Clinical Classification of Targeted Agents Used for Anticancer Treatment

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The introduction of targeted agents has resulted in a breakthrough in advanced cancer treatment. We propose a new classification for these agents to evaluate them in appropriate clinical trials according to agent class. Class I agents that inhibit driver oncogene activities result in massive and rapid tumor shrinkage, with response rates as high as 70% when administered to patients with appropriate targets. These agents can be evaluated in single-arm phase II trials with response rate as the primary endpoint. Class II agents inhibit one oncogene that is partially responsible for accelerating tumor cell proliferation. Their clinical features include synergism with cytotoxic agents and moderate single-agent activity, as shown by response rates of between 10% and 30%. Randomized phase II trials in patients with over-expressed targets are appropriate for the evaluation of these agents. Class III agents inhibit proliferation regulators that are not always oncogenic. Their clinical activity is unique, as they confer a survival benefit on patients with a minimum tumor shrinkage effect. Class IV agents target environmental molecules that act on normal cells surrounding tumor cells, such as the endothelial cells that form vessels. Placebo-controlled randomized phase II trials are required to identify the clinical activities of both class III and IV agents. Class V agents act by enhancing anti-tumor immunity. Immune-related response criteria should aid the evaluation of these agents. We believe that this classification for targeted agents should facilitate their further clinical development.

Keywords: clinical trial design; driver mutations; targeted agents; oncogene addiction; targeted cancer therapy

Introduction

Cancer is a major health problem worldwide. About 12.7 million people were diagnosed with cancer and 7.6 million died of this disease globally in the year 2008 (Jemal et al. 2011). During the last century, many cytotoxic anticancer agents were developed, but the survival benefits in patients with distant metastases have been limited. A phase III trial for patients with advanced non-Hodgkin’s lymphoma demonstrated that dose-intensive chemotherapy did not show any survival benefit over conventional chemotherapy, despite the initial promise demonstrated in phase II trials (Fisher et al. 1993). A breakthrough in the prognosis of non-Hodgkin’s lymphoma was achieved by introducing rituximab, a monoclonal antibody against the cluster of differentiation (CD) 20, which is expressed on the surface of B-cell lymphomas (Coiffier et al. 2002; Habermann et al. 2006; Coiffier et al. 2010). Similarly, the introduction of tyrosine kinase inhibitors improved the efficacy of several cancer treatments in the 2000s.

These targeted agents were initially considered to be highly effective against cancers without causing severe toxicity in normal tissues. However, fatal drug-induced lung injury was observed during the clinical development of gefitinib, an epidermal growth factor receptor (EGFR) inhibitor (Inoue et al. 2003). In addition, the efficacy of gefitinib for the treatment of advanced non-small cell lung cancer was difficult to establish in randomized trials. Two large randomized phase III trials of platinum-doublet chemotherapy with or without gefitinib involving more than 1000 advanced non-small cell lung cancer patients failed to demonstrate a synergistic effect of gefitinib, compared with standard chemotherapy (Giaccone et al. 2004; Herbst et al. 2004). Another phase III trial of gefitinib monotherapy versus a placebo in nearly 1700 patients showed no survival benefit of gefitinib over the placebo in the second-line setting (Thatcher et al. 2005).

The situation took a turn for the better once activating EGFR mutations were identified as the real target of gefitinib in 2004 (Lynch et al. 2004; Paez et al. 2004). Two small, but crucial randomized phase III trials in patients with EGFR mutation-positive advanced non-small cell lung
cancer showed that the progression-free survival, the primary endpoint of these trials, was much better for gefitinib than for platinum-based chemotherapy (Maemondo et al. 2010; Mitsudomi et al. 2010). Therefore, the clinical development of novel targeted agents for cancer therapy is likely to be impeded without appropriate consideration of the clinical trial design (Saijo 2004).

**Classification of targeted agents for clinical development**

Targeted agents that inhibit specific molecules implicated in tumor cell growth have been classified according to (1) the site of action (tumor-specific and tumor-environment-specific), (2) the mechanism of action (the target pathways associated with tumor growth and survival), and (3) pharmaceutical formulations (small molecular compounds and macromolecules such as antibodies) (Saijo 2004). These classifications, however, are derived from the viewpoint of pharmaceutical preclinical development.

From a general survey of clinical trials of targeted agents, we noticed that most of these agents could be categorized into 1 of 5 classes with a few exceptions (Table 1). One of the distinct clinical features of class I agents is the massive and rapid tumor shrinkage that occurs when the agent is administered to patients who have the appropriate target (Fig. 1). For example, the response rate of gefitinib monotherapy in patients with EGFR mutation-positive lung adenocarcinoma has reached as high as 70% (Maemondo et al. 2010). The mechanism of this clinical observation is well explained by the concept of oncogene addiction and its disruption. Oncogene addiction describes the acquired dependence of tumor cells on a single activated oncogene for their sustained proliferation and survival; without the oncogenic activity, the tumor cells undergo rapid apoptosis (Sharma and Settleman 2007).

Several phase III trials involving the combination of a class I agent and standard cytotoxic chemotherapy have failed to show synergistic effects on survival, although target selection was not performed for the patients enrolled in these trials (Giaccone et al. 2004; Herbst et al. 2004). The study population for clinical trials must be limited to patients who have tumors with the drug target, typically a mutated driver oncogene. Cancers arising from different organs may share the same target gene, and study populations could be defined not by the site of the cancer, but by the target itself (Mano 2012). Because this type of agent has an obvious tumor shrinkage effect, the clinical activity can be evaluated in single-arm phase II trials in previously treated patients, using the response rate as the primary endpoint. Whether placebo-controlled phase III trials are needed is controversial (Sharma and Schilsky 2012). Some agents, including imatinib for gastrointestinal stromal tumors and crizotinib for non-small cell lung cancer with an anaplastic lymphoma kinase-fusion protein, have been approved by the U.S. Food and Drug Administration without undergoing phase III trials (Dagher et al. 2002; Scagliotti et al. 2012).

Class II agents inhibit one oncogene that is partially responsible for accelerating tumor cell proliferation and survival (Fig. 1). The clinical features of class II agents include moderate monotherapy activity, with response rates of between 10%-30%, and synergism with cytotoxic agents. One of the best examples is trastuzumab, a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2) oncoprotein, which is overexpressed in 20%-30% of human breast cancers. Trastuzumab acts either by enhancing receptor downregulation, by inhibiting extracellular domain cleavage and the generation of

<table>
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<tr>
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<td>II</td>
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<td>Trastuzumab to MBC; cetuximab to CRC; rituximab to B-cell lymphoma</td>
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<tr>
<td>III</td>
<td>Proliferation regulators</td>
<td>Signaling inhibition</td>
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<tr>
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ADCC, Antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CML, chronic myelogenous leukemia; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; NSCLC, Non-Small Cell Lung Cancer; RCC, renal cell carcinoma.
phosphorylated p95, by blocking receptor dimerization, or by recruiting immune system processes such as antibody-dependent cellular cytotoxicity (Hudis 2007). The rapid and successful clinical development of this agent has been attributed to its early clinical trials, which included only patients with HER2-overexpressing metastatic breast cancer with overexpression levels evaluated as 2+ or 3+ using immunohistochemistry (Cobleigh et al. 1999; Vogel et al. 2002). These phase II trials showed that when used as a single agent, trastuzumab yielded a response rate of 18%-35% in patients with HER2-overexpressing tumors at the 3+ level, while the response rate was ≤ 6% in patients with HER2-overexpressing tumors at the 2+ level. In addition, long periods (> 6 months) of disease stabilization were observed in a substantial number of patients who did not achieve an objective response. Furthermore, trastuzumab demonstrated a synergistic effect on the response rate and survival benefit when used in combination with conventional chemotherapy (Slamon et al. 2001).

Several discussions of trial designs are required to evaluate class II agents. The success of clinical trials largely depends on whether the study patient population can be defined clearly according to the target status. In contrast to class I agents, the response rate of class II agents is moderate and varied; therefore, single-arm phase II trials with a threshold response rate may fail to detect the clinical activity of a new agent. Randomized phase II trials are required in many cases to identify clinical activity.

Class III agents target proliferation regulators that are involved in cell proliferation but that are not always oncogenic (Fig. 1). One of the distinct clinical features of class III agents is their unique single agent activity, providing an obvious survival benefit but exerting a minimum tumor shrinkage effect. One of the best examples is sorafenib, a multikinase inhibitor of Ras/Raf, vascular endothelial growth factor receptor-1 to 3, platelet-derived growth factor receptor-b, c-kit, and Flt-3. A phase III trial of sorafenib versus a placebo in patients with advanced renal cell carcinoma resistant to standard therapy showed that the median overall survival time was significantly prolonged in the sorafenib arm (19.3 months versus 15.9 months; hazard ratio, 0.77; 95% confidence interval, 0.63-0.95) with a
response rate as low as 10% (Escudier et al. 2007). Similarly, sorafenib had a significant survival benefit over a placebo in patients with advanced hepatocellular carcinoma, with a response rate of only 2% (Llovet et al. 2008). Thus, randomized phase II trials with a placebo-controlled arm are required to identify the clinical activity of class III agents. Compared with class II agents, it may be difficult to define patient populations for clinical trials of class III agents according to the target status, partly because these agents have multiple action sites. To enrich the target population, randomized discontinuation trials may be suitable (Ratn et al. 2006). No combinations of class III agents and cytotoxic agents have been evaluated in phase III trials because no cytotoxic agents have shown activity against renal cell or hepatocellular carcinoma.

Class IV agents target environmental molecules that support tumor growth such as regulators of angiogenesis (Fig. 1). An example of this class of agents is bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor. This agent showed a significant anti-tumor effect in patients with advanced colorectal cancer, non-small cell lung cancer, and metastatic breast cancer when combined with standard cytotoxic chemotherapy, but was not effective as a monotherapy (Kazazi-Hyseni et al. 2010). Although its mechanisms of action have not been fully defined and may vary among different tumor types, one of the potent mechanisms of bevacizumab is the normalization of the tumor vasculature and the improvement of chemotherapy delivery to the tumor (Ellis and Hicklin 2008). This mechanism explains the clinical characteristics of bevacizumab and its antitumor activity against a broad spectrum of tumor types. Extensive studies have failed to identify patients who are likely to receive the maximum benefit from bevacizumab-containing chemotherapy.

Class V agents regulate immunomodulatory molecules so as to enhance anti-tumor immunity (Fig. 1). Ipilimumab is a fully human monoclonal antibody that binds to cytotoxic T lymphocyte antigen 4 (CTLA-4). Because CTLA-4 provokes the inhibitory signal of cytotoxic T cell activity, blocking this molecule results in T cell activation against tumors. A phase III trial of dacarbazine versus dacarbazine plus ipilimumab in treatment-naive patients with metastatic melanoma showed that overall survival improved with ipilimumab (9.1 versus 11.2 months, respectively $P < 0.001$) (Robert et al. 2011). The clinical features of class V agents include variable patterns of response and durable objective responses and stable disease in a small percentage of patients. Thus, immune-related response criteria could be helpful for evaluating these agents (Wolchok et al. 2009).

The classification presented here is tentative, and its revision may be required once larger bodies of evidence and knowledge on cancer biology have been accumulated. Class I and II agents are highly distinct from each other with regard to their response rate, which we think can be explained by the role of the target oncogene in tumor cells, that is, whether the tumor cells are entirely addicted to the oncogene or not. The distinction in the response rates of the two classes, however, may be due to suboptimal target inhibition by the class II agents. In this case, the targets of class I and II agents are essentially not different.

Strategies to overcome resistance to class I agents can be illustrated systematically, since their mechanisms of resistance are known. Secondary mutations in the target gene are a common mechanism of resistance to class I agents, which have been identified in a large proportion of resistant tumors. Another mechanism of resistance is the bypass of the original oncogene signaling by the activation of other oncogenes (compensatory signaling). Class III agents that have multiple target sites may be useful for suppressing the occurrence of this type of resistance. Resistance to class IV agents seems unlikely to be acquired easily, since the targets of these agents are located within normal cells that do not develop spontaneous mutations as frequently as tumor cells, although physiological adaptation can be provoked without mutations.

In conclusion, we have proposed a classification for targeted agents for anticancer treatment according to their clinical features to facilitate the clinical development of these new types of agents.

Conflict of Interest

The authors have no conflict of interest to declare.

References


