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THE ROLE OF TARGETED THERAPY IN CANCER TREATMENT

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INTRODUCTION

Since the mid-twentieth century, cytotoxicity has been the basic mechanism underlying effective chemotherapy. Since malignant cells are capable of uncontrolled proliferation, early pharmacologic therapies centered on preventing cell replication by causing DNA damage and microtubule inhibition. This approach exploits processes that are ubiquitous among the myriad human cancers, and it is therefore applicable to almost any malignancy.

Recent advances, however, have elucidated more detail about the pathogenesis of malignant transformation, and the search for novel therapies has been directed toward specific metabolic pathways or genetic mutations. Not surprisingly, as our understanding of the molecular biology of tumor growth has translated into improved therapies, our ability to predict the likely response to treatment and the overall prognosis in certain malignancies has been enhanced. Here we provide an overview of the current clinical implications of molecular-based therapeutics.

CYTOTOXIC CHEMOTHERAPY

First it must be stressed that despite the above-mentioned technological developments and the identification of potential molecular targets, the first line of therapy for many malignancies remains cytotoxic chemotherapy focused on inhibiting cell division by attacking DNA replication and microtubule organization. Currently used agents that damage DNA include platinoids, alkylating agents, structural nucleotide analogs, and topoisomerase inhibitors. Microtubule inhibitors, such as taxanes, epothilones, and vinca alkaloids, provide an alternative and complimentary therapeutic target. Either alone or in combination,

these drugs have been the mainstay of treatment in medical oncology.

Unfortunately, since these drugs target cell division, a universal process, their dose is usually limited by toxicity to tissues with rapid turnover such as bone marrow and the lining of the GI tract. Also problematic are class-specific toxicities, such as neurotoxicity from platinoids.

TARGETED THERAPY

Targeted therapy differs markedly in its approach. In their landmark paper, “The Hallmarks of Cancer,” Hanahan and Weinberg describe six capabilities that cells acquire when they transform from normalcy into malignancy. Through a sequence of several mutations, cancer cells:¹

- acquire self-sufficiency in growth signals;
- are insensitive to growth-inhibitory signals;
- evade programmed cell death;
- have limitless replicative potential;
- sustain angiogenesis;
- have the capacity for tissue invasion and metastasis.

With many of these hallmarks in mind, research has focused on identifying molecular targets at each step that are specific to malignant cells, thus avoiding dose-limiting toxicity. Furthermore, elucidation of the pathways involved in tumorigenesis, and the genes involved, has facilitated the identification of mutations that confer a specific prognosis or are associated with a particular response to a given therapy. Ultimately, targeted therapy promises personalized treatment with better prediction of outcomes for each patients’ tumor subtype.

The archetype for such “rationally designed” therapeutics was imatinib, an oral tyrosine kinase inhibitor that specifically targeted an aberrant fusion protein that is pathognomonic for chronic myelogenous leukemia. While its discovery certainly allowed the development of a targeted therapy, its success is likely the exception rather than the rule. First, chromosomal analyses of patients with CML led to the identification of a reciprocal translocation between chromosomes 9 and 22 that creates a truncated chromosome 22 known as the Philadelphia chromosome. This leads to the generation of a novel fusion gene, BCR-ABL, which encodes a constitutively active tyrosine kinase that is specific to leukemic cells—an ideal therapeutic target. In a Phase I dose-escalation study of imatinib (STI571), 53 out of 54 patients demonstrated complete hematologic response and 29 of 54 demonstrated cytogenetic responses.² This outcome is undoubtedly impressive, but it does not guarantee that similar results can be achieved in other malignancies. Table 1 includes key genetic targets in the treatment of some of the most common malignancies.

BREAST CANCER

For women, the lifetime probability of developing breast cancer is 1 in 6, and approximately 40,000 women will die this year from the disease.³ Molecular medicine has impacted the prognosis and treatment of breast cancer patients in many ways. First-line therapy for individual patients is now determined by estrogen and progesterone receptor

positivity as well as over-expression of the HER2 gene. For pre-menopausal women with tumors that are Estrogen Receptor positive, adjuvant treatment with tamoxifen can decrease yearly breast cancer mortality by one-third.⁴ (Tamoxifen binds to estrogen receptors, but it has multiple other effects that can seem contradictory.)

Additionally, 25-30% of human breast cancers over-express the HER2 gene, which in the past was associated with a much poorer prognosis and decreased overall survival. However, this changed dramatically when the monoclonal antibody trastuzumab was developed to bind and inhibit the HER2 cell-surface receptor. In a randomized clinical trial using trastuzumab as first-line therapy in women with metastatic breast cancer who refused cytotoxic chemotherapy, trastuzumab achieved an objective response rate of 26%. Further, using retrospective fluorescent in-situ hybridization analyses for evidence of HER2 gene amplification, patients with HER2 over-expression had a 34% response rate, similar to the response rate seen with conventional chemotherapy but with less toxicity. In contrast, patients without gene amplification only demonstrated a 7% response rate.⁵ This represents a fundamental difference from traditional cytotoxic chemotherapy, which generally achieves some efficacy in all patients.

In addition to generating therapeutic targets, understanding the molecular basis of a patients’ breast tumor can aid in clinical decision-making. A genetic signature marketed as Oncotype DX generates a recurrence score based on 21 genes. The score

Table 1. Therapeutic Molecular Targets in Selected Malignancies

Malignancy	Mutation	Drug	Efficacy
Breast	Hormone Receptor (ER/PR)	Tamoxifen	↓ annual mortality by 31%
	HER2/NEU	Trastuzumab	Objective response rate = 34%
Colon	Vascular Endothelial Growth Factor (VEGF)	Bevacizumab	Median survival 20.3 mo v 15.6 mo
	Epidermal Growth Factor Receptor (EGFR)	Cetuximab	Overall survival 6.1 mo v 4.6 mo
Lung	Epidermal Growth Factor Receptor (EGFR)	Gefitinib	PFS1 10.8 mo vs. 5.4 mo
	Anaplastic Lymphoma Kinase (ALK)	Crizotinib	1-yr survival 70% vs. 44%
Melanoma	Cytotoxic T-Lymphocyte Associated Antigen 4 (CTLA-4)	Ipilimumab	Overall survival 10.1 mo vs. 6.4 mo
	Serine Threonine Protein Kinase (BRAF)	Vemurafenib	6-mo overall survival 84% vs 64%

Table 2. Gene Signatures for Prognosis and Treatment Decisions

Signature	Malignancy	Types of Genes	Clinical Utility
Oncotype DX	Breast	Ki67, STK15, Survivin or BIRC5, CCNB1 or Cyclin B1, MYBL2, GRB7, HER2, ER, PGR, BCL2, SCUBE2, MMP11 or stromelysin 3, CTSL2 or cathepsin L2, GSTM1, CD68, and BAG1, and 5 reference genes	predicts recurrence risk and benefit from adjuvant chemotherapy
MammaPrint	Colon	70-gene signature - cell cycle, invasion, metastasis, angiogenesis	prognostic in women with node-negative cancer; high negative predictive value for distant recurrence after adjuvant treatment
Oncotype DX	Lung	7 recurrence genes (BGN, MYC, FAP, GADD45B, INHBA, MK167, and MYBL2), 6 treatment response genes, 5 reference genes (ATP5E, GPX1, PGK1, VDAC2, and UBB)	prognostic value of recurrence score but treatment score is not predictive of chemotherapy benefit
(unnamed)	Melanoma	15 genes - ATP1B1, TRIM14, FAM64A, FOSL2, HEXIM1, MB, L1CAM, UMPS, EDN3, STMN2, MYT1L, IKBKAP, MLANA, MDM2, ZNF236	prognostic marker and predictive of chemotherapy benefit in high-risk group

not only predicts disease recurrence, but also predicts benefit from adjuvant chemotherapy for breast cancer patients who are lymph node negative and hormone receptor positive. The assay includes the estrogen receptor as well as HER2 and additional markers of cell proliferation. In a retrospective study of patients treated with tamoxifen alone or tamoxifen and chemotherapy, the Oncotype DX recurrence score predicted response to chemotherapy.⁶ Patients with a high recurrence score (≥ 31) derived substantial benefit from adjuvant chemotherapy, RR 0.26 (95% CI 0.13-0.53), whereas patients with a low recurrence score (< 18) derived minimal to no benefit from adjuvant chemotherapy, RR 1.31 (95% CI 0.46-3.78). However, for patients with intermediate recurrence scores, the potential benefit from adjuvant chemotherapy remains obscure.⁶ A second genetic signature, MammaPrint, uses 70 genes including those regulating cell cycle, invasion, metastasis, and angiogenesis to predict poor prognosis. The signature consistently demonstrated a high negative predictive value, correctly identifying 100% of women at low risk for developing distant metastases in one study, enabling clinicians to spare patients from unnecessary adjuvant chemotherapy.^{7,8} Table 2 describes the available gene signatures and their composition.

Finally, molecular analyses have led to the identification of two breast cancer susceptibility genes, BRCA 1 and BRCA 2, which carry a lifetime risk of invasive breast cancer of 55-85% as well as a lifetime risk of ovarian cancer of 15-65%. In patients with an extensive family history of breast cancer, particularly in patients of Ashkenazi Jewish descent, clinicians should suspect germline mutations in BRCA 1 or 2. Such patients benefit from bilateral prophylactic mastectomy and have an estimated annual incidence of breast cancer of 2.5% with regular follow-up alone.⁹

COLON CANCER

Colon cancer is the third most common cancer in men and the second most common in women; more than 100,000 new cases are diagnosed each year, with more than 50,000 deaths.³ Medical therapy for metastatic colon cancer has made impressive advances over the past decade with targeted therapies playing an increasingly important role.

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). As discussed previously, angiogenesis is critically important for tumor growth. In a randomized trial of 813 patients with previously-untreated metastatic colorectal cancer, the median survival was 20.3 months in the group

receiving bevacizumab plus chemotherapy versus 15.6 months in the group receiving chemotherapy alone.¹⁰

Immunohistochemical studies of tumor specimens recently led to the identification of tumors expressing epidermal growth factor receptors (EGFR), which offered another oncogenic mediator for potential targeted therapy. In a trial of 572 patients with metastatic colon cancer that expressed EGFR, and who were previously treated with chemotherapy, cetuximab (a chimeric monoclonal antibody that inhibits EGFR) was associated with a significant increase in overall mean survival (6.1 months vs 4.6 months) and was associated with improved quality of life based upon global health status scores.¹¹

The KRAS gene encodes a protein critical to growth factor signaling. Patients with a mutated KRAS gene who have metastatic colon cancer do not respond to EGFR inhibitors. A follow-up study of wild-type (normal) KRAS was found to be a predictive biomarker for response to treatment with cetuximab plus a cytotoxic regimen that includes irinotecan, fluorouracil and leucovorin. Similarly, mutations of BRAF (a gene that encodes a protein important in directing cell growth) in tumor specimens conferred a poor prognosis.¹² Finally, panitumumab, a fully human anti-EGFR monoclonal antibody was evaluated in combination with chemotherapy as first-line treatment in a randomized phase III trial. The combination regimen significantly improved progression free survival (9.6 months vs. 8 months) and there was a non-significant increase in overall survival, with a similar association between wild-type KRAS and anti-EGFR activity.¹³ It is clear that the molecular characterization of a given patients' colon cancer genotype has both prognostic and therapeutic implications.

With all this in mind, recent advances have focused on the development of genetic signatures capable of predicting recurrence of disease and response to treatment. Investigators analyzed RNA expression among tumor specimens from patients with stage II and III colon cancer treated with either surgical resection alone or surgery in combination with fluorouracil and leucovorin. They ultimately identified 7 recurrence-risk genes, 6 treatment-response genes, and 5 reference genes to comprise a molecular signature. In a validation study of this multi-gene assay for prediction of disease recurrence, investigators confirmed the prognostic value of the recurrence score

(RS), but found that the treatment score (TS) was not predictive of chemotherapy benefit.¹⁴

LUNG CANCER

Lung cancer is the second most common cancer in both men and women as well as the leading cause of cancer related death. One area of active research is gene expression profiling to predict overall prognosis and response to therapy, but results have been variable thus far. A recent meta-analysis examined the predictive value of ERCC1 (DNA repair gene) expression among non small cell lung cancer (NSCLC) patients. Overall response to platinum-based chemotherapy was significantly higher in patients with low ERCC1 expression (OR 0.48, $p < 0.00001$), and median survival time was significantly prolonged (HR 0.77, $p < 0.00001$).¹⁵ Additionally, gene expression studies have attempted to identify the subset of patients with early stage NSCLC who benefit from adjuvant chemotherapy. A 15-gene signature which stratified patients into high and low risk groups found significant differences in survival (HR 15.02, $p < 0.001$). Further, an improvement in survival with chemotherapy was demonstrated for the high-risk group (HR 0.33, $p < 0.0005$) that was not seen for low-risk patients (HR 3.67, $p < 0.0133$).¹⁶

Molecular research has also led to the development of targeted treatment for NSCLC. Currently reserved for use only in metastatic disease, Gefitinib is an oral EGFR inhibitor evaluated for use as first-line treatment for EGFR-positive NSCLC. A randomized clinical control trial was designed to compare gefitinib with combination cytotoxic therapy (carboplatin-paclitaxel) in treatment-naive patients with metastatic NSCLC known to be EGFR-positive. The study was terminated early as interim analysis demonstrated that the gefitinib group had significantly longer progression-free survival (10.8 months vs. 5.4 months) and a significantly higher response rate (73.7% vs 30.7%).¹⁷ These studies illustrate both the promise and pitfalls with molecularly-targeted therapies. Such treatments have the potential to be incredibly efficacious, but for only a subset of patients. Additionally, this trial emphasizes the importance of subdividing and reclassifying tumors to avoid missing clinically relevant treatment entities. Erlotinib is another oral EGFR tyrosine kinase inhibitor with proven efficacy and tolerability as a second-line agent. A recent study, Sequential Tarceva in Unresectable NSCLC, was conducted to assess the use of erlotinib as maintenance

therapy in patients with non-progressive disease after they received 4 cycles of platinum-based doublet chemotherapy. Median progression-free survival was increased with the use of erlotinib (12.3 weeks vs 11.1 weeks, $p < 0.0001$).¹⁸

Further molecular characterization of (NSCLC) tumors has led to the identification of another therapeutic target: anaplastic lymphoma kinase. An estimated 4% of NSCLC tumors possess aberrant ALK activity secondary to a chromosomal rearrangement that forms the oncogenic EML4-ALK fusion gene.¹⁹ A phase 1 trial of an ALK-inhibitor, crizotinib, demonstrated an objective response rate of 61% and progression-free survival of 10 months in patients with advanced, ALK-positive NSCLC, compared with less than 10% and less than 3 months, respectively, in patients receiving standard chemotherapy. This trial led to the accelerated approval of crizotinib for treatment of ALK-positive advanced NSCLC. In a comparison between 30 ALK-positive patients given crizotinib as 2nd or 3rd-line treatment and a control group of 23 ALK-positive patients who were receiving any other 2nd line therapy, investigators found that median overall survival for crizotinib-treated patients had not been reached, whereas in ALK-positive, crizotinib-naïve patients, median overall survival was 6 months. Similarly, 1-year survival in the two groups was 70% vs 44%, respectively; 2-year survival was 55% vs 12%, respectively.¹⁹

MELANOMA

Malignant melanoma is an increasingly prevalent disease with a devastating prognosis in the metastatic setting. Toxicity associated with existing approved agents prompted the search for alternative treatment options. Ipilimumab, a monoclonal antibody against CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) received FDA-approval in March 2011. A phase III trial of 676 patients with metastatic melanoma had demonstrated that median overall survival of patients receiving ipilimumab—either alone or with melanoma tumor specific antigen gp100—was improved by 10.1 and 10.0 months respectively, while in those receiving gp100 alone survival improved by only 6.4 months. However, the trial did raise concern about severe adverse events, which occurred in 10-15% of those treated with ipilimumab, compared with only 3% of those treated with gp100.²⁰

Another exciting advance in the treatment of melanoma was the discovery of an activating V600E

mutation in the serine-threonine kinase B-RAF, now thought to be present in nearly 50% of patients. This discovery prompted the rational design of an oral BRAF inhibitor, vemurafenib, capable of inducing tumor regression and improving overall survival in patients harboring the V600E mutation. A multi-center phase 1 dose-escalation trial found complete or partial tumor regression in 81% of patients with the V600 mutation who were treated with vemurafenib.²¹ Subsequently, the more traditional endpoint of overall survival was studied in 675 patients with mutation-positive, metastatic melanoma previously untreated with V600E who were randomized to receive either vemurafenib or decarbazine. Six-month overall survival was 84% in the vemurafenib group, compared with 64% in the decarbazine group, with a relative reduction of 63% in the risk of death.²² Recently, a multicenter phase II trial of vemurafenib with long-term follow-up examined the durability of treatment response with a reported median overall survival of 15.9 months.²³

CONCLUSIONS

Cytotoxic chemotherapy will remain a key component of medical oncology due to its ability to decrease tumor burden and its ubiquitous efficacy across all subsets of patients. However, most researchers agree that we have optimized its success and must supplement regimens with alternative therapies. Advances in laboratory techniques have led to an enhanced understanding of the molecular basis of tumorigenesis and to the identification of numerous potential drug targets.

To exploit this wealth of information, we must fundamentally change the way we think about cancer, from a classification based on tissue of origin to one based upon acquired mutations and characteristics of malignant cells. Understanding the tumor genotype has allowed risk stratification of patients who will benefit from therapy and enhanced clinical prognostication. There are many advantages to this approach, but also a few important caveats:

- Targeted therapy promises to better differentiate malignant from normal cells, leading to more tolerable side effect profiles;
- Targeted therapies are efficacious only for subsets of patients possessing exploitable underlying mutations. As evidenced above, identification of patients with susceptible mutations has led to impressive, clinically-meaningful responses in traditionally deadly tumors;

- Targeted therapy has important implications for future clinical trials. It requires a departure from traditional randomized clinical trials examining overall survival, in favor of examining tumor regression and progression-free survival. It also requires study designs that allow pre-selection of patients based upon underlying tumor genotype;
- The ability to pre-select patients who are most

likely to respond to a given therapy should lead to an expedited approval process, as these agents are unlikely to require large-scale phase III trials to demonstrate efficacy.

Finally, targeted therapy represents a significant departure from traditional drug development and testing that has already demonstrated significant potential for cancer treatment. It is easy to foresee these drugs as a bedrock of oncology treatment in the future.

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