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Supplement Article

XIV. The rationale for combining targeted and biological anti-lymphoma drugs

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Introduction

Over the past 30 years, the survival rate of patients with non-Hodgkin lymphoma and Hodgkin lymphoma has significantly improved. In the mid 1970s, patients with non-Hodgkin lymphoma were expected to have a 5-year survival of approximately 45%. In 2008, it is estimated that 60–70% of patients with non-Hodgkin lymphoma would be alive after 5 years from diagnoses. The improvement in patient's survival is not restricted to one histologic subtype. Data from recent randomized trials and retrospective analysis of large data bases showed improvement in survival of patients with diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma. Surprisingly, with the exception of rituximab, no major treatment changes were introduced over the last 30 years. For example, cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone chemotherapy that was introduced in the 1970s remains the most widely used backbone in the majority of frontline regimens. Similarly, most salvage therapy has not changed over the past three decades, with the majority being platinum-based regimens. In the meantime, our understanding of the basic genetic and biologic features of lymphoma has tremendously improved over the past few years. In the 1970s, the lymphoma diagnosis was based on the Rappaport classification that grouped lymphoma into four major categories. Today, with the use of molecular and genetic tools, more than 60 distinct subtypes of lymphoma can be identified using the WHO classification. This improved ability to precisely diagnose subset of lymphoma, however, did not translate into improvement of treatment outcome. The lack of progress is clearly not related to lack of drugs. To the contrary, the number of oncologic drugs available for evaluation in the clinical and clinical settings continues to increase.

Today, there are more than 800 compounds being evaluated. On the other hand, there is an increase in the failure rate of drugs that are evaluated in phases I, and II and even phase III trials. For example, in 2011, there were 101 phase II clinical trials that actively enrolled patients with different types of lymphoma in North America. During the same period, only five phase III clinical trials were available. This clearly illustrates that significantly fewer compounds are advancing from phase II to phase III studies. This high failure rate is mainly due to either lack of significant clinical activity, excessive toxicity or both. A review of recently reported phase II studies of novel agents in patients with relapsed lymphomas showed that these agents frequently produce response rates below 30%, which is not sufficient to secure an approval strategy based on single agent activity [1]. Furthermore, in most of these phase II trials, the median duration of response rarely exceeds 6 months.

Strategies for improving treatment outcome of novel agents in lymphoma

Patients selection based on predictive biomarkers

Because the overall response rate of single gents in unselected patients with relapsed lymphoma is low, future development strategies should focus on evaluating drugs in a pre-selected patient population that are likely to have a higher response rate. For this strategy to be successful, a link between drug clinical activity and predictive biomarkers will be required [2].

In the most simple way, patients can be identified on the basis of the presence of a single 'driver' genetic alteration that can be targeted with novel agents. An example is bcr-abl translocation in chronic myelogenous leukaemia (CML). This genetic abnormality is present in almost all patients with CML, and targeting bcr-able with small molecules results in a high-response rate. Another recent example is preselecting patients with non-small cell lung cancer based on the presence of anaplastic lymphoma kinase (ALK) translocation. This genetic defect is present in less than 10% of patients with non-small cell lung cancer. However, when patients are pre-selected on the basis of this genetic abnormality, a 50% response rate

can be achieved with anaplastic lymphoma kinase targeted agents, such as such as crizotinib. These successful strategies inspired intensive search to find similar genetic driver alterations in lymphoma. With the recent sequencing of the genome of several types of lymphomas, including diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt lymphoma, the next step will be to identify driver alterations and to develop targeted agents for such genetic abnormalities. Because most genetic mutations reported in lymphoma occur at a low frequency, it will be difficult to envision development of different treatment strategies based on these rare mutation events. Although one can develop treatment strategy for a genetic defect in non-small cell lung cancer that occurs in less than 10% of the patients, such as strategy is impractical because of the lower incidence of non-Hodgkin lymphoma compared with lung cancer. Instead, it would be more practical to group several genetic alterations in one unifying oncogenic pathway. Thus, rather than targeting each genetic defect individually, one can develop treatment strategies to target different components of a well-defined signalling pathway that may result from one or more genetic alterations. For example, the PI3 kinase/AKT/mTOR pathway can be targeted at any of these protein levels regardless of whether they are mutated or not. In fact, these oncogenic signalling pathways are frequently activated by aberrant production of cytokines and growth factors. Thus, targeting activated oncogenic signalling pathways can be explored therapeutically regardless of the cause of pathway activation, it will be important to develop a diagnostic method to accurately measure pathway activation that can potentially be used as a predictive biomarker.

Combination strategies

Most tumour cells depend on multiple parallel or interactive networks of signalling pathways that contribute to the oncogenic process (Figure 1). It is, therefore, not surprising that most of the single agents that target one signaling pathway produce low response rates. Targeting multiple signaling pathways frequently results in an enhanced anti-tumour effect [3]. Furthermore, when tumour cells are treated with certain signal transduction inhibitors, they frequently activate alternative signaling pathways that undermine the activity of the drug. In these cases, it is logical to develop mechanism-based combination regimens that take into account the ability to block such negative feedback loops.

In recent years, the US Food and Drug Administration provided guidelines for the development of novel combination regimens. The development of such regimens should be based on preclinical or preliminary clinical studies suggesting that the combination results in a greater than additive activity of the single agents and/or more durable responses achieved with single agents. Mechanistically, to achieve these goals, such combinations can target multiple components in the same signalling pathway (such as targeting PI3K and mTOR), block multiple parallel signalling pathways (such as inhibiting PI3K/AKT/mTOR and JAK/STAT pathways) or block resistance negative feedback loops.

Examples of combination strategies to block negative feedback loops include combining mTOR and Histone deacetylase (HDAC) inhibitors and JAK2 and MAP kinase inhibitors. When lymphoma cell lines are treated with

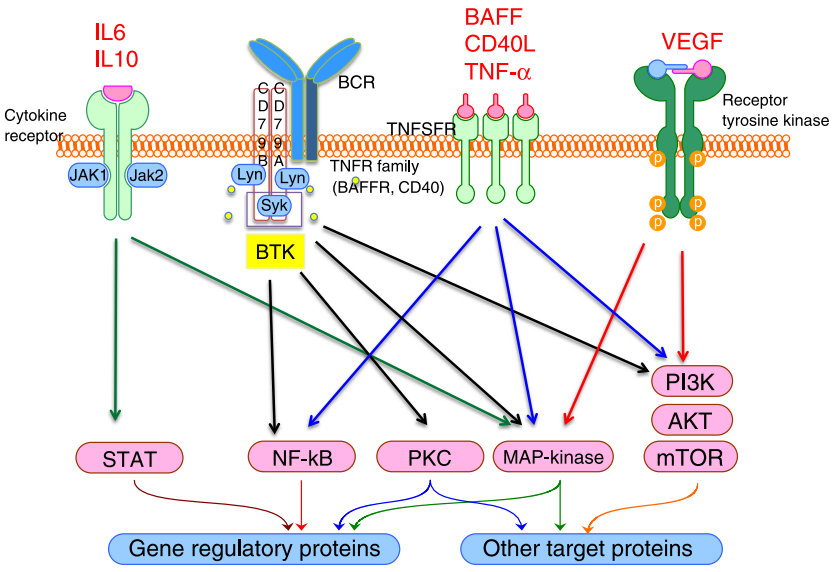

Figure 1. Most tumour cells utilize several parallel and overlapping signalling pathways to promote their survival. In B-cell lymphoma, oncogenic signalling pathways are frequently activated by extracellular cytokines and growth factors leading to activation of JAK/STAT, NF-kB, MAP kinase and PI3K signalling pathways. To achieve an optimal cell kill, combination of drugs that inhibit these pathways will be required

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mTOR inhibitors, they frequently phosphorylate AKT through a negative feedback involving mTORC2. In turn, this attenuates the anti-tumour effect of mTOR inhibitors. On the other hand, HDAC inhibitors can inhibit AKT phosphorylation, providing a mechanistic rationale for combining both agents [4,5]. Similarly, JAK2 inhibitors can inactivate STAT3 phosphorylation leading to cell cycle arrest and death. However, in some cases, inhibition of JAK2 is associated with MAPK activation and ERK phosphorylation [6]. This observation provides a rationale for combining JAK2 inhibitors with MAP kinase inhibitors.

Conclusions

With the increasing number of anti-cancer agents, the failure rate of drug development continues to rise. Current treatment strategies are focusing on identifying predictive biomarker to preselect patients for these new drugs. A second strategy is based on rational design combination strategies. These complimentary strategies are actively being tested in clinical trials and will hopefully accelerate drug development for patients with lymphoma. Finally, a revised response criteria to evaluate the efficacy of novel agents should be considered to take properly into account patients' benefit [7].

Conflict of interest

The authors have no competing interest.

References

1. Younes A. Beyond chemotherapy: new agents for targeted treatment of lymphoma. *Nature Reviews. Clinical Oncology* 2011; **8**(2): 85–96.
2. Younes A, Berry DA. From drug discovery to biomarker-driven clinical trials in lymphoma. *Nature Reviews. Clinical Oncology* 2012; **9**(11): 643–653.
3. Yang Y, Shaffer AL, Emre NC, *et al.* Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma. *Cancer Cell* 2012; **21**(6): 723–737.
4. Lemoine M, Derenzini E, Buglio D, *et al*. The pan-deacetylase inhibitor panobinostat induces cell death and synergizes with everolimus in Hodgkin lymphoma cell lines. *Blood* 2012; **119** (17): 4017–4025.
5. Gupta M, Ansell SM, Novak AJ, Kumar S, Kaufmann SH, Witzig TE. Inhibition of histone deacetylase overcomes rapamycin-mediated resistance in diffuse large B-cell lymphoma by inhibiting Akt signaling through mTORC2. *Blood* 2009; **114** (14): 2926–2935.
6. Derenzini E, Lemoine M, Buglio D, *et al*. The JAK inhibitor AZD1480 regulates proliferation and immunity in Hodgkin lymphoma. *Blood Cancer Journal* 2011; **1**(12): e46.
7. Younes A, Hagenbeek A, Coiffier B. Optimising the lymphoma response criteria in the era of targeted therapy. *The Lancet Oncology* 2011; **12**(7): 616–617.

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