Targeted Therapy in Oncology

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Introduction

Cancer incidence is increasing worldwide. New cases have an increasing tendency to be concentrated in developing countries, WHO estimating that 66% of all new cases will be diagnosed within such regions. Also the majority of patients are diagnosed in advanced stage, requiring systemic therapy. Hence chemotherapy has been the traditional mainstay of treatment for such patients. Unfortunately such therapy acts in a non specific manner, resulting in significant toxicity. Therefore there has been an urgent need to find alternate avenues of management for such patients. Advances in understanding the biology of cancer cells and their metabolic functioning have led to the recognition of several molecule and processes that are unique to the cancerous cells. Over the last few years, these have been (successfully in several instances) explored as potential targets for cancer directed therapy.

This gave birth to the era of targeted therapy. Targeted therapy is defined as a drug or molecule causing tumour cell kill by interacting with predefined target(s) present on malignant cells. Such an approach has obvious advantages. The most important being that it would selectively attack the cell surface molecules, signalling of metabolic pathways that are unique to the malignant cells. This has the potential to spare the normal cells, thereby reducing toxicity and improving quality of life while continuing to have greater efficacy.

Types of targeted therapy: Depending on the mode of action and the specific “targets”, various agents can be classified in sub-categories. Some of the important ones are Monoclonal antibodies, Tyrosine Kinase Inhibitors, Proteasome inhibitors, Cyclin-Dependent Kinase (CDK) Inhibitors, Raf Kinase Inhibitors, Antiangiogenic agents, Matrix Metalloproteinase Inhibitors Farnesyltransferase Inhibitors, Protein Kinase C Inhibitors, Glutathion-S-transferase Inhibitors, Histone Deacetylase Inhibitors, Cox-2 inhibitors, Antisense

Technology and Gene Therapy. Important targeted therapy molecules which are currently approved for human use are listed in Table 1.

Table 1

Important targeted therapy drugs approved for human use

Name	Target	Indication
Rituximab	CD20	Non-Hodgkin lymphoma
Trastuzumab	HER/neu	Breast cancer
Gemtuzumab ozogamicin	CD33	Acute myeloid leukemia
Alemtuzumab	CD52	Chronic lymphocytic leukemia
Ibritumomab tiuxetan	CD20	Non-Hodgkin lymphoma
Bevacizumab	VEGF	Colorectal cancer
Bortezomib	Proteasome	Multiple myeloma
Cetuximab	EGF receptor	Colorectal cancer
Gefitinib	Tyrosine kinase	Non small cell lung cancer
Imatinib	Tyrosine kinase	Chronic myeloid leukemia
Tositumomab	CD20	Non-Hodgkin lymphoma
Sorafenib	Serine/threonine and receptor tyrosine kinases	Advanced renal cell carcinoma
Sunitinib maleate	Multiple kinases receptors	Gastrointestinal stromal tumour, advanced renal cell carcinoma

According to their mechanism of action, targeted therapy molecules can be classified into following categories:

1. **Monoclonal antibodies:** It was G. Kohler and C. Milstein [1] in 1975 who developed the hybridoma technology which provides monoclonal antibodies (MAbs) capable of highly specific associations with their target antigens. They produce hybrid cell lines by fusing antibody-producing cells from immunized mice with antibody-secreting mouse cells derived from myeloma and spleen cells. These hybrid cell lines can be cloned and cultured indefinitely. Because of this technology it was possible to produce large amount of individual antibodies. In

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1984, both scientists were honoured with the Nobel Prize for their work. MAbs were instantly applicable in diagnosis. However therapeutic use was fought with problems. When these antibodies, produce in mice cell lines, were injected in human they were quickly recognized as foreign proteins and rejected by auto-antibodies, some times even causing serious allergic reactions. It took time for such problems to be tackled. Now it is possible to produce chimeric and humanized mAbs that are therapeutically effective.

MAbs mediate their action via variety of mechanisms, and some pathways that are still poorly understood. Some of the known mechanisms include Antibody dependent cellular cytotoxicity (ADCC), Complement-dependent cytotoxicity(CDC), Signal transduction changes, Immunomodulation [2,3] and delivery of cytotoxic payloads (as transport vehicle for other agents) [4].

2. **Tyrosine Kinase Inhibitors:** Tyrosine kinases are group of enzymes which are responsible for cellular proliferation, survival, differentiation, function, and motility. After successful invention of imatinib, these are considered as excellent targets for the development of anti cancer therapy. Some of the clinically important types of tyrosine kinases are epidermal growth factor receptor, platelet derived growth factor receptor, vascular endothelial growth factor receptor, and cytosolic Abelson tyrosine kinase.
Examples-Imatinib Mesylate (STI571), Gefitinib (ZD1839), Erlotinib (OSI-774), CI-1033, EKB-569, etc.
3. **Proteasome inhibitors:** Proteasome is an enzyme complex that is responsible for the degradation of intracellular proteins, including several involved in cell cycle control and the regulation of apoptosis. Bortezomib is the most important proteasome inhibitor, which is used for the treatment of multiple myeloma. Trials are undergoing for its possible role in leukemia, Waldenstrom Macroglobulinemia, malignant lymphoma, and several solid tumour types. Example – bortezomib (Velcade).
4. **Cyclin-Dependent Kinase (CDK) Inhibitors:** CDK inhibitors are able to produce cell cycle arrest and induce apoptosis. Example- flavopiridol (HMR1275) is found to be active in colon cancers, NSCLC and ovarian cancer either as a single agent or in combination with chemotherapeutic agents.
5. **Raf Kinase Inhibitors:** Raf kinase inhibitors interfere with mechanism of production of Ras. Example- Sorafenib (BAY 43-9006) found to be effective in renal cell carcinoma
6. **Antiangiogenic agents:** Initially tumour growth depends upon its host for its blood supply. But for growing beyond a certain size, angiogenesis is required. Many local as well genetic alterations are responsible for angiogenesis by upregulating vascular endothelial growth factor (VEGF) or downregulating thrombospondin-1 (TSP-1; a naturally occurring angiogenesis inhibitor). Agents that inhibit the angiogenesis process may play important role in tumour regression and kill.
 - a. **VEGF inhibitors:** Various VEGF inhibitors that are in use or under clinical trials are SU5416 (Semaxanib) for various advanced malignancies and ZD6474 for NSCLC.
 - b. **Anti-VEGF and VEGFR Antibodies:** Bevacizumab is the most important agent in this group. It is approved for the treatment of colon cancer and is under trial for other malignancies like gastric and lung cancer.
7. **Matrix Metalloproteinase Inhibitors:** Matrix Metalloproteinases(MMP) are responsible for degradation of the basement membrane and the extracellular matrix, which help in tumour growth, invasion, and spread. Important MMP inhibitors which are under trials are Marimastat (recurrent GBM and anaplastic gliomas), Metastat (recurrent high-grade gliomas) & Prinomastat (NSCLC & GBM).
8. **Farnesyl Transferase Inhibitors:** Farnesyl transferase inhibitors (FTIs), act through competitive inhibition of farnesyl protein transferase. Farnesyl transferase is the critical enzyme responsible for the production of intracellular substrate proteins such as Ras. These agents are found to have an important role in the treatment of myeloid malignancies. Example- Tipifarnib (R115777)
9. **Protein Kinase C Inhibitors:** Protein kinase C (PKC) family of enzymes mediate signals from the cell surface to the nucleus and play a key role in cellular signalling pathways produced by variety of extracellular stimuli, like growth factors, hormones, and neurotransmitters. One of the important PKC inhibitor is Enzastaurin which is under phase-II trial for therapy of NSCLC.
10. **Glutathion-S-transferase Inhibition:** Glutathion-S-transferase (GST) P1-1 play role in chemotherapy resistance and may be over expressed in many malignancies. GST inhibitors preferentially targets chemotherapy resistant cells. One example of these

agents is TLK286 which showed activity in NSCLC [5] and now under phase- III trial.

11. **Histone Deacetylase Inhibitors:** Histone deacetylase (HDAC) inhibitors act as antiproliferative agents by upregulation of tumour suppressor genes. Various trials [6] are ongoing to find out their activity in solid and haematological malignancies. It is also found to modulate effect of radiation response to tumour [7].
12. **Retinoids:** Alteration of retinoid X receptors (RXR) expression is found in various solid and lymphoid tumours. RXR is responsible for regulation of proliferation and differentiation. Example of X receptor-specific retinoid with anti-tumour activity is Bexarotene which is approved for cutaneous T cell lymphoma. In one study it showed an overall response rate of 44.4% when used as a second line therapy [8].
13. **COX-2 Inhibitors:** Cyclooxygenase-2 (COX-2), is a the rate-limiting enzyme of the prostaglandin cascade. Its activity is related to mutagenesis, mitogenesis, angiogenesis, and deregulation of apoptosis of tumour cells. COX-2 inhibitors are found to be active as preventive agents, in combination with chemotherapy agents and also as radiosensitizers[9]. Unfortunately its potential for causing death due to cardiotoxicity is a major setback.
14. **Antisense Technology:** Various Antisense oligonucleotides are under evaluation for their role as antineoplastic agents in a series of clinical trials. G3139, a phosphorothioate oligomer which targets the initiation codon region of the bcl-2 mRNA is under evaluation for advanced melanoma, myeloma, and chronic lymphocytic leukemia (CLL).
15. **Gene Therapy:** Gene therapy is another prospective cancer targeted therapy. Clinical trials are ongoing or have been planned in carcinoma prostate, carcinoma breast, glioblastoma multiforme, malignant melanoma & NSCLC. The main technical problem faced in gene therapy is to find a safe and efficient vector technology for gene transfer. In NSCLC intramural injection of recombinant adenovirus expressing wild type p53 produced response rate of 8% [10]. Recently, a gene therapy system has received marketing approval in China – the first such approval globally.

Clinical Application of specific Targeted Therapy for Hematological Malignancies & Solid Tumours

Rituximab: Rituximab was approved in 1997 for treatment of non-Hodgkin lymphoma expressing CD20

surface receptor. It induces apoptosis, antibody-dependent cell cytotoxicity, and complement-mediated cytotoxicity [11]. The update results of GELA trial [12] showed a 5-year event free survival reported of 47.6% in R-CHOP arm versus 28% in CHOP arm (P values = 0.00002). It further showed benefit in progression free survival, disease-free survival, and overall survival in favour of R-CHOP arm with P values of 0.00001, 0.00031, and 0.0073, respectively. Rituximab has also been found to be beneficial in other haematological disorders like chronic lymphocytic leukaemia, multiple myeloma, hairy cell leukaemia and Waldenstrom Macroglobulinemia.

Gemtuzumab ozogamicin: Gemtuzumab ozogamicin was approved in 2000 for treatment of Acute Myeloid Leukemia. It targets CD33 surface receptor expressed by 90% of myeloid leukaemic blasts but absent on normal cells. Gemtuzumab linked with a molecule calicheamicin, which is a potent cytotoxic antibiotic, can augment inhibition of DNA synthesis and induction of apoptosis. In spite of its potential myelosuppressive and hepatic toxicity, in relapse AML it showed 33% overall response rate [13]. Results of phase 2 studies may be able to answer questions regarding its role as combination with other chemotherapeutic agents.

Alemtuzumab: It was approved in 2001 for treatment of B-cell chronic lymphocytic leukaemia expressing CD52 surface receptor. In one trial, in 93 fludarabine-refractory patients, it showed overall objective response of 33%, with 2% complete remission and 31% partial remission. The median time to progression for responders was 9.5 months [14]. It can also be used as front line therapy, where response rates are expected to be higher as compare to its use in refractory patients [15].

Y⁹⁰-Ibritumomab Tiuxetan: In 2002, this became the first radioconjugated antibody approved for treatment. It is found active in relapsed or refractory low grade and follicular B-cell non-Hodgkin lymphoma and also active in rituximab refractory disease. It showed a 73% to 83% overall response rate in various published studies and providing new hope in refractory patients [16].

Tositumomab: A radiolabeled anti-CD20 murine monoclonal antibody, this was approved in 2003 for treatment of relapsed and refractory follicular/low-grade and transformed non-Hodgkin lymphoma. In a combined report of five clinical trials, the response rate was 47% to 68%; complete response rates ranged from 20% to 38%. With a median follow-up of 5.3 years, the 5-year progression-free survival reported was 17% [17].

Imatinib Mesylate: This is now established as a drug of choice for CML patients who are unable to undergo allogeneic stem cell transplant. It is also approved for

treatment of relapsed and metastatic gastrointestinal stromal tumours. It inhibits protein tyrosine kinases, bcr-abl abnormal fusion protein in CML and c-kit (CD117) in gastrointestinal stromal tumours. The only concern seems to be the emergence of imatinib resistance – usually caused by mutations [18].

Bortezomib: Bortezomib, a proteasome inhibitor, approved in 2003 for use in multiple myeloma for patients who had received at least two prior therapies and had demonstrated progression of disease on their last therapy. It is now used in both refractory setting and denovo patients usually before autologous stem cell transplant. A comparative phase III trial of bortezomib versus high dose dexamethasone showed statistically significant difference in time to disease progression and survival benefit - in favour of patients who received bortezomib [19].

Trastuzumab: Trastuzumab, a humanized monoclonal antibody, inhibits cell growth by binding to HER2 protein tyrosine kinase receptor present in breast tumour cells. In a phase 3 trial the response rate in combination therapy was found to be 50% versus 32% for chemotherapy alone [20]. After establishing its role in the metastatic setting, trastuzumab actively is now also proven for adjuvant therapy in early breast cancer.

Gefitinib: Gefitinib received approval in 2003 for its use as a third-line treatment for non-small cell lung cancer. Two large phase-II trials, IDEALs 1 and 2, were conducted in patients previously treated with one or more chemotherapy regimens [21,22] These showed response rates in the range of 9 to 19%, comparing favourably with 7% for docetaxel. It was also observed that a 250 mg dose was better tolerated than 500 mg, and at even lower dose more than 40% of patients enjoyed symptomatic improvement. Another trial (ISEL) showed interesting pharmacogenomic results. Patients of Asian origin demonstrated a significantly higher response rate as compared to Caucasians [23; personal communication Dr Alex Chang]. Indian patients also showed good benefit, even among males and smokers – groups that were initially thought to be refractory to gefitinib (unpublished data).

Gefitinib has also been tried in combination with docetaxel, with promising early results. Disease control (partial response plus stable disease) was seen in 63% of those receiving gefitinib combined with docetaxel compared with 32% for docetaxel alone [24]. Gefitinib may also have a role in recurrent or metastatic head and neck cancer [25] as well as with chemoradiotherapy [26]. High complete response (CR) rates (88%) and lack of synergistic toxicity with chemoradiotherapy show that this is a promising approach.

Cetuximab : This chimeric human and murine monoclonal antibody that competitively binds to the extracellular domain of EGFR is approved for the treatment of advanced colorectal cancer (in combination with chemotherapy) and has also shown activity in squamous cell carcinoma of head and neck. In advanced colorectal cancer, single-agent cetuximab has produced a partial response in 9% to 11.6% of patients and stable disease in 21.6% to 36.8%. In irinotecan-resistant disease, the combination of cetuximab and irinotecan has resulted in partial responses in 17% to 22.9% of patients and stable disease in 31% to 32.6% [27].

In squamous cell carcinoma of head and neck it is used in recurrent/metastatic setting. In a recently published trial its concurrent use with radiation showed a median duration of locoregional control of 24.4 months among patients treated with cetuximab plus radiotherapy and 14.9 months among those given radiotherapy alone which is statistically significant [28].

Bevacizumab: Bevacizumab is a recombinant humanized mAb, approved as a first-line therapy for treating metastatic colorectal cancer. In a phase III study irinotecan, 5-fluorouracil, leucovorin (IFL) plus bevacizumab (5 mg/kg every 2 weeks) was compared with IFL plus placebo [29]. The median duration of overall survival was found 20.3 months for those in the bevacizumab group and 15.6 months in the placebo group ($P < .001$).

Sorafenib: Sorafenib tosylate was approved in December 2005 for use in advanced renal cell carcinoma. It is an multikinase inhibitor and able to decrease tumour growth and angiogenesis. Its approval is based on a phase III trial [30] which showing that treatment with sorafenib doubled median progression-free survival (PFS) relative to placebo.

Sunitinib maleate: In January 2006, sunitinib maleate was approved for treatment of gastrointestinal stromal tumour (GIST) after disease imatinib mesylate failure as well as for the treatment of metastatic renal cell carcinoma. It is also a multikinase inhibitor targeting several receptor tyrosine kinases.

Conclusion

The cancer cell is a perpetual teacher. Just as conventional chemotherapy was reaching its limits, we now have additional information that leads to a newer option - Targeted therapy. The potential benefits to the patients are so enormous that most major multinational pharmaceutical pipelines are chockablock with such molecules and several exciting ones are already into phase III studies. Efficacy of molecules used in targeted therapy needs to be evaluated differently. The benefit to patients usually does not occur with dramatic tumour

shrinkage rather it is with respect to overall survival and symptom control. Also the therapeutic window can be much larger than with conventional chemotherapeutic drugs.

Conflicts of Interest

None identified

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