trastuzumab, a recombinant monoclonal antibody against HER2, was studied in women with metastatic breast cancer that overexpressed HER2. The women who received trastuzumab and chemotherapy had slower tumor growth, greater reduction in tumor size, and longer survival than the women who received chemotherapy alone. But in another trial, women who received trastuzumab by itself, the tumor got smaller or disappeared in 14% of them. Further clinical trials on this molecule are under way. Trastuzumab is also being studied in clinical trials for other types of cancer, including osteosarcoma (a type of bone cancer) and cancers of the lung,⁵ pancreas, salivary gland, colon, prostate,⁶ endometrium (lining of the uterus), and bladder. Some patients with these types of cancer have tumors that overexpress the HER-2 protein. These patients will be possible candidates for future clinical trials with trastuzumab.

Four therapies targeting EGFR inhibition are currently being evaluated. These are gefitinib (tyrosine kinase inhibitor), cetuximab (a mouse monoclonal antibody), ABX-EGF (a human IgG2 monoclonal antibody), and erlotinib (synthetic receptor inhibitor) (see Table). The response to these agents has not been as dramatic as in case of imatinib. In September 2002, 12 patients with adenocarcinoma of the lung assembled in front of the FDA oncology committee to enable approval of the drug. These patients had a major response with this new drug¹. There had been reluctance on part of FDA to approve this drug, owing to inconsistent results. Of 275 patients who had been treated with this drug, only 25 had a response, but those who did respond it was indeed dramatic. The same day Wall Street Journal brought

Table 1 : Available and under evaluation targeted therapies

| Drug | Trade name | Target | Application | FDA approval |
|-------------|------------|---------------------------------|---------------------------------------|---------------------------|
| Imatinib | Gleevac | PDGF tyrosine kinase inhibitor. | CML Gastrointestinal stromal tumor | May 2001 February 2002 |
| Trastuzumab | Herceptin | HER-2 protein | Carcinoma Breast | May 2002 |
| Gefitinib | Iressa | EGFR tyrosine kinase | Non-small cell cancer lung | September 2002 |
| Cetuximab | Erbitux | EGFR antibody | Colon Cancer | February 2004 |
| Bevasizumab | Avastin | VEGF inhibitor | Colon Cancer | February 2004 |
| Erlotinib | Tarceva | EGFR receptor inhibitor | Lung Cancer | Under development |
| ABX-EGF | | EGFR antibody | Breast Cancer | Under development |

out a news item, "FDA to patients: drop dead". This probably prompted FDA to approve the drug, for limited compassionate use in resistant cases of carcinoma lung.¹

Various questions about gefitinib have indeed being answered. This drug, targeting EGFR, did act against lung and colon cancer, but not against glioblastoma multiforme, where EGFR mutation is more common. Molecular biology has answered this query. The site where the mutation occurs is of importance. In lung cancers, the mutation is in form of single alteration in intracellular kinase domain. In contrast, in glioblastoma multiforme the mutation consists of extensive deletions and missense mutations in the extracellular and regulatory domains.⁷ Intact extra-cellular domain is hence a pre-requisite for this drug to act. Cetuximab and erlotinib also specifically act against the extracellular domain.⁷

Even amongst lung cancers, only a few were responsive. In one study, amongst 119 samples of lung cancer analyzed, only 16 had EGFR mutations.⁸ The mutation also seems to be region-specific, with 15 of these mutations amongst 58 Japanese patients, and only one in the 61 North American patients.⁸ In another study published in May 2004, all nine of the 25 responders for whom adequate tissue samples were available had EGFR mutations. None of the seven non-responders had this mutation. Interestingly the responsive patients were predominantly females, never smokers, with an adenocarcinoma.⁹ This finding calls for evaluating all gefitinib therapy to be investigated for intracellular EGFR mutations as a predictor of response. Hence this drug is likely to benefit only a small minority of lung cancer patients.

Experience with other EGFR targets is more limited. Cetuximab has been tried in colonic carcinomas, and got FDA approval in February 2004. At this time, it is not known whether cetuximab will improve symptoms of colorectal cancer or help patients live longer. In clinical trials¹⁰ in patients with EGFR positive tumors, no longer responding to conventional chemotherapy, addition of cetuximab shrunk tumors in 22.9% of patients and treatment with cetuximab alone shrunk tumors in 10.8%. Interstitial lung disease has been reported in patients treated with this drug. Further trials with this drug are currently underway. FDA has also approved a test kit, to detect HER-1 in tissue samples, which determines if patient is eligible for colon cancer treatment with cetuximab.

Erlotinib is a small molecular, once-a-day, orally active inhibitor of the EGFR tyrosine kinase. In phase I trials in healthy volunteers and patients with refractory cancers, erlotinib was well tolerated and showed activity against non-small-cell lung cancer and other tumors. However results from recent studies on more

than 1000 patients with non-small cell lung cancer (TALENT and TRIBUTE), have reported that the addition of erlotinib to conventional chemotherapy did not improve response rate, time to progression, or survival.¹¹ Researchers are investigating the reasons for the lack of relationship between EGFR expression and clinical outcome, and the reasons for the failure of the front-line combination trials. An interesting finding has been the presence of skin rash in those who respond to this drug.¹² A small sub-group of young patients showed 23 month survival with this drug in comparison to 10 month survival in those who received placebo. This survival advantage was not seen in all patients. ABX-EGF is the latest entrant in EGFR targeted drugs, and early trials with this drug are underway.¹³

Bevacizumab, the first angiogenesis inhibitor approved in February 2004, is a genetically engineered mouse antibody that targets vascular endothelial growth factor (VEGF). VEGF stimulates neo-angiogenesis, especially in neoplastic tissue.¹⁴ The safety and efficacy of bevacizumab was primarily shown in a randomized, double-blind clinical trial of more than 800 patients with metastatic colorectal cancer designed to find out if it provided any survival advantage.¹⁵ Roughly half the patients received IFL(ironotecan, 5-fluorouracil (5FU) and leucovorin) regimen, and the other half received bevacizumab once every two weeks in addition to IFL. Overall, patients given Bevacizumab in combination with IFL survived about five months longer and the average time before tumors started re-growing or new tumors appeared was four months longer than patients receiving IFL alone. The overall response rates to the treatment with add-on therapy with bevacizumab was 45% compared to 35% for the conventional therapy.¹⁵

More targets are undergoing discovery. Recently phosphatidyl inositol 3-kinase (PI3K) mutation has been identified in 25 to 32% of gastric, breast and colonic carcinomas.¹⁶ Development of more such specific inhibitors may generate a new target against cancers.

Various issues have emerged as this new therapy takes shape. These issues range from benefit of stand alone vs combination targeted therapy. Tumors with specific mutations need to be rapidly identified. Since these mutations occur early, would it be more prudent to use these drugs as first-line agents, rather than as the last resort. Are we somehow moving towards pre-neoplastic treatment of cancers, if we are somehow able to identify those at the risk of such mutations.⁷ There is also a flip side to the initial enthusiasm. Cancer growth is not as simple as a single

defect which drives growth. Combinations with conventional chemotherapy may not work, as drug penetration into the tumor would be impeded if there is an abundance of surrounding necrotic material. It is the common sense which has driven researchers to devise this new therapeutic mode, but the pessimists amongst us would always warn that the things that make sense do not always work in medicine !!

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