Seminars in Oncology 43 (2016) 222–232

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/ysonc

Preclinical modeling of novel therapeutics in chronic lymphocytic leukemia: the tools of the trade

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ARTICLE INFO

Keywords:
Chronic lymphocytic leukemia
Co-culture systems
Mouse models

ABSTRACT

In the last decade our understanding of chronic lymphocytic leukemia (CLL) biology and pathogenesis has increased substantially. These insights have led to the development of several new agents with novel mechanisms of action prompting a change in therapeutic approaches from chemotherapy-based treatments to targeted therapies. Multiple preclinical models for drug development in CLL are available; however, with the advent of these targeted agents, it is becoming clear that not all models and surrogate readouts of efficacy are appropriate for all drugs. In this review we discuss in vitro and in vivo preclinical models, with a particular focus on the benefits and possible pitfalls of different model systems in the evaluation of novel therapeutics for the treatment of CLL.

Published by Elsevier Inc.

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world [1]. It is characterized by the expansion of monoclonal, auto-reactive B cells that display decreased cell death and increased proliferation rates [1,2]. Standard treatment for physically fit symptomatic patients is chemo-immunotherapy (such as FCR—fludarabine, cyclophosphamide, and rituximab); however, these agents are not well tolerated by elderly patients and do not perform well in patients with adverse cytogenetic profiles (such as deletion of the short of arm of chromosome 17) [3,4]. In the past few years treatment of CLL has started to undergo dramatic changes; moving away from traditional chemotherapeutics towards targeted agents. While there are multiple preclinical models for drug development, evaluation of therapeutics for the treatment of CLL is typically done using in vitro cultures of either cell lines or primary CLL cells collected from the peripheral blood, using cell death as the preferred readout. With the advent of targeted agents, it is becoming clear that not all models and measures of activity are appropriate for the evaluation of all drugs.

In the context of this review we define novel therapeutics as kinase inhibitors (such as ibrutinib and idelalisib), immunomodulatory agents (such as antibodies against PD-1, PD-L1, or CTLA4), and BH3-mimetics (such as ABT-199). Kinase inhibitors are at the forefront of investigation for the treatment of CLL; with ibrutinib and idelalisib demonstrating impressive clinical activity as single agents [5–7], as well as in combination with anti-CD20 monoclonal antibodies [8,9]. These agents work by inhibiting both intrinsic signaling pathways, as well as disrupting tumor-microenvironment interactions [10–15]. Because of this latter mechanism, these drugs differ greatly from traditional chemotherapy, which works primarily through the direct induction of cell death, suggesting that changes in cell viability may not be the most appropriate readout to evaluate these agents. Similarly, immunomodulating agents are used to enhance immunity, for example by blocking PD-1 signaling in T cells leading to a reversal of T-cell anergy [16,17]. Unlike many agents currently used in the treatment of CLL, this latter class of agents does not necessarily target the CLL cell, but rather accessory cells such as T cells. Lastly, BH3-mimetics target anti-apoptotic proteins key to CLL cell survival [18,19]. Although these agents act directly on the CLL cells and are cytotoxic, preclinical evaluation of these agents requires a culture system that mimics the upregulation of anti-apoptotic proteins observed in vivo [20].

Herein we discuss in vitro and in vivo preclinical models, with a particular focus on the benefits and potential pitfalls of different model systems to evaluate novel therapeutics for the treatment of CLL.

2. Preclinical modeling in vitro

Most preclinical modeling of CLL is performed in vitro using either primary CLL cells or tumorigenic cell lines mimicking the

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http://dx.doi.org/10.1053/j.seminoncol.2016.02.007
0093-7754/Published by Elsevier Inc.