

Preface

Over the past 30 years numerous provocative studies have provided clues suggesting that vitamin D may play an important role in cancer. In vitro studies have shown that cancer cells metabolize vitamin D and that vitamin D compounds can induce differentiation, inhibit cellular proliferation, and induce cell death. In addition, epidemiologic data suggest that vitamin D compounds may play a role in the prevention of cancer. In the past few years the understanding of the molecular effects of vitamin D has expanded substantially and investigators have begun to delineate the role of genetic factors that influence the response to vitamin D.

With this considerable history of development of vitamin D and cancer, it is timely and appropriate to summarize the current “state of the art” in the study of vitamin D and cancer. Scientists who have made many of the seminal contributions to this field of study have contributed to this volume. These collected data describe the foundation and current state for this important domain of cancer research – a domain that the coeditors of this book believe will yield important advances in cancer prevention and therapy.

Vitamin D Analogues as Antineoplastics: A Prologue Long Overdue?

Numerous investigators have drawn attention to the high prevalence of the vitamin D receptor (VDR) in human and murine cancer cells, the frequent evidence of intact vitamin D signaling pathways in such cells, and the ability of high concentrations of vitamin D analogues to inhibit the replication of cancer cells, induce apoptosis, and even inhibit angiogenesis. These data are cited in preceding and following chapters. Had such studies been completed with a new molecule – e.g., a new “targeted agent” – it is very likely that the following steps would have been undertaken promptly:

- (a) Careful in vivo delineation of schedule and dose dependencies of these anticancer activities
- (b) Careful determination of the maximum tolerated dose of analogues and exploration of optimal biologic dose

- (c) *Direct* comparisons of toxicity and antitumor efficacy of analogues and parent compound (calcitriol) using the apparently most active drug schedules

Unfortunately, for vitamin D based studies in cancer, very little of this rudimentary work has been carried out. Studies with most analogues of vitamin D (paricalcitol, seocalcitol, inecalcitol) have employed continuous dosing schedules even though practically all in vitro and in vivo studies which have shown anticancer activity of vitamin D have exposed cells and tumors to intermittent, high-pulse doses. Many have been encouraged by the study of daily dosing of analogues and parent compound (calcitriol) and finding the analogue causes less hypercalcemia. Often and not surprisingly, the analogue binds less avidly to VDR. Such studies have led to small to medium sized studies using daily dosing algorithms which have shown no antitumor effects and been halted without any toxicity remotely resembling those defensible in patients with advanced cancer.

Further limiting work with calcitriol has been the absence of a formulation suitable for high-dose therapy. This limitation is due primarily to the lack of an economic motivation for the development of such formulations.

The following chapters provide excellent and comprehensive discussions of the potential role of vitamin D based therapies in breast, colorectal, prostate cancer, and leukemia and myelodysplastic syndromes. These chapters also point out that the focus on these diseases is largely determined by the interests and expertise of the outstanding scientists who have chosen to pursue vitamin D based cancer therapeutics. To our knowledge, every tumor type ever evaluated has shown some biochemical and antiproliferative response to vitamin D. Similarly, vitamin D analogues, especially calcitriol, potentiate almost every cytotoxic agent with which combination therapies have been tested. In our view the slow and halting development of vitamin D based cancer therapeutics could be greatly accelerated by following standard principles of anticancer drug development:

- (a) Development of a standardized formula.
- (b) Determination of MTD (current data indicate the MTD of calcitriol on an intermittent [weekly] schedule is ≥ 100 mcg). No reliable oral MTD have ever been determined and few data on the optimal biologic dose developed in the laboratory, much less in the clinic.
- (c) Conduct of carefully designed clinical trials.

The field of vitamin D based cancer therapeutics has very few such data items available. Perhaps the extensive preclinical data on the antitumor effectiveness of high-dose vitamin D analogue therapy are misleading or in fact wrong. But until the agent is examined in the fashion one would follow for an antineoplastic – we will never know. The following chapters point out what is known and the direction that can be followed in clinical development of vitamin D as an anticancer agent.

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Vitamin D and Cancer

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2011, XI, 342 p. With 1 4-color insert., Hardcover

ISBN: 978-1-4419-7187-6