Report of the 14th International Conference on Malignant Lymphoma (ICML) Closed Workshop on Future Design of Clinical Trials in Lymphomas

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Abstract

The 14th ICML held in Lugano in June 2017 was preceded by a closed workshop (organized in collaboration with the American Association for Cancer Research and the European School of Oncology) where experts in preclinical and clinical research in lymphomas met to discuss the current drug development landscape focusing on critical open questions that need to be addressed in the future to permit a more efficient drug development paradigm in lymphoma. Topics discussed included both preclinical models that can be used to test new drugs and drug combinations, as well as the optimal design of clinical trials and the endpoints that should be used to facilitate accelerated progress. This report represents a summary of the workshop. Clin Cancer Res; 24(13); 2993–8. ©2018 AACR.

Introduction

Advances in preclinical research resulting in a better understanding of the biology of lymphomas and improvements in antibody technology have supported the discovery and subsequent clinical evaluation of a high number of new therapeutic compounds. From 2010 until today, five new drugs (three molecularly targeted agents and two monoclonal antibodies) have gained FDA approval for different lymphoma subtypes (1–7). However, despite these recent approvals, the success rate of new drugs for lymphomas is very low, similar to the low rate of drug approvals (less than 5% of new agents entering clinical development) that is observed overall in oncology (8).

Hundreds of clinical trials are actively enrolling patients with lymphoma each year (ClinicalTrials.gov, https://clinicaltrials.gov/), providing grounds for some optimism that better therapies will be developed to improve treatment outcomes. Conversely, no standard methodological criteria exist to guide the conduct of clinical trials in patients with cancer, including lymphoma (9). Although the classical path of clinical drug development advances from dose-finding phase I, to efficacy-evaluation phase II, and finally to randomized phase III comparative trials against established standard regimens (10), this model is being challenged in several situations. Among the five recent drug approvals in lymphomas, only one drug was approved on the basis of the results of a randomized phase III trial (7), all others being approved on the basis of the results of single-arm phase II trials that used response rate as their primary endpoint (1–6).

In an attempt to describe the current drug development landscape in lymphoma and provide a working path for the future development of guidelines for preclinical and clinical trials methodology, a closed workshop was held in Lugano, Switzerland, on June 13, 2017, prior to the opening of the 14th ICML. The purpose of the workshop was to bring together experts in the field of drug development in lymphomas spanning basic biology, biomarkers, translational research, clinical medicine and biostatistics. Professors Anas Younes and Emanuele Zucca co-chaired the meeting which first addressed key topics in preclinical and early clinical evaluation of new compounds, and subsequently focused on the endpoints and designs of phase II and phase III clinical trials. Here, we provide a concise summary of the discussions and recommendations of that workshop.

In Vitro and In Vivo Models

Lymphoma cell lines can be used as screening platforms for the discovery and efficacy evaluation of new therapies. Cell lines grow easily, they are relatively inexpensive, and can be used for high-throughput testing of therapeutic agents (11). Changes in gene expression following pharmacologic inhibition of one or more targets can be studied in vitro and may provide the basis for translational research that can be applied to primary tumor samples in clinical trials (12). Cell lines can also be used to test drug combinations, including molecularly targeted agents that inhibit elements of the same or of different molecular pathways (13, 14). Because in vitro synergy can be observed with many agents in some cell lines and at some concentrations, prioritization for future development should be based on unbiased comparison of several doublings across several cell lines.
There are numerous limitations for using cell lines in preclinical testing to model drug sensitivity or resistance in human clinical trials, including potential for cross contamination, loss of heterogeneity, genomic instability, possibility of modifying the characteristics of the cells, infections with Mycoplasma, difficulty in establishing cell lines from indolent lymphomas, in addition to inability to study the dynamic interaction between lymphoma cells and the microenvironment (15). In vivo models using patient-derived xenografts (PDXs) may better represent the actual clinical tumor biology, and can complement cell line experiments. However, PDX also have limitations, including lack of engraftment of many indolent lymphomas and the requirement of engraftment in immune-deficient mice (Table 1). The use of genetically engineered and humanized mouse models may open new possibilities for the evaluation of new drugs that interact with the host microenvironment or immune effectors including evaluation of immunotherapies (16). The optimal number of unique tumors that should be tested in PDX experiments remains undefined, although most recent influential publications produce supportive data from one to three experiments.

### Phase I Trials

Phase I trials represent the first critical step toward the clinical evaluation of a new drug aiming not only to define a tolerable and active dose, but also to generate the first potential efficacy signals that are used to prioritize and direct a more expedient subsequent development of active drugs (17). Over the last decade, several molecularly targeted agents and monoclonal antibodies have entered evaluation in phase I trials for patients with lymphoma. Several issues were discussed during the meeting, including the optimal methods of dose escalation both for first-in-class single agents and novel–novel combinations (18), how to best capture late toxicities, the usefulness of molecular selection of patients treated with molecularly targeted agents and the importance of response rate seen with a new drug in phase I (Table 2).

Regarding dose-escalation methods, the Continual Reassessment Method (CRM) may be used in phase I trials as it can accelerate dose escalation and eliminate lower dosing levels faster while preserving patients’ safety (16). CRM type designs have been shown to be superior in both accuracy, that is, finding the correct dose, and efficiency, that is, finding the right dose with fewer patients compared with $3+3$ or designs that use less structured models (19, 20). Dose-escalation trials involving two drugs have used the $3+3$ design, when the dose of one drug is fixed and only the dose of the second drug is being escalated. However, recent trials in targeted therapy and immunotherapy require the dose exploration of both drugs simultaneously to find the optimal dose combination (18). In such cases, when dose escalation is planned for both drugs a CRM design for unknown toxicity ordering is more efficient in exploring all dose combinations with as few patients as possible (21). Such a design could likely result in multiple MTDs that can be further evaluated (22). A significant attention should be paid when planning combination

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>- CRM may be used in phase I trials as it can accelerate dose escalation and eliminate subtherapeutic doses faster</td>
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<td>- CRM may also be used in two drug combinations that require exploration of the dose of both drugs</td>
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<td>- Registered drugs in combinations can be used at their standard dose and increase only the dose of the experimental drug; a $3+3$ design can be used in these trials</td>
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<td>- Efforts should be made to define molecular subsets of patients most likely to benefit from MTAs</td>
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<td>- Statistical models may be helpful, but they need to be evaluated via simulated trials before implementing them in future clinical trials</td>
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<td>- A threshold of 30% response rate in unselected patients is a desirable minimum requirement of activity of single agent before moving to phase II trials</td>
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<td>- Agents with lower response rate may still guarantee further development if a biomarker is available or in drug combinations</td>
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**Table 2. Phase I trials for lymphomas**

**Table 1. Common uses and limitations of lymphoma cell lines and patient-derived xenograft models**

<table>
<thead>
<tr>
<th>Common uses/advantages</th>
<th>Limitations</th>
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<tr>
<td><strong>Lymphoma cell lines</strong></td>
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<tr>
<td>- Screening platforms</td>
<td>- Genomic instability</td>
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<td>- High-throughput testing of new agents</td>
<td>- Possibility of modifying the characteristics of the cells</td>
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<td>- Changes in gene expression for discovery of biomarkers</td>
<td>- Inability to study the interactions between lymphoma and microenvironment</td>
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<td>- Test of drug combinations</td>
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<td><strong>Patient-derived xenografts</strong></td>
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<tr>
<td>- May better represent the actual biology</td>
<td>- Lack of engraftment for indolent lymphomas</td>
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<tr>
<td>- Can complement cell line experiments</td>
<td>- Requirement of engraftment in immune-deficient mice</td>
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Abbreviations: CRM, Continual Reassessment Method; MTAs, molecularly targeted agents.
studies, as there are now several examples of significant toxicities when combining new drugs even in chemotherapy-free regimens (23). Methods of dose escalation in combination studies may include either cohorts that use alternate increases of both drugs or use of one drug in its standard single-agent dose and increase only the dose of the second drug (18). Registered drugs or drug combinations may be used at their standard schedule and doses and increase the dose of the experimental drug only.

Although dose escalation is typically based on lack of DLTs during cycle 1, grade 3–4 toxicities are frequently observed in later cycles, especially with chronically administered drugs (up to 57% of grade 3 and 4 toxicities are late-onset; ref. 24). The example of late-onset toxicities observed with the PI3K inhibitor idelalisib (25), which has an impressive activity in indolent lymphomas, further supports the need for a better definition of a dose that can be chronically administered to patients. This may require patients’ monitoring for adverse events beyond cycle 1 or the evaluation of intermittent schedules for chronically administered drugs. Statistical models may help to estimate the risk of late toxicities or account for the potential of late-onset toxicities without delaying accrual of new patients who can enroll in the trial. However, their performance and safety need to be evaluated via simulated trials prior to implementing them in future clinical trials (26). Finally, specific clinical characteristics of the different lymphoma subtypes must be taken into consideration when planning a phase I trial with a new agent, with regards to patient selection and dose escalation. In fact, some toxicities may be different among different lymphoma subtypes leading to different recommended phase II doses. The development of the BCL-2 inhibitor venetoclax required indeed different schedules of administration and resulted in three different target doses in chronic lymphocytic leukemia, in some forms of lymphomas with leukemic presentation (e.g., mantle cell lymphoma) and in other lymphomas due mainly to the occurrence of tumor lysis syndrome in the former two entities (27, 28).

With regards to patients’ selection based on molecular signatures, there is currently a lack of information in patients with lymphoma. Among the currently approved molecularly targeted agents none of them was developed on the basis of a molecular selection of patients in any of the clinical stages of development. On the other hand, lymphoma is not a homogeneous disease and the diverse histological subtypes not only are characterized by different clinical behavior, but they are also molecularly heterogeneous. Thus, responses of patients to a specific therapy can be variable (29). There are now several examples of molecularly targeted agents that have shown impressive activity in phase I studies in patients with indolent lymphoma and chronic lymphocytic leukemia, including PI3K inhibitors, which have only limited single-agent activity in solid tumors, bruton tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors, the latter two having been specifically designed and developed for patients with lymphoma and chronic lymphocytic leukemia. However, no predictive biomarkers of response have been identified for these agents and current trials with new molecularly targeted agents enroll patients based on the histologic subtype of lymphoma.

The more recent example of the EZH2 inhibitor tazemetostat that resulted in 92% response rate in patients with follicular lymphoma carrying a mutated EZH2 versus 26% response rate in those with wild-type disease, underlines the need of a better definition of specific patients populations that may most benefit from a specific treatment with molecularly targeted agents (30). A major effort should be made in future phase I trials testing new drugs in lymphomas to collect tumor tissue from all patients aiming to identify predictive biomarkers of response that could be further evaluated in later stages of development. The feasibility of new methods of molecular responses, including minimal residual disease assessment and the use of liquid biopsies should be encouraged in future phase I trials.

Early-phase trials increasingly include several dose expansion cohorts with the aim to obtain preliminary efficacy data in distinct patient or disease populations before moving into a phase II study (31). Response rates in phase I trials may predict single agent activity in subsequent stages of clinical development. A threshold of 30% response rate has been generally used as a desirable minimum requirement of single-agent activity and among the recently approved drugs in lymphoma, all of them had response rates above this bar in the respective phase I trials (32–34). Drugs with lower response rates may still guarantee further clinical development if preclinical data provide evidence of additive/synergistic responses when used in combination.

**Phase II and III Trials**

An important issue discussed during the meeting was the usefulness of phase II studies and if it would be more appropriate to move forward directly from phase I to III, skipping phase II trials. For single-agent approval, phase II studies are necessary and activity of the agent needs to be demonstrated in phase II before moving to phase III studies. The overall activity of a drug is frequently reported as disease control rate (DCR), which combines complete response (CR) + partial response (PR) + stable disease (SD). However, SD lumps minor tumor reductions and growth in one group. Accordingly, DCR may be more clinically meaningful when CRs and PRs are combined with minor tumor responses (MR; ref. 35). New drugs with modest single-agent activity in a specific disease type (e.g., response rate less than 30%) may be tested in combination with standard regimens in large-scale phase Ib-II studies to define subset of patients that may most benefit from the new combination (e.g., the combination of venetoclax with R-CHOP; ref. 36).

On the other hand, agents with established single agent activity may be combined with standard regimens to evaluate safety in phase Ib studies and then move directly to phase III trials. There are currently at least two examples of phase III trials (AVD chemotherapy+brentuximab vedotin vs. ABVD chemotherapy and ibritinib + R-CHOP chemotherapy vs. R-CHOP chemotherapy) that were preceded by phase I trials and then moved directly to phase III skipping phase II trials (37, 38). This approach could certainly spare time but the risks of underestimating the toxicities of the new combination before moving to phase III studies is higher in comparison with the standard approach.

Phase II studies are critical in the evaluation of new drug combinations. Priority should be given to testing combinations that are based on strong biological rationale. Phase II studies should evaluate patients’ subsets and biomarkers and they should use a high-efficacy bar (either in terms of response rate or time-related end points) to move forward. Although genome-sequencing data are increasingly used to select patients for targeted therapy, it is necessary to better standardize the methods that are used and the bioinformatics as different sequencing platforms may give different results due to sample preparation, sequencing methods and bioinformatics analysis tools (39). Phase II
Seamless adaptive trials can be more efficient performed sequentially, and combine all phases in one large trial. In contrast, phase I, II, and III studies that are traditionally performed sequentially, and combine all phases in one large trial, are often long for completing these studies (43). Recently, current basket trials in solid tumors include patients with different tumor types, such as lung, colon, breast, and other cancers. In lymphoma, where more than 60 different subtypes exist, it will be important to design lymphoma-specific trials that can capture patients with different lymphoma subtypes based on shared genetic biomarkers.

Adaptive designs for randomized phase II/III clinical trials may increase the efficiency of these trials by reducing the need for enrolling a large number of patients, and therefore, reducing the time for completing these studies (43). Recently, seamless adaptive designs have become more popular, as they blur the boundaries between phase I, II, and III studies that are traditionally performed sequentially, and combine all phases in one large trial (44). Seamless adaptive trials can be more efficient as they allow flexibility in trial modifications during the conduct of the study, including increasing sample size, and adding new cohorts to evaluate different dosing schedules and/or to examine treatment efficacy in biomarker-defined subpopulations (44). In fact, recent examples of seamless trials evaluating immune checkpoint inhibitors encompassed an entire drug development program in a single trial. This trial design is most suitable for drugs with impressive efficacy, as they can accelerate drug approval bringing these effective patients quickly to benefit patients. Therefore, agents with weak or modest clinical efficacy may not be suitable candidates for this design.

The implementation of seamless adaptive designs in lymphomas could be explored in diffuse large B-cell lymphoma (DLBCL), where classical designs going from phase II to phase III trials have failed to improve first-line treatment despite hundreds of trials performed and thousands of patients treated (45). The recognition of the molecular heterogeneity of DLBCL based on the cell-of-origin which distinguishes two main molecular subtypes (germinal center B-cell–like and activated B-cell–like) and the identification of different oncogenic pathways that are altered and can be potentially targeted, could form the basis for a master protocol design testing different combinations of new drugs with the standard first-line R-CHOP treatment. However, such a trial would require major efforts and international collaborations between academia, pharma, and regulatory agencies.

The optimal statistical endpoints to use in phase II/III studies, traditional endpoints such as response rate, progression-free survival (PFS) and overall survival (OS) are being used on the basis of the specific lymphoma subtype. In DLBCL, PFS at 24 months is proposed as a surrogate for OS (46). In addition to these endpoints, new endpoints, including minimal residual disease should be explored in future clinical trials (Table 3; refs. 47, 48).

**Unique Clinical Trials Endpoints**

OS remains the gold standard for measuring success of new therapies. However, to show improvement in OS survival requires long-term follow up, sometimes exceeding 10 years. To accelerate the development of new regimens there is a tremendous interest in using surrogate biomarkers that may predict improvement in OS. This is mainly relevant to clinical trials in patients with indolent B-cell lymphomas, such as follicular lymphoma and marginal zone lymphoma. Early progression or events have been proposed as new surrogate endpoints to OS in patients with follicular lymphoma treated with frontline regimens (49, 50). However, these endpoints have not been validated prospectively in modern era, where PET imaging is used for staging. Similarly, maintaining complete remissions for 30 months has also been proposed as a surrogate endpoint for follicular lymphoma (51), but this also needs validation in prospective studies. Other surrogate endpoints include eradication of circulating tumor DNA, which could be applied across lymphoma types.

**Conclusions and Future Directions**

The meeting ended with an overview of the conclusions drawn from both presentations and discussions. There was uniform agreement that we need standardization of clinical trials.
methodology in patients with lymphoma. This meeting has represented a first attempt to describe current drug development in lymphomas and to focus on some open critical questions that will need to be addressed in the future. It was agreed that a follow-up meeting will take place to establish guidelines of drug development and clinical trial methodology in lymphoid malignancies.

Disclosure of Potential Conflicts of Interest
J.F. Seymour reports receiving commercial research grants from Janssen, Celgene, Roche, and Abbvie; reports receiving speakers bureau honoraria from Abbvie and Roche; and is a consultant/advisory board member for Abbvie, Celgene, Janssen, Roche, Sunesis, and Takeda. V. Ribrag is a consultant/advisory board member for Gilead, Infinity, MSD, Bristol, Myers Squibb, Epizyme, Nanostring, Incyte, and Pharmamar. E. Zucca reports receiving speakers bureau honoraria from Gilead, and is a consultant/advisory board member for Roche.

References
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