Original Study

Activity of 129 Single-Agent Drugs in 228 Phase I and II Clinical Trials in Multiple Myeloma

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Abstract

This is the first comparative analysis of single-agent drug activity in multiple myeloma. Our work suggests that a cutoff of 22% single-agent best-reported partial response activity in early clinical trials has been highly predictive of clinical success.

Background: More than 400 preclinical studies report ≥ 1 compound as cytotoxic to multiple myeloma (MM) cells; however, few of these agents became relevant in the clinic. Thus, the utility of such assays in predicting future clinical value is debatable. **Patients and Methods:** We examined the application of early-phase trial experiences to predict future clinical adoption. We identified 129 drugs explored as single agents in 228 trials involving 7421 patients between 1961 and 2013. **Results:** All drugs in common use in MM (melphalan, dexamethasone, prednisone, cyclophosphamide, bendamustine, thalidomide, lenalidomide, pomalidomide, bortezomib, carfilzomib, and doxorubicin) demonstrated a best reported response rate of ≥ 22%. Older agents, including teniposide, fotemustine, paclitaxel, and interferon, also appear active by this criterion; however, if mean response rates from all reported trials for an agent are considered, then only drugs with a mean response rate of 15% partial response are in clinical use. **Conclusion:** Our analysis suggests that thresholds of 20% for best or 15% for mean response are highly predictive of future clinical success. Below these thresholds, no drug has yet reached regulatory approval or widespread use in the clinic. Thus, this benchmark provides 1 element of the framework for guiding choice of drugs for late-stage clinical testing.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. 4, 284-90
Keywords: Drugs, Early clinical trials, Multiple myeloma, Phase 1, Single-agent activity

Introduction

After decades of minor improvements, the introduction of 5 new United States Food and Drug Administration (FDA)—approved therapeutic agents since 1999 marks a milestone in the history of multiple myeloma (MM) therapy. Overall response rates to induction therapy are now consistently > 90% in recent trials, and progression-free and overall survival have more than doubled, with a minority of MM patients likely being cured. Nevertheless, a majority of patients still relapse and develop drug resistance. The commercial success of novel drugs in MM has attracted significant pharmaceutical industry attention for a less common malignancy, and a large number of potentially useful therapeutics have been explored in preclinical and early- and late-phase clinical trials. It is encouraging that a multitude of new compounds and drug classes have been identified to be cytotoxic to multiple myeloma (MM) cells in cell lines, primary tumor samples, or mouse models. However, preclinical assays and models tend to overemphasize antitumor effects, and indeed, it seems there is no limit to the number of compounds that are cytotoxic to MM cell lines at high enough concentration. Recently, a number of therapeutics with promising preclinical studies have disappointed in later-stage clinical testing (eg, vorinostat,[1] siltuximab[2]). By Internet- and library-based literature search, we identified > 400 compounds that were preclinically tested in MM, of which 129 went to early-phase clinical studies in MM patients. In retrospect, it has been unclear what basis there is for deciding which agents should advance to late-phase clinical testing or which agents further the likelihood of a preclinical investigation predicting clinical success. In this analysis, we explore these issues and provide some guidance for determining the likelihood of ultimate clinical success, which might be employed at least as a positive predictor for ongoing clinical trial analysis.

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Submitted: Sep 12, 2013; Revised: Dec 17, 2013; Accepted: Dec 23, 2013; Epub: Dec 28, 2013

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Methods

To identify preclinical studies and early-phase single-agent trials of drugs tested in MM, we performed an extensive literature search, utilizing the Mayo Clinic library, Internet-based research tools, and

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2013.12.015

the US National Institutes of Health National Library of Medicine (pubmed.gov), as well as screening annual meeting abstracts from the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), the European Hematology Association (EHA), and the International Myeloma Workshop (IMW). Any early-phase study, irrespective of age group, study population, or eligibility, that utilized a drug as a single agent was assessed. We excluded trials using concomitant drugs (eg, steroids) or high-dose regimens that require autologous stem cell rescue. We also excluded any study with < 5 evaluable patients. We documented the quantity and the quality of published response for each trial, as well as the number of evaluable patients, the study phase, and the year of publication. Because trials were conducted over many decades and definitions have changed over time, partial response (PR) rates ($> 50\%$ reduction in measureable paraprotein) or better were counted as true responses, as this metric and its laboratory protein electrophoresis measurement has remained constant. When we identified > 1 study for a drug, we noted the best reported response and also calculated the mean response rate across all studies. To establish a comparative ranking of drug activity that was less dependent on patient cohort selection, we aimed to assess the activity under the most beneficial conditions for each drug. We therefore additionally screened for subgroup analyses and considered the highest activity reported for each single drug, if the minimum requirements (eg, patient cohort size > 5) were met.

Results

We identified 129 single-agent drugs, explored in 228 early clinical trials (phase I/Ib/II) published between 1961 and 2013 (see Supplemental Table 1 and Supplemental References in the online version). In aggregate, these trials treated a total of 7421 MM patients. The trials identified included a mean of 32 patients per trial (median, 22) with a mean number of patients tested per drug of 58 (median, 24). A remarkable increase in single-agent trials in MM was seen in the past decade (Fig. 1), most frequently utilizing small molecules (especially kinase and histone deacetylase inhibitors, as well as heat shock proteins), followed by monoclonal antibodies, proteasome inhibitors, and immunomodulatory drugs (Table 1).

Interestingly, only 26% of early-phase single-agent trials published in MM over the past 52 years investigated classical cytostatic agents. Nevertheless, the most potent drug in our ranking of clinical activity was an alkylating agent, melphalan,[3] that has been continuously used in MM therapy since the 1960s and remains the backbone of many therapeutic regimens.

Most of the trials identified were performed in relapsed or relapsed and refractory patients (203 of 228, 89%), only 26 (11%) in previously untreated patients. The proportion of trials reporting active drugs was significantly higher in studies with untreated patients than in trials with relapsed and refractory patients (23 of 27, 84.6% vs. 114 of 203, 56.1%, $P = .005$). Additionally, the mean response rate differed significantly whether a targeted agent or conventional compound was tested. Trials using a targeted agent reported greater activity in pretreated patients (15.67% vs. 9.68%, $P = .016$) as well as in untreated patients (41.11% vs. 25.18%, $P = .034$).

The Majority of Tested Drugs Show No Anti-MM Activity

Figure 2 shows that anti-MM activity was described in ≥ 1 patient in nearly 60% of the 228 reported trials, with a mean response rate on all trials of 15.30%.

However, this result is biased by differences in publication frequency within the compounds, as preferentially more trials were performed in active agents than in nonactive agents. The most frequently tested single agent was thalidomide (25 of 228, 11% of all trials) followed by the novel agents carfilzomib (13 of 228, 5.7%),

Figure 1 Distribution of Single-Agent Studies Over Time