PRECISION CANCER THERAPIES

OWEN A. O'CONNOR SERIES EDITOR

VOLUME 2

Immunologic Approaches for the Treatment of Lymphoid Malignancies

From Concept to Practice

Editors

Owen A. O'Connor · Stephen M. Ansell · John G. Gribben

WILEY Blackwell

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Volume Foreword

Immunologically-based treatment for lymphoid malignancies has evolved dramatically in the quarter century since the human-murine chimeric monoclonal antibody, rituximab, became the first FDA-approved anticancer immunotherapy and entered routine clinical use. This agent emerged from early proof of principle work in B-cell lymphomas with anti-idiotype and, later, anti-CD20 and anti-CD19 monoclonals developed by Levy and others (Maloney et al. 1994, 1997; Meeker et al. 1985; Nadler et al. 1981). As a "naked" antibody, rituximab engaged intrinsic cytotoxic T-cell immunity and complement-based mechanisms and proved efficacious as a single agent in relapsed or refractory follicular lymphoma (McLaughlin et al. 1998) and, in short order, for other indolent B-cell malignancies. In pivotal phase 3 trials, rituximab combined with cytotoxic chemotherapy significantly improved cure rates and survival in diffuse large B-cell lymphoma, setting a standard of care which remains to this day (Coiffier et al. 2002; Habermann et al. 2006). Further progress was built upon this foundational work via the characterization of targetable surface antigens, and technologies that create chimeric and humanized antibodies with enhanced clinical activity.

Volume 2 of ***Precision Cancer Therapies*** provides a timely compendium of progress in both antibody- and cellular-based immunotherapeutics that leverage novel mechanisms of action to improve outcomes for patients with lymphoid malignancies. Broadly viewed, these include "weaponizing" monoclonal antibodies via radioimmunoconjugates and antibody-drug conjugates (ADC) that target B-cell malignancies via antigens such as CD19, CD20 or CD79b, as well as T-cell and Hodgkin lymphomas via CD30 targeting. More recently, bispecific T-cell engaging antibodies and chimeric antigen receptor-T-cells (CAR-T) have demonstrated durable responses in relapsed and refractory B-cell lymphomas, with CAR-T therapy outperforming traditional high-dose chemotherapy and autologous stem cell transplantation at first relapse of diffuse large B-cell lymphoma (Kamdar et al. 2022; Locke et al. 2022). Immune checkpoint inhibitors are firmly established for relapsed Hodgkin lymphoma, and are poised to become integrated into front-line therapy for those with advanced-stage disease (Ansell et al. 2015; Herrera et al. 2023). This Volume also explores novel targets for lymphoid malignancies such as CD47, the "don't eat me" signal that, when blocked, therapeutically leads to phagocytosis and destruction of tumor cells.

The theme of rational therapeutic development and targeting is apparent throughout these chapters. The advances reported are built upon a deep and expanding knowledge of lymphoma biology and interactions within the tumor microenvironment, including an increased understanding of the mechanisms of treatment response and resistance. Predictive biomarkers across the many lymphoma subtypes will guide precision medicine approaches for individual patients. Until recently, curative-intent therapy for diffuse large B-cell lymphoma, the most common non-Hodgkin lymphoma entity, involved an anti-CD20 monoclonal antibody plus combination chemotherapy as noted above that cures only 50–60% of patients. Recent insights into the underlying biologic complexity of DLBCL are emerging via molecular profiling and identify unique lymphoma subtypes (Mondello and Ansell 2021; Wilson et al. 2021). These subtypes may be highly responsive to the incorporation of novel agents into current regimens, and diagnostic precision will facilitate clinical trials focused on biologically relevant entities.

How will these powerful advances improve the cure of lymphomas in the coming decade, and potentially reduce early- and late-onset treatment related toxicities? Traditional cytotoxic chemotherapy regimens will be de-escalated in intensity – or eliminated completely – in favor of immunotherapeutic agents alone or in combination with immunomodulatory agents, B-cell receptor pathway inhibitors and apoptosis-inducing agents. New metrics to determine the depth of remission will become standard, and will complement or perhaps even replace imaging-based assessments such as PET/CT scans. Highly sensitive determinations of measurable residual disease (MRD) in the peripheral blood or bone marrow will identify early disease progression and relapse, and dynamic assessment of the MRD kinetic response during induction therapy will enhance risk-adapted treatment approaches (Hoster et al. 2023; Melani et al. 2018).

The exciting progress of the past 25 years continues at an ever-accelerating pace, encompassing an array of therapeutic targets and modalities coupled with vital insights to

lymphoma entities and their unique biology. It is indeed a hopeful and promising time for our patients, as is the need for ongoing international collaboration of laboratory and clinical scientists. The opportunities and dedication to progress are apparent in these pages, and provide a roadmap to continued success.

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Volume Preface

Cancer immunotherapy, the science of mobilizing the immune system to treat cancer, has been pursued for more than 150 years, yet it is only relatively recently that this powerful strategy has finally come of age and taken center stage in oncology. The history and background of the field is described in this Volume in Chapter 1 where we read that the concept of activating the immune system to treat cancer was initially tested in the 1860's. Despite the attraction of the approach and anecdotal evidence of success and continued efforts, immunotherapy was nonetheless largely displaced in mainstream oncology by the advent of chemotherapy and radiotherapy. However, the specificity of the immune response and the potential to develop therapy with less toxicity continued to make immunotherapy an attractive if still somewhat elusive goal, and led to much further pre-clinical work.

The major advances that have laid the foundation for this new era of immunotherapy largely came in the last decades of last century. A major advance came with the development of monoclonal antibodies (1) for which Milstein and Köhler were awarded the Nobel prize with Niels Jerne in 1984. Not much later, advances in understanding of T cell anti-tumor biology, and genetic engineering led to the concept and design of chimeric antigen receptor (CAR) T cells (2). The process of humanization of monoclonal antibodies led to clinical success (3) and approval in 1997 of the anti-CD20 monoclonal antibody rituximab and not long thereafter, CAR T cells targeting CD19 were in clinical development (4). Increases in our knowledge of the mechanisms whereby tumor cells usurp physiologic processes in a pathological way to avoid immune recognition led to clinical development of checkpoint inhibitors to enhance anti-tumor responses (5). These clinical advances all have in common that they were built upon our increased scientific understanding of the immune system and increased bioengineering prowess.

This century has heralded the era of chemo-immunotherapy in which use of at least some form immunotherapy is considered standard of care for almost all cases of B cell lymphoma.

The challenge now is to maximally exploit the power of the immune system without unleashing unwanted auto-immune complications.

This volume on *Precision Cancer Therapies* focusing on immunotherapy in lymphoma is, therefore, very timely. Sections are organized around select concepts of targeting cell surface receptors, use of antibody drug conjugates, use of immune checkpoints, targeting macrophages, targeting EBV, targeting tumor associated antigens using autologous T cells, chimeric antigen receptor T cells and other approaches. The concept of the sections follows the same approach that was used for drug development in Volume 1, namely:

i) What is the immunological target;
ii) What are the immune targeting agents at my disposal;
iii) What is the data supporting their use;
iv) How do we build upon, improve and optimize the therapy.

In this field with so much scientific advancement occurring at speed obviously leads us to question if text books such as this still have any place left in a modern world? Surely online learning is the way forward and how soon will it be before our diagnostic and therapeutic prowess is challenged by advances in artificial intelligence (AI) in medicine. However, even the most sophisticated AI systems still require learning tools and the quality of the chapters presented here assures me that this volume represents the state of the art of immunotherapy for lymphoma and the suggested reading from each chapter which ensure a solid foundation in the principles of immunotherapy for lymphoma for readers. As always, it is not just the overview of the field that each author brings, but their knowledge and perspective of where we are and where we need to go next that make this Volume so rewarding.

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Series Preface

The pace of growth in scientific literature has been a subject for scientists who like to study bibliometric data, for decades. As early as 1951, Derek John de Solla Price, often regarded as one of the pioneers in studying rates of change in scientific literature, noted that the development of scientific information follows the law of exponential growth (de Solla Price 1951). In 1976, Price concluded that "at any time the rate of growth is proportional to the ... total magnitude already achieved – the bigger a thing is, the faster it grows" (de Solla Price 1976). More recently, in 2018, Fortunato et al. concluded that "early studies discovered an exponential growth in the volume of scientific literature ... a trend that continues with an average doubling period of 15 years" (Fortunato et al. 2018). Barabási and Wang suggested that if the scientific literature doubles every 15 years, "the bulk of knowledge remains always at the cutting edge" (Barabási and Wang 2021). That means, that the bulk of what a typical physician learns in undergraduate, graduate, or medical school is potentially obsolete by the time they assume responsibility for the care of patients, or that the information they rely on today was not yet in the textbooks that laid the foundation for their career.

For practicing oncologists, there in lies the problem. How does one stay abreast of these incomprehensible changes in scientific knowledge, much less understand it in a manner that can be used to help their patients. Cancer medicine has become a field where the need to appreciate basic science, and I emphasize "appreciate" not "comprehensively understand," has become indispensable. Cancer medicine has become the place where fundamental cellular biology, pharmacology, and clinical medicine all collide, as physicians struggle to understand how they should integrate and evaluate diverse streams of information in order to arrive at the best solution for the patient sitting before them. It has become a field where translating the details of science has taken on larger and larger roles as physicians consider how to cure a disease, palliate pain, or improve the status quo, using only the information they have at their disposal.

Precision Cancer Therapies is designed to try and meet that very need. The volumes that will be produced in the series, the first two of which are devoted to the lymphoid malignancies, are developed around categories of diseases that share common themes in their pathogenesis, and, potentially, the strategies one might consider in targeting their dysregulated biology. Sections are organized around select mechanistic themes in disease biology established as being potentially important in disease pathogenies, followed by a chapter on the pharmacology of drugs identified as effective in nullifying that abnormal biology. Subsequent chapters in each section are focused on the translational aspects: how does one use the drugs at hand to alter the pathology in a therapeutically meaningful manner. Succeeding chapters highlight actual clinical data with specific drugs as both monotherapies and in "rational" combination. The sections within a volume are designed to share information using the same kind of logic a clinician might invoke in thinking about their patient. Here are some pertinent questions:

(i) What is the disease biology causing the problem?
(ii) What are the drugs at my disposal?
(iii) What is the data for the use of these drugs?
(iv) Are there ways to improve on these drugs' efficacy by considering combination effects?

The sections take a decidedly translational approach to the problem.

With the advent of so much web-based learning and now the passion around how artificial intelligence (AI) might transform our approach, some might suggest, why another book, let alone a series of books. The answer lies in the simple fact that there is no substitute or singular surrogate that can replace your very own fund of knowledge. Perhaps the most widely recognized and touted AI approach ever to come to our attention did so in 2011, when we watched, with complete astonishment I might add, IBMs Watson beat the famed Ken Jennings and Brad Rutter in Jeopardy. Jennings and Rutter were the greatest Jeopardy champions of all time: more wins

and more money than any other contestants in the history of the show. But, despite their intellectual prowess, they were no match for a computer that had intensely trained for years and "learned" how to beat Jennings and Rutter by playing simulated games against 100 of the best Jeopardy contestants ever. Yes, Watson too had to learn, and read, and assimilate years of information to compete with the human brain. While Jeopardy may be the most widely recognized and successful adventures for a room-sized computer, other forays of AI – and Watson in particular – in the field of oncology have, thus far at least, fallen short. IBM's Watson for Oncology has been in development since 2012. It is being developed to provide state-of-the-art personalized treatment recommendations for patients with very specific kinds of malignant disease. Watson has undergone extensive "learning" at some of the most prestigious cancer centers in the world, being nurtured on the nuances of cancer medicine. Comprehensive details around the interpretation of blood tests, pathology, genetics, imaging data, and patient-oriented detail get fed into the computer. Then, the computational prowess of Watson combs through the vast medical literature we discussed above, to generate an evidence-based treatment recommendation for that specific patient. Why did Watson outperform on Jeopardy and underperform in oncology? One reason may be obvious. The state of cancer research and its impact on the practice of cancer medicine is extremely dynamic and in constant flux, at times it relies on instinct and experience, apparently making an appearance on Jeopardy look easy. Encyclopedic facts about the real world change slowly, if at all. Acknowledging that this type of AI technology is in its infancy (though most of us completed medical school, residency, and fellowship in the time Watson has been in development), the decade-long experience of Watson in cancer medicine has to date been less than flattering. The lay press has taken a decidedly negative impression of Watson's first steps (watson-ibm-c), suggesting that while AI may have enormous appeal to the average observer, it is likely to never replace the intellectual prowess – and instinct – of that physician sitting in front of a patient. It re-enforces a centuries-old and fundamental truth, "knowledge itself is power," at least as Sir Francis Bacon understood it.

And so, with some data in hand, and curiosity in endless supply, *Precision Cancer Therapies* intends to help keep physicians, scientists, health care providers, and the motivated reader stay up to date on the dynamic and every growing state of information in our fascinating profession. Sure, Watson and PubMed and Society Guidelines can aid us in our decision-making. However, there is nothing that can replace a good old-fashioned education nor the instinct of an informed practitioner of this most rewarding of crafts.

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