Cancer Etiology, Diagnosis and Treatments

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Targeted Therapy for Solid Tumors and Hematologic Malignancies

Alfonso Quintás Cardama
Don L. Gibbons ❖ *Vince Cataldo*
Editors

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ALFONSO-QUINTAS-CARDAMA
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AND
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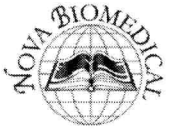
EDITORS



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Preface

Endocrine malignancies are rare tumors that are derived from endocrine cells located throughout the body. They encompass a heterogeneous group of malignancies, derived from different endocrine and neuroendocrine cells and have different clinically. The majority of endocrine neoplasms are benign, where the potential for invasion or metastasis is very low. Nevertheless, there is a group of endocrine neoplasms with malignant potential, and thus come under the management of medical oncology, often requiring systemic therapy. These include neuroendocrine tumors, anaplastic and medullary thyroid carcinomas, pheochromocytomas or paragangliomas, and adrenocortical carcinomas. While surgery continues to play a seminal role, the management of advanced endocrine neoplasia is more complex due to their rarity and heterogeneity. This book discusses the use of targeted therapy in the treatment of solid tumors and hematologic malignancies.

Chapter I- Management of cancer patients has undergone a tremendous evolution, from an absence of hope to the promise that each patient could choose from a plethora of agents the one to which their particular tumor would respond; from a single option of a life-threatening attempt at surgical excision to a combined approach of surgery, chemotherapy, targeted agents, radiation, and supportive care. This has come about as the authors understanding of cancer has evolved from a nebulous curse to an appreciation for the logical complexities that make up uncontrolled growth. And while there is still much to learn, they find themselves in an exciting era where they have the blueprint of the entire genome, an ability to test the full spectrum of genetic perturbations in a patient, and technologies to allow development of an arsenal against of such defects. Herein the authors will describe many of the classes of agents that might allow such treatments, and the technologies that let them define a patient's malignancy.

Chemotherapy originated from the observation that World War I soldiers exposed to sulfur mustard gas developed pancytopenia. Charged with discovering potential therapeutic values to such toxins, Louis Goodman and Alfred Gilman designed nitrogen mustard, collaborated with thoracic surgeon Gustav Lindskog, and achieved a partial remission in a non¬Hodgin's lymphoma patient(1). Similar trial and error experiments continued, with the only patient specific facets to therapy being observations of which cancer patients responded. As investigators gained a better understanding of the biologic processes driving cancer, advances in chemistry allowed generation of site-specific inhibitors, and technologic discoveries improved high-throughput analysis of thousands of compounds, it became

possible to generate compounds against specific pathways. With completion of the human genome project and advancements in tumor analysis methods such as gene sequencing and microarrays, evaluation of patient-specific pathways has become possible. Improvements in trial design hope to marry the advancements in therapeutic agents and patient tumor profiling to complete the promise of patient-directed therapy.

Chapter II- The primary goal of most phase I studies is to determine the correct dosing and scheduling for a drug or combination of drugs under investigation, as well as the associated pharmacokinetics. [1] The same holds true for phase I oncology studies. [2] These data are then used to design phase II and phase III studies with larger numbers of patients collecting prospective data to determine efficacy of the treatment under investigation. While the primary objectives of most phase oncology I studies are in regard to dosing and the related issue of toxicity, many patients and clinical investigators hope that a patient who enrolls in a phase oncology I study will experience a beneficial clinical effect in regard to his or her malignancy. [3-7] This is especially the case in phase I oncology patients given that most of these patients have exhausted other approved and mainstream treatments for their respective diseases. Accordingly, most phase I oncology trials also have as secondary objectives preliminary assessments of response to treatment, including response as assessed by radiographic, serologic, and tissue studies. Despite the fact that phase I trials are traditionally designed to determine drug dosing and scheduling, many patients do in fact have favorable responses to phase I study drugs. In fact, in a recent analysis of 683 patients treated on 24 consecutive phase I oncology trials between August 2004 to August 2008 at MD Anderson Cancer Center, 27.2% of patients were still receiving the study drug 3 months after starting treatment, indicating the patients' malignancies were responsive to therapy without inducing significant toxicity in the patients. [8] Additionally, for these patients the median overall survival from the time of starting on phase I treatment was 238 days, or approximately 8 months, which is higher than many physicians and oncologists estimate the survival rate to be for patients on end-line treatments. [9-11] It is notable that 97.7% of these 683 patients were receiving at least one targeted therapy as part of their respective treatments. In fact, most phase I oncology studies in the current era include treatment with at least one targeted agent, either alone or in combination with another targeted agent(s) and/or another traditional cytotoxic agent(s).

While the medical community is happy for what success there has been for patients receiving phase I treatments, clearly there is room for improvement. For this reason, phase I investigators are learning from their successes how to better evaluate patients for participation in clinical trials more likely to benefit their respective diseases. Given the large number of cellular and extracellular targets which have been identified preclinically, and the fact that there are a correspondingly large number of agents currently available to target many of them which are already in use in the clinics, such an understanding is especially critical. Application of such understanding offers patients the highest chance of favorable response to treatment, and offers the agents under investigation the highest chance of receiving a marketing indication for use in the treatment of human malignancy.

In this chapter, the authors discuss the emerging role of phase I trials in the development of targeted therapies in this emerging era of personalized cancer care. Over the course of the last several years, the field of phase I drug discovery in oncology has seen significant changes. Specifically, beyond successful determination of dosing and pharmacokinetics, phase I studies are beginning to make significant contributions to the development of

personalized targeted anticancer treatment in three key areas. These areas in no particular order of significance are (1) the rapid acceleration of development of novel targeted agents, for example using phase I data to take an agent from the phase I study directly to a phase III registration trial, (2) the development of agents from bench to bedside, and (3) the development of agents from bedside to bench and back to bedside. The authors begin by discussing three case studies, one in each of the three areas listed above. Each case study is a representation of a general mechanism by which a well conducted phase I study has been instrumental in the development of a targeted therapy. Beyond drawing attention to individual success stories in drug development, the cases highlight some of the reasons the phase I investigators in each case were able to achieve the successes they did, and point out challenges and strategies for achieving similar success with future phase I studies.

After discussion of the impact of phase I trials in the three key areas given above, we move to discussion of emerging strategies for optimization of obtaining efficacy data from phase I studies and optimization of phase I trial efficiency. Despite the fact that phase I studies do not usually include collection of efficacy data as primary endpoints, the increasing cost and utilization of other resources in conducting clinical trials of targeted agents makes this a naturally desirable goal, especially when some of these methods are relatively inexpensive and easy to implement. The strategies discussed include (1) using phase I patients as their own internal controls in the assessment of treatment efficacy, and (2) bundling of individual but related trials into single, more comprehensive studies.

Finally, the authors conclude with a discussion of the newest directions in which phase I studies are moving in an attempt to elucidate the patients and clinical scenarios in which novel molecules entering the clinic have to potential to be helpful. This is part of an attempt to minimize the shelving of molecules under development which may have otherwise been helpful, but whose potentials were not uncovered secondary to the way in which the molecules were studied. As the architects of clinical trials become more aware of the issues and methodologies discussed in this chapter, and their implementation becomes more widespread, oncology patients should increasingly receive cancer care which is optimally personalized to each one of their respective diseases.

Chapter III- Protein kinases constitute a large family of proteins that can be further subdivided into protein serine/threonine kinases and protein tyrosine kinases. Both groups are involved in critical steps of intracellular signaling transduction, and therefore, regulate important biological processes such as cell proliferation, differentiation, and apoptosis. Thus, it comes as no surprise that protein kinases are implicated human cancer. For that reason, over the last two decades, important drug discovery efforts have been directed at developing agents with the ability to block the enzymatic activity of protein kinases regulating important signaling pathways involved in cancer. Given the critical role of protein kinases such as BCR-ABL1, EGFR, or HER2 in chronic myeloid leukemia (CML), non-small cell lung cancer, and breast cancer, respectively, the latter were the first protein kinases to be considered target candidates for the development of small-molecule inhibitors. For years, BCR-ABL1 kinase had been regarded as the critical driver of the pathogenesis of CML and therefore molecules with activity against this kinase represented ideal candidates for clinical development. Yet, skepticism surrounded the initial development of such agents on the basis of lack of specificity as all members of the kinase family bind the same nucleotide cofactor, ATP, therefore, implying that such intervention might be associated with excessive toxicity due to untoward inhibition of a wide spectrum of kinases. However, the preclinical and clinical

development of BCR-ABL1 tyrosine kinase inhibitors (TKIs) for the treatment of CML during the last decade has demonstrated the feasibility and tremendous activity of such therapeutic approach and has paved the way for the development of TKIs in a wide range of human malignancies driven by constitutively active protein kinases.

Chapter IV- Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in the western world accounting for 25% of leukemias. It is a clonal malignancy of B-cells that leads to the accumulation of defective mature lymphocytes. There are several therapeutic options that exist for these patients including purine analogs and other cytotoxic agents that can induce remission, yet these treatments do not lead to cure. However, there are several new exciting targeted agents that show promise in improving survival of patients with CLL. Acute lymphoblastic leukemia (ALL) is the most common cancer in children. Adults patients with ALL have worse survival compared to the pediatric cohort; the 3-year overall survival for patients less than 30 years old is 66% whereas in patients between 30 to 59 years, the survival is 36%. Patients with ALL with Philadelphia positivity (Ph+) have a worse prognosis; however, there are several targeted agents directed against the Ph chromosome that may lead to improved prognosis for these patients.

The use of targeted agents coupled with chemotherapy has generated several different treatment regimens for patients with CLL. Some chemoimmunotherapy regimens have led to increased complete remission rates (CR) of up to 70% in the frontline treatment of CLL with durable remission rates lasting up to 7 years [1-3]. These prolonged remission durations have been a breakthrough, they have yet to translate into survival benefit. However, two retrospective analyses have suggested that adding targeted agents to immunotherapy may lead to a survival benefit. The Cancer and Leukemia group B (CALGB) compared the combination of fludarabine and rituximab to historical data from prior CALGB trials that used fludarabine monotherapy; the addition of rituximab led to a significant difference in survival [4]. Multivariate analyses that controlled for pretreatment characteristics for patients receiving fludarabine and rituximab showed an increase in both the 2-year disease free survival (DFS) and overall survival (OS) in favor of the addition of rituximab to fludarabine. Another retrospective study by M.D. Anderson Cancer Center showed that the addition of rituximab to fludarabine and cyclophosphamide (FCR) led to an increased 4-year survival of 85% compared to 70% with fludaribine and cyclophosphamide in a historical control population. These data need to be interpreted cautiously as they were retrospective analyses, but it suggests that targeted therapy with rituximab holds great promise in the treatment of CLL.

Several new agents are now available that target the CLL clone at various levels. Several of these drugs include monoclonal antibodies (rituximab, alemtuzumab), bcl-2 antagonists (oblimersen), cyclin-dependent kinase inhibitors, Heat shock proteins, tyrosine kinase inhibitors, and microenvironmental modulators. Although data exists for the efficacy of these agents in the frontline or relapsed setting, there is a paucity of data as to their effectiveness when they are combined. While patients with CLL often have durable remissions with fludarabine-based regimens (ie, FCR), they often relapse and are more resistant to subsequent retreatment with a similar regimen. In many cases, patients with CLL have been exposed to several prior treatment regimens prior to enrollment on clinical trials using targeted agents. In addition to rituximab, consideration should be made to use other targeted therapies available and to use them earlier in the treatment of CLL. Dr. O'Brien recently published a thorough review of new agents in the treatment of CLL [5]. In this chapter, we expand on her review

with a focus on the currently available targeted agents available in the management of CLL. In addition, we will discuss the various targeted agents used for patients with ALL who are Ph+.

Chapter V- Acute myeloid leukemia (AML) is a malignancy characterized by the proliferation and accumulation of malignant myeloid blasts. It is defined by the presence of more than 20% myeloid blasts in the bone marrow [1]. The pathophysiology of AML is characterized by molecular abnormalities which lead to an increase in proliferation, decreased maturation and resistance to apoptosis. The presence of certain molecular abnormalities (PML-RARAgene, FLT3 mutations) defines specific subsets of patients with AML with different prognosis, potentially allowing for the development of risk-adapted treatment strategies [2]. Current standard treatment options for patients with AML include chemotherapy (regimens with anthracycline and cytarabine) and allogeneic stem cell transplantation (SCT) and are curative in a fraction of patients, mainly younger with good performance status and cytogenetic characteristics.

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic stem cell disorders characterized by ineffective hematopoiesis, increased apoptosis and a propensity to transformation to AML [1]. Their natural history is quite varied, with some cases having an indolent course and a life expectancy of many years, and in others patients the disease follows a very rapid and aggressive course. This heterogeneity is captured by prognostic indexes, such as the International Prognostic Scoring System (IPSS) [3] or the more recent WHO Prognostic Scoring System (WPSS) [4]. Molecular and genetic abnormalities also play important roles in MDS, and help define subtypes of disease which may respond to specific treatment interventions (i.e., deletion(5q)). In the past, MDS was a disease where treatment options were limited to supportive care, such as transfusions and use of growth factors. This has changed in the last years, with development of drugs such as hypomethylating agents [5] and lenalidomide [6].

Together with an effort to develop new therapies, the study of the molecular biology of AML and MDS has led to the development and a better understanding of the mechanisms of action of several agents which could be targeted to specific molecular alterations encountered in the leukemic cell. It is expected that these therapies may lead to an improvement in the natural history of these diseases particular in older patients.

Chapter VI- Multiple myeloma, a clonal malignancy of plasma cells, accounted for 1.4% of all cancers in 2009. With over 20,000 new cases being diagnosed each year, multiple myeloma is the most common hematologic malignancy in the United States. [1] Despite advances in the treatment of this disease through adjuncts such as high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), multiple myeloma is still considered to be an incurable disease. However, the last decade has brought forth a plethora of promising agents for the treatment of multiple myeloma.

From the 1960s to the 1980s, melphalan and steroids offered the best treatment modality for multiple myeloma. Vast research published in the 1980s revealed the efficacy of high-dose-steroid-containing regimens such as vincristine, doxorubicin, and dexamethasone as well as high-dose therapy followed by ASCT. In 1999, the therapeutic approach to multiple myeloma changed dramatically when Singhal et al. reported on the efficacy of thalidomide in the setting of refractory multiple myeloma, ushering in a novel treatment approach to a largely resistant disease. [2]

Since this advancement, thalidomide and its derivative lenalidomide have changed the approach to newly-diagnosed multiple myeloma. In addition, novel agents such as the proteasome inhibitor bortezomib have uncovered new, effective pathways for the treatment of this disease.

Chapter VII- Targeting the estrogen receptor is the oldest molecular targeted therapy approach, and widespread use of the selective ER modulator tamoxifen in breast cancer is responsible for major improvements in cure rates, quality of life and disease prevention during the past 25 years. The estrogen receptor, receptor tyrosine kinase and DNA repair pathways are key to understanding the growth and progression of invasive breast cancer and how interference of these pathways results in anti-cancer activity. Currently, the systemic treatment of breast is characterized by the discovery of multiple cancer targets leading the treatments more sophisticated and specific than the conventional cytotoxic chemotherapy and hormonotherapy. Targeting both HER-2 (human epidermal growth factor receptor 2) with trastuzumab and the vascular endothelial growth factor (VEGF) with bevacizumab in combination with chemotherapy has become a further milestone of molecular targeted therapy in breast cancer. A large number of novel targets have been recently discovered, and in parallel multiple approaches to anticancer therapy have recently emerged from the literature. These approaches referred as "targeted therapies" consist in targeting the malignant cell signal transduction machinery including crucial process involved in cell invasion, cell metastasis, apoptosis, cell cycle, and tumor-related angiogenesis. Among them, one class of compounds that has shown great progress is those targeting tyrosine kinases (TK) which is carry on by small molecules or monoclonal antibodies. However, intrinsic and acquired resistance to endocrine and/or cytostatic treatments is still a common feature that limits the benefits for these novel therapeutic strategies. Therefore, clinical trials of endocrine or cytotoxic therapies combined with growth factor pathway inhibitors or their downstream signaling elements are warranted. In this chapter we describe the most promising studies using these new molecular agents as and their novel combinations of targeted therapies with traditional cytotoxic agents.

Chapter VIII- Gastrointestinal (GI) malignancies consist of a wide variety of diseases derived from several types of tissues, including mesenchymal, lymphoid, epithelial, and neuroendocrine. Perhaps the largest group of malignancies of the GI tract is epithelial malignancies, commonly referred to as carcinomas. Adenocarcinoma and squamous cell carcinoma (SCC) are the two predominant histologic types of GI carcinomas. Each organ-specific carcinoma has its own epidemiology, etiology, and natural history. As such, each is associated with a specific treatment algorithm. Globally, an estimated 3.28 million people were diagnosed with GI carcinomas in 2002, resulting in 2.44 million deaths. Worldwide, the three most common GI cancers are gastric cancer, colorectal carcinoma (CRC), and hepatocellular carcinoma (HCC); among GI cancers, these three are responsible for the most cancer-related deaths in the United States. In 2009 in the United States, 275,720 new cases of GI cancer were diagnosed, and 135,830 died of this disease. The three most common GI cancers in the United States are CRC, gastroesophageal (GE) cancer, and pancreatic cancer.

Effective screening programs can detect the earlier stages of disease, leading to a higher curative rate. Unfortunately, the only cost-effective public screening program in the United States is the use of colonoscopies to detect CRC. Since the introduction of public colorectal screening programs in the United States in the early 1980s, the incidence of CRC has steadily decreased. This is not the case, however, for patients with non-colorectal GI cancers; more

than 60% of these patients (except for those with anal carcinoma) have advanced or metastatic disease at the time of diagnosis. This translates into poor survival outcome, with an estimated median 5-year survival rate of less than 15%. In fact, for 2009, the crude mortality rates from esophageal cancer, pancreatic cancer, and HCC were estimated to be 88%, 83%, and 80%, respectively.

In the early stages of GI cancer, surgery is the only chance for cure; in all other stages, treatment options include chemotherapy, chemoradiotherapy, or symptom control with best supportive care (BSC). For patients with metastatic GE cancer, treatment with systemic chemotherapy results in less than 5% survival at 5 years. Clearly, currently available therapy for patients presenting with advanced or metastatic GI cancers is inadequate and contributes only minimally to overall survival (OS). With more than 250,000 American lives affected by GI cancers in 2009, the present lack of clinically relevant effective therapy underscores the need for improved and innovative therapeutic options.

With our increasing insight into molecular tumorigenesis, targets have been identified for drug development. In recent years, an abundance of biologically targeted agents have been introduced into clinical research and development. In fact, since 2000, more than 17 new targeted agents have been approved by the Food and Drug Administration (FDA) for cancer therapy. Even more relevant is the fact that along with the development of targeted therapy, biomarkers have been discovered that are capable of identifying specific patients who may benefit from such therapy. Hence, improved prospects for patients with GI cancers rest in targeted therapy and individualized cancer treatment. This chapter reviews targeted therapies currently in use or in development to treat GI carcinomas.

Chapter IX- Bladder cancer has an estimated incidence of 68,810 new cases in 2008. The male to female distribution is 3:1 [Jemal 2008]. Approximately 25% of patients initially present with advanced (muscle-invasive or metastatic) disease, requiring systemic chemotherapy. Seventy percent of patients presenting with superficial disease (ie, tumors that do not invade the muscularis mucosa) will develop disease recurrence, and the subset that progresses to invasive disease will in 50% of cases require systemic chemotherapy within 5 years. In excess of 90% of bladder cancers diagnosed in the US are transitional cell carcinomas of the urothelium. They can also arise from the urothelial lining of the urinary collecting system, including the ureter, renal pelvis, and urethra, behaving similar to those originating in the bladder. Thus, these tumors are referred to as urothelial carcinoma (UC). UC is a chemotherapy-sensitive malignancy, but early responses to chemotherapy are not typically durable, and the vast majority of patients develop disease recurrence with no current standard of care in the second-line setting. While there is research focus of single agent conventional chemotherapeutic agents in this setting, increasing understanding of the biology of UC has resulted in new trials incorporating novel targeted therapies in the management of advanced UC.

Chapter X- In 2006, a landmark advance in the treatment of head and neck squamous cell carcinoma (HNSCC) occurred with the approval of cetuximab, an antibody targeting the epidermal growth factor receptor (EGFR), by the U.S. Food and Drug Administration (FDA) as a single agent and in combination with radiation therapy (RT). As the first new drug approved for HNSCC in 45 years, this molecularly targeted drug has been rapidly adopted as a new standard of care.

FDA approval of cetuximab for treatment of HNSCC was based on results of two studies [1, 2]. The first study, a phase III trial of cetuximab combined with RT, demonstrated a

greater survival advantage in patients who received the combination of cetuximab with RT than in patients treated with RT alone (49 vs. 29 months after 54 months of follow-up) [1]. The second study was a phase II trial of cetuximab as a single agent for HNSCC patients with platinum-refractory recurrent or metastatic disease [2]. In this trial, 13% of tumors responded to treatment, and 46% demonstrated disease control (response or stable disease). The early success of cetuximab has paved the way for numerous clinical studies investigating the use of this agent in combination with traditional cytotoxic chemotherapies and also has opened the door for studies of other targeted agents.

In the United States, new cancers of the head and neck in 2008 numbered 47,560, with 11,260 resulting deaths [3]. HNSCC tumors arise from the upper aerodigestive tract and most commonly involve the oral cavity, larynx, oropharynx, and hypopharynx [2]. Although early-stage (stage I and II) head and neck cancer has a 5-year survival rate of 53–82% following surgery or RT [4], advanced disease can be difficult to control, even with multimodality treatments involving chemotherapy, RT, and/or surgery. Furthermore, because of the anatomic complexity of the head and neck region, treatment of these tumors can result in significant and long-lasting morbidities that affect the patient's speech, swallowing, and cosmetic appearance.

This overview will address risk factors for and molecular progression of HNSCC, systemic therapies focusing on cetuximab, targeted therapy plus radiation therapy, predictive biomarkers, chemoprevention, and thyroid cancer.

Chapter XI- Ovarian cancer remains the most prevalent and lethal gynecologic malignancy in the United States. In 2007, over 22,000 new cases were diagnosed, and greater than 15,000 women died from this disease. [1] Due to increasing utilization of multi-modality approaches, advances in surgical techniques, and optimization of available cytotoxic chemotherapies, five-year survival for women with ovarian cancer increased from 37% in the 1970s to 45% in the 1990s. In the United States, the number of deaths from ovarian cancer has declined over the past two decades. However, with our aging population, there has been no change in the cure rate over this period. [1] New insights into the molecular mechanisms and the biological basis for clinical behavior of ovarian cancer are needed to increase the number ovarian cancer survivors. This chapter will consider the spectrum of genetic and epigenetic changes in various ovarian cancers as well as signaling pathway alterations that underlie differences in clinical behavior that could serve as targets for intervention.

Chapter XII- Endocrine malignancies are rare tumors that are derived from endocrine cells located throughout the body. They encompass a heterogeneous group of malignancies, derived from different endocrine and neuroendocrine cells and have different clinically. The majority of endocrine neoplasms are benign, where the potential for invasion or metastasis is very low. Nevertheless, there is a group of endocrine neoplasms with malignant potential, and thus come under the management of medical oncology, often requiring systemic therapy. These include neuroendocrine tumors, anaplastic and medullary thyroid carcinomas, pheochromocytomas or paragangliomas, and adrenocortical carcinomas. While surgery continues to play a seminal role, the management of advanced endocrine neoplasia is more complex due to their rarity and heterogeneity. Whether the cancers are indolent or aggressive clinically, patients with advanced disease or distant metastases are rarely curable and therapy is palliative. In addition to being laden with significant toxicities, systemic cytotoxicity treatment options are often ineffective without robust evidence that they add meaningful clinical benefits. Novel effective treatment options are desperately needed. Considered

unprofitable, drug developments for these rare malignancies rarely make it to any pharmaceutical companies' agenda. However, in recent years, there are more interest to develop therapy for rare or orphan malignancies, motivated in part by the advent of biological targeted therapy and the recognition that the process to drug approvals for rare or orphan diseases are more expeditious than more common cancers. In this chapter, we will focus on targeted therapy in malignant endocrine neoplasms, particularly those diseases with therapy already in phase III clinical trials. Developing targeted therapy in neuroendocrine tumor (NET), medullary thyroid carcinoma (MTC), and adrenocortical carcinoma (ACC) will be discussed below.

Chapter XIII- Tumors that originate within the brain parenchyma are known as primary brain tumors. An estimate of 12,740 deaths were attributed to primary malignant brain tumors and central nervous system (CNS) tumors in the United States in 2007 (American Cancer Society 2007). The incidence of all malignant and non malignant primary brain tumors is 16.5 cases per 100,000 person-year (9.2 per 100,000 person-year and 7.3 cases per 100,000 person-year) (CBTRUS 2007-2008). This translates to an estimate of 51,410 new cases of primary brain tumors are expected to be diagnosed in 2007. Among all primary brain tumors, 40% are malignant. Gliomas account for 36% of all tumors and 81% of malignant tumors, (CBTRUS data 2000-2004, www.cbtrus.org).

Chapter XIV- Over the last several years, there has been both a clinical and research drive towards being able to offer unique treatments to cancer patients that can target specific genetic aspects of their diseases. This emphasis has been predicated on the fact that not all cancers are the same pathologically or physiologically or behave the same. Two patients may have the same category of cancer fueled by entirely different biologic mechanisms. Therefore, offering targeted therapy to attack the cause of disease has become personalized out of necessity.

It appears that up till this point, personalized therapies in cancer have been the purview of primarily medical oncologists. One must not, however, forget about the other oncologic specialties that are more critical to local control, radiation oncology and surgical oncology. In fact, it is probably safe to argue that radiation oncologists have been using unique, personalized treatments for their cancer patients from the inception of the field. With improving technology, targeting of disease with radiation has become even more accurate. Finally, with the use of concurrent chemo/biological therapy with radiation, an effort has been made to specifically target molecular pathways in primarily tumor cells to promote radiation sensitivity and improve the therapeutic ratio. In this review, we will summarize the latest technologies allowing for more accurate targeting of patient tumors for radiation therapy and explain the role of concurrent chemotherapies / biologic agents with radiation in personalizing this type of treatment. Unlike systemic therapy, it is essential to discuss both the technology/physics and concurrent treatments in describing the unique personalization and tumor targeting in radiation. For the purposes of this review, all radiation described will be from external beam sources.

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Chapter I

Therapeutic Agents and Approaches in the Age of Personalized Cancer Care

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Abstract

Management of cancer patients has undergone a tremendous evolution, from an absence of hope to the promise that each patient could choose from a plethora of agents the one to which their particular tumor would respond; from a single option of a life-threatening attempt at surgical excision to a combined approach of surgery, chemotherapy, targeted agents, radiation, and supportive care. This has come about as our understanding of cancer has evolved from a nebulous curse to an appreciation for the logical complexities that make up uncontrolled growth. And while there is still much to learn, we find ourselves in an exciting era where we have the blueprint of the entire genome, an ability to test the full spectrum of genetic perturbations in a patient, and technologies to allow development of an arsenal against of such defects. Herein we will describe many of the classes of agents that might allow such treatments, and the technologies that let us define a patient's malignancy.

Chemotherapy originated from the observation that World War I soldiers exposed to sulfur mustard gas developed pancytopenia. Charged with discovering potential therapeutic values to such toxins, Louis Goodman and Alfred Gilman designed nitrogen mustard, collaborated with thoracic surgeon Gustav Lindskog, and achieved a partial remission in a nonHodgin's lymphoma patient(1). Similar trial and error experiments continued, with the only patient specific facets to therapy being observations of which cancer patients responded. As investigators gained a better understanding of the biologic processes driving cancer, advances in chemistry allowed generation of site-specific inhibitors, and technologic discoveries improved high-throughput analysis of thousands of compounds, it became possible to generate compounds against specific pathways. With completion of the human genome project and advancements in tumor analysis methods such as gene sequencing and microarrays, evaluation of patient-specific