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Perspective

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Moving towards the chemo-free treatment of lymphoma: hype or reality?

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Abstract

A new generation of novel, effective targeted drugs and cellular therapies include monoclonal antibodies directed at the cell surface, such as the anti-CD-19 tafasitamab which, combined with lenalidomide, is the first therapy approved by the Food and Drug Administration for second-line treatment of diffuse large B-cell lymphoma. Other agents interfere with pro-survival intracellular signaling pathways including drugs that inhibit Bruton tyrosine kinase, phosphatidylinositol-3 kinase (PI3-kinase), and bcl-2. An increasing number of therapies impact the microenvironment, notably checkpoint inhibitors and bispecific antibodies. Chimeric antigen receptor-T cell therapy has improved the outcome of patients with a variety of histologies of lymphoma. Whereas in the past, such therapies would be used inrelapsed and refractory settings, they are now being evaluated as initial treatment in selected patients. With an improved ability to individualize treatment approaches, chemo-free will be a reality for lymphoma patients.

Keywords: Lymphoma, targeted therapies, chemo-free, bispecifics, BTK inhibitors, PI3k inhibitors, CAR-T cell

BACKGROUND

The beginnings of chemo-free approaches

The possibility of treating diseases such as cancer with immunologic therapies dates back two centuries to the imagination of Pro. Paul Ehrlich, the father of modern immunology. Ehrlich[1] conceptualized the Magic

Bullet, which bore a startling likeness to the structure of an antibody, that would attack the invaders while sparing normal cells. Nonetheless, it took more than a century for Kohler and Milstein[2] to develop the hybridoma technology that would enable the production of adequate quantities of monoclonal antibodies for clinical use and a few more years for Nadler *et al.*[3] to identify a suitable protein (B1, now known as CD20) on the malignant cell to target. After initial demonstrations of its activity in patients who had been previously treated[4,5], Ghielmini *et al.*[6] demonstrated impressive activity for the chimeric anti-CD20 monoclonal antibody rituximab in patients with and without prior therapy for their follicular lymphoma. Countless trials ensued, combining rituximab with various chemotherapy regimens as initial treatment of follicular and diffuse large B-cell lymphoma (DLBCL) and demonstrating a consistent survival advantage[7-10]. Meanwhile, in a parallel universe began the pursuit of a chemo-free approach. In 2003, investigators from what was then the Cancer and Leukemia Group B were the first to embark on a series of biological doublets, first with two monoclonal antibodies in previously untreated patients with follicular lymphoma: rituximab with the anti-CD80 galiximab[11] achieved an overall response rate (ORR) of 72%, with 48% complete remissions (CRs), with ORR and CR rates of 92% and 75%, 80% and 48%, and 55% and 27%, respectively, for low, intermediate, and high follicular lymphoma international prognostic index (FLIPI) scores. The progression-free survival for the low FLIPI patients was 75% at three years. Rituximab with the anti-CD22 epratuzumab[12] achieved an ORR of 87%, including 42% CRs. They next combined the anti-CD20 with the immunomodulatory agent lenalidomide, creating the regimen they called R^2. Their first study in relapsed patients showed a significant benefit compared with lenalidomide alone[13]. When used as front-line therapy, each of these regimens was not only well-tolerated, but achieved response rates from 85%-95%[14], similar to what was achieved with chemoimmunotherapy regimens. Moreover, these responses were durable, many of which often lasting beyond a decade without recurrence. R^2 was pursued by other investigators[15] and is now approved for relapsed and refractory follicular and other indolent non-Hodgkin lymphomas (NHL) based on data from the Augment trial[16]. In the front-line RELEVANCE trial, R^2 showed similar efficacy with a more favorable toxicity profile compared with chemo-immunotherapy[17]. Unfortunately, the study did not meet its superiority endpoint.

The next generation of chemo-free agents

Over the last few years, a new wave of targeted agents has further enhanced interest in chemo-free approaches to lymphoid malignancies. A first-in-class oral inhibitor of activating mutation of Enhancer of zeste homolog 2, tazemetostat, offers a new option in patients with follicular lymphoma[18]. Impressive results with the covalent Bruton tyrosine kinase inhibitors such as ibrutinib, acalabrutinib, and zanubrutinib leukemia[19-24], and the non-covalent LOXO-305[25] have recreated the landscape for chronic lymphocytic leukemia (CLL) as well as other lymphoma histologies[26-30]. In addition, the bcl-2 inhibitor venetoclax has assumed a major role as a single agent, but more so in combinations[31,32]. Also active are the PI3k inhibitors idelalisib[33,34], copanlisib[35], duvelisib[36], and umbralisib[37]. As a result of these highly active, well-tolerated agents, CIT is now a blur in the rear view mirror for CLL and small lymphocytic lymphoma, patients with MYD88 mutated Waldenström macroglobulinemia, relapsed and refractory mantle cell lymphoma and marginal zone lymphomas. These therapies have rapidly moved to the front line in appropriate patients[31,32].

Chemo-free agents for Hodgkin and aggressive lymphomas

Now that we have taken care of the indolent diseases, at least for a while, what is the possibility of eschewing chemotherapy in the more aggressive histologies? For Hodgkin lymphoma, the universe shifted with the availability first of the antibody-drug conjugate brentuximab vedotin, and subsequently with the checkpoint inhibitors, nivolumab and pembrolizumab. After demonstrating single-agent activity in the relapsed refractory setting[33-40], these agents have been combined and sequenced with chemotherapy for relapsed/refractory patients as well as part of initial therapy[41,42]. Recently a trial of BV-Nivo in untreated HL patients who were older or considered unsuitable for chemotherapy, demonstrated a

cure without chemotherapy[43].

The last bastion appeared to be DLBCL. Aggressive diseases need aggressive treatment, right? Perhaps not! For patients who have already been failed by chemoimmunotherapy, repeating similar programs makes little sense. One of the newer regimens for relapsed or refractory DLBCL to even include a modest chemotherapy drug has been the combination of polatuzumab vedotin, the anti-CD79b antibody-drug conjugate, with bendamustine and rituximab, which has been approved in the United States as a third or subsequent line of therapy. Indeed, the new therapies have tended to rely more on targeted approaches. Indeed, the first regimen to be approved by the FDA for patients following a single prior line of therapy is L-MIND, the combination of the anti-CD19 monoclonal antibody tafasitamab with the immunomodulatory agent lenalidomide. This non-chemotherapeutic regimen achieves an overall response rate of 58% with 40% CRs, median duration of response of 34.6 months, with a median PFS of a year, at least as good as many multi-agent chemotherapy regimens in this setting[44]. More recently, loncastuximab tesirine, a CD-19 directed antibody-drug conjugate, was granted accelerated FDA approval for patients with relapsed and refractory DLBCL beyond the second line, based on the results of a multicentre phase II study LOTIS-2. The overall response rate was 48.3% with 24.1% CR rate and a median response duration of 10.3 months[45]. Selinexor, an oral inhibitor of nuclear transport protein exportin 1, induces responses in 28% of patients with 12% CR and a median duration of response of 9.3 months[46]. Based on these data from the SADAL trial, this drug was granted accelerated approval by the FDA for patients who have progressed following two or more lines of therapy. Although the single-agent results with this drug are modest, the drug has a promising future in combination with other drugs.

The potential of new cellular and immunotherapies

Presentations at the American Society of Hematology Annual Meeting in 2020 describing results with bispecific T-cell engagers and cellular therapies also strongly support a chemo-free future[47,48]. Not only does the CD3xCD20 bispecific mosunetuzumab exhibit activity in relapsed and refractory DLBCL and FL[49], but, in previously untreated, older, frail patients, it achieved responses in 57%-75% of patients, based on dose, including 37.5%-50% complete remissions, some of which were ongoing beyond a year[50]. Causing at least as much excitement were the results of ZUMA-12, a phase II study of the Chimeric antigen receptor-T (CAR-T) product axicaptagene ciloleucel as first-line therapy in patients with high-risk DLBCL characterized by being a high-grade B-cell NHL with *MYC* and *BCL2* and/or *Bcl-6* translocations, or an IPI score ≥ 3. The ORR was 85% with 74% CRs. 70% of responses were ongoing beyond the median follow-up of 9.3 months[51].

Nonetheless, the road to a chemo-free world has not always been a smooth one[52]. In a number of instances, combining agents either with chemotherapy or even with others, each with a favorable safety profile led to life-threatening or even fatal toxicities. The experience with CAR-T has certainly been a steep learning curve. As more targeted drugs and cellular therapies become more readily available in general practice, the temptation to arbitrarily combine them in general practice will be powerful. However, multi-agent combinations must first be carefully monitored in clinical trials before subjecting patients to a risk of serious, unforeseen adverse effects.

One chemo-free approach does not fit all

Before we can totally banish chemoimmunotherapy from our armamentarium, a number of challenges must be overcome. First and foremost, biomarkers must be identified to help direct specific treatments to individual patients. Second, rather than what is usually empiric, targeted combinations should be based on sound scientific rationale for efficacy, with careful consideration for avoiding overlapping toxicities. Adaptive randomized trial design incorporating multiple arms and rapidly dropping those that fail to demonstrate sufficient efficacy or tolerability may help facilitate the completion of studies while preventing

patients from receiving knowingly ineffective regimens.

A number of assays are currently available to distinguish between patients with a high likelihood of responding to standard treatment versus those almost certainly to fail. Nonetheless, these patients are generally treated exactly the same. In the near future, patients will be assessed prior to therapy with respect to molecular signatures[53,54], circulating tumor DNA[55], total metabolic tumor volume[56], next-generation sequencing[57] and others to determine for whom conventional treatments are satisfactory, or, alternatively, which patients should be referred directly to investigational studies[58]. To be sure, the burgeoning number of increasingly effective drugs and cellular therapies should provide convincing evidence that patients with lymphoid malignancies can look forward to the reality of an improved outcome in a chemo-free world.

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Authors' contributions

The author contributed solely to the article.

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Conflicts of interest

The author consults or participates in advisory boards with Abbvie, ADC Therapeutics, AstraZeneca, Beigene, Epizyme, Genmab, Incyte, Lilly, Morphosys, Karyopharm, Pharmacyclics, Kite, Merck, Symbio. He is on speakers bureaus for Beigene, Incyte, Morphosys.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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