endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, a causal relationship must be considered. In the IgM type, a gammopathy-associated PN is likely (50% have anti-myelin-associated glycoprotein activity), whereas a chronic inflammatory demyelinating polyneuropathy with a coincidental MGUS is the most likely diagnosis in the IgG and IgA types.

The main skin conditions related to M proteins are cryoglobulin (IgG/IgM) vasculitis with petechiae, purpura, or ulcers; Schnitzler syndrome (mostly IgM with chronic urticaria, recurrent fever, arthralgia, and neutrophilic leucocytosis); pyoderma gangrenosum (IgA, ulcers with central necrosis); necrobiotic xanthogranuloma (IgG with yellow subcutaneous papules, plaques, or nodules mainly in the periorbital area, legs, arms, and chest); scleromyxedema (IgG-IgA with mucocutaneous deposition and occasional systemic involvement with cardiomyopathy, pulmonary fibrosis, or reduced esophageal motility), and acquired generalized cutis laxa (mostly IgG and IgG-IgA with elastolysis of the skin resulting in premature aging, occasionally associated with fibrillary glomerulopathy and heart or lung involvement).

The most frequent ocular M-protein-related condition is crystalline keratopathy consisting of Ig deposition, corneal thickening, photophobia, and finally visual loss. Bleeding can result from factor X deficiency in AL amyloidosis, acquired factor VIII deficiency leading to von Willebrand disease, or by impaired platelet aggregation induced by the M protein.

Given the high prevalence of MGUS in the elderly with nonrelated comorbid diseases, the diagnosis of MGCS requires the reasonable exclusion of a chance association. A biopsy to demonstrate the monoclonal Ig in the affected organ or tissue and the appropriate immunohistologic and electron microscopy studies must be performed. Autoantibody titers, serum complement levels, cryoglobulin determination, factor X and factor VIII measurements, and platelet aggregation studies can be also helpful. In several cases, such as in Schnitzler syndrome, pyoderma gangrenosum, or scleromyxedema, the association is supported only by epidemiologic data. Despite an extensive evaluation, including organ or tissue biopsy, in some cases in which an association between the M protein and the organ injury is highly suspected, no definitive evidence of causality has been found. These cases require a careful multidisciplinary evaluation (ie, hematologist plus nephrologist or hematologist plus dermatologist) to decide whether or not to treat the MG. In cases that are highly suspicious, a short treatment test such as 2 or 3 courses of bortezomib and dexamethasone (with treatment continuation in case of a favorable response) would be most reasonable.

In summary, the introduction of the novel concept of MGCS is important because it can increase clinicians’ awareness of the fact that a small amount of M protein can cause severe and several clinical conditions. When suspected, the causal relationship between the M protein and organ or tissue damage must be promptly investigated. Finally, if a causal relationship is proven or highly suspected, therapy against the plasma cell clone (rituximab-based in IgM types and bortezomib-based [including autologous stem cell transplantation] in non-IgM types) should be initiated.

Conflict-of-interest disclosure: J.B. and M.T.C. declare lectures honoraria from Janssen.

REFERENCES

© 2018 by The American Society of Hematology

CLINICAL TRIALS AND OBSERVATIONS

Comment on Morschhauser et al, page 1486

Next-generation therapy for follicular lymphoma

Loretta J. Nastoupil | MD Anderson Cancer Center

In this issue of Blood, Morschhauser et al report the safety and efficacy of lenalidomide in combination with obinutuzumab and establish the recommended phase 2 dose (RP2D).1 Rituximab in combination with lenalidomide (R2) has favorable efficacy and toxicity in relapsed and untreated follicular lymphoma (FL) and is now entering the treatment landscape of FL.2-4 Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC), may be an attractive partner to lenalidomide that can exert immunomodulatory effects via natural killer (NK) and T cells for the treatment of relapsed or refractory (R/R) FL. The question is whether the potentially enhanced ADCC activity of obinutuzumab will translate into enhanced synergism with lenalidomide and result in an improved next-generation R2.

Outcomes for FL have improved over the past few decades, and many patients diagnosed in the modern era can anticipate a normal life expectancy.5 However, FL remains a disease associated with continued risk for relapse.

© 2018 by The American Society of Hematology

blood® 4 OCTOBER 2018 | VOLUME 132, NUMBER 14 1465
Currently, the greatest unmet need in new drug development is to alter the natural history among those who experience early relapse (<24 months) following frontline chemoimmunotherapy. Identifying effective, well-tolerated therapies that result in meaningful remission duration without negatively impacting quality of life remains fundamental to clinical research in this field. Providing insight into treatment selection and sequencing of therapy is also desirable given the list of therapeutic approaches is nearly as long as the natural history of this disease. With those ground rules, how do we interpret/incorporate the findings of this phase 1b dose-escalation study into the ever-expanding treatment landscape of FL?

Obinutuzumab is US Food and Drug Administration (FDA) approved for R/R patients with FL based on the GADOLIN study, which compared obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximab-refractory indolent lymphoma. With a median progression-free survival (PFS) of 25.8 months vs 14.1 months, the obinutuzumab-containing arm was superior to chemotherapy alone. Neutropenia, an adverse event associated with obinutuzumab was one of the most common grade 3 or higher adverse events observed at 27.5%. GADOLIN provides a snapshot of the efficacy and safety of obinutuzumab in combination with bendamustine in rituximab-refractory. Though superior to chemotherapy alone, it is less clear whether obinutuzumab is superior to rituximab in this setting based on the study design.

Targeted therapies have been promising in R/R FL. Idelalisib, a phosphatidylinositol 3-kinase δ (PI3Kδ) inhibitor, and copanlisib, a pan-PI3K inhibitor with predominant activity against α and δ isoforms, are both approved for the treatment of R/R FL patients who have failed at least 2 prior lines of therapy. Idelalisib was associated with a 57% objective response rate (ORR) and 11-month PFS among patients refractory to rituximab and an alkylating agent. Copanlisib was associated with an ORR of 59% and median PFS of 11 months. Though similar in efficacy, the safety profile of these 2 PI3K inhibitors is different, with less gastrointestinal toxicity and higher rates of hyperglycemia and hypertension associated with copanlisib.

The toxicity profile of PI3K inhibitors (ie, pneumonitis, colitis, transaminitis, rash, and infection) has likely impacted the uptake of these drugs despite their efficacy profile in poor-risk patients.

R² is under active exploration for relapsed indolent lymphoma. The phase 3 AUGMENT study met its primary end point of superior PFS of R² compared with rituximab monotherapy in relapsed follicular and marginal zone lymphoma. The details are forthcoming but will likely lead to FDA approval of R² for R/R FL. The control arm is likely to impact the excitement surrounding this study, but it is important nonetheless to allow exploration of the impact of combination over R monotherapy. The MAGNIFY study is examining 12 cycles of R² followed by R² maintenance vs rituximab maintenance in indolent and mantle cell lymphoma. Preliminary efficacy has been reported for the FL subgroup including cohorts of early-relapse or double-refractory (CD20 monoclonal antibody and alkylating agent) patients. R² was associated with an ORR of 66% and 1-year PFS estimates of 70% for R/R FL. The early-relapse and double-refractory cohorts had less favorable but meaningful outcomes, with ORRs of 47% and 45% and 1-year PFS estimates of 49% and 65%, respectively. Neutropenia was one of the most common grade 3 or 4 adverse events at 29%. R² appears to be an effective, manageable strategy for R/R FL. It remains unknown whether the greatest uptake will be in third-line or earlier lines of therapy.

This leads us to the current study: obinutuzumab in combination with lenalidomide in R/R FL. This dose-escalation study established the RP2D of lenalidomide at 20 mg in combination with a fixed dose of obinutuzumab (1000 mg). Only 19 patients were evaluable for safety and efficacy and had favorable features. Mean age was 61.5 years, and most had excellent performance status (80% Eastern Cooperative Oncology Group 0), responded to prior rituximab (60%) or prior lymphoma therapy (80%), and had nonbulky disease (75% with lymph nodes <5 cm in size). With a median follow-up of 38.1 months, the 3-year PFS was 52% and ORR was 63%. The most common grade 3 or higher adverse event was neutropenia at 26%. Therefore, the combination appears effective and manageable, with no new safety signals. Commendable is the schedule (6 cycles of therapy). In an era where longer duration of therapy is commonly pursued, this is an important distinction for this study. Larger studies are necessary to understand whether this is a superior option to the available therapies, most importantly, its predecessor (R²).

Where do we go from here? The importance of this study is establishing the RP2D for the potentially practice-changing trials. An important study, SWOG S1608, is a randomized phase 2 study exploring 3 arms for early-relapsing FL. One arm is obinutuzumab and lenalidomide. The other arms include a PI3Kδ inhibitor in combination with obinutuzumab and a chemotherapy arm. Understanding how to approach early-relapse FL is critical and will address the greatest unmet need. Obinutuzumab and lenalidomide have a critical role in one of the most important modern-day FL studies.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Downloaded from http://ashpublications.org/blood/article-pdf/132/14/1465/1406897/blood868117.pdf by guest on 03 November 2021


DOI 10.1182/blood-2018-08-868117
© 2018 by The American Society of Hematology

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Scarfò et al, page 1495

Getting the most from your CAR target

David M. Barrett | Children’s Hospital of Philadelphia

In this issue of Blood, Scarfò et al describe a new target for chimeric antigen receptor (CAR) T cells, CD37, that reveals how the field of immunotherapy is adapting after the landmark success of CD19 CAR T cells.

The US Food and Drug Administration approval of both isatigeneceilucel for pediatric leukemia and axicabtagene ciloleucel for adult lymphoma was based on the stunning efficacy of targeting CD19-positive malignancies.2-3

I remember quite clearly the first 2 pediatric patients at the Children’s Hospital of Philadelphia who were treated with isatigeneceilucel. The first patient experienced grade 4 cytokine release syndrome, received the first ever dose of tocilizumab for this event, and entered a deep remission that lasts to this day. The second patient also had a complete response but sadly became the first case of CD19-negative or escape-variant relapse only 2 months after infusion and later died of her leukemia.4 The second patient illustrates a key problem in the field, how to treat or prevent relapse as a result of single antigen loss, which is addressed by the Scarfò et al article.

Antigen-loss variants make up a substantial portion of the relapses seen with CD19 CAR therapies.5-6 Landmark work with CAR T cells targeting CD22 was the first to target these relapses, but low antigen density and the evolution of cancer to resist immune therapies have resulted in lower initial response rates than that seen with CD19 CARs, and antigen escape remains a problem.7 Scarfò et al describe CD37, a surface antigen on some B-cell and T-cell malignancies, as a potential CAR target that can be used in combination with CD19 in the setting of first-line therapy or as a treatment for CD19 antigen escape variants. In the field of immunotherapy, the approach to validating a new CAR target is fairly standardized: (1) validate expression on the relevant malignancy, (2) construct a CAR with your favored costimulatory domain, (3) test for killing and cytokine release in vitro, and (4) test in a mouse model. Scarfò et al hit all these benchmarks, and their approach and controls are of high quality. What sets their article apart is an additional and highly impactful observation about their target as well as the combination of their CAR with a CD19 CAR to make a 2-antigen targeting version.

As we learned from CD22 and CD19, there is no guarantee that any single antigen is a perfect target, and this is likely true when considering combination CAR T therapy. The concept of combinations can take many forms, including simply 2 CARs in 1 T cell or more complex single chain structures such as the TanCAR approach described by Ahmed and colleagues.8 Scarfò et al take the latter approach, chaining together the anti-CD37 and anti-CD19 recognition domains into a single long CAR molecule with 1 set of signaling domains. Then they validate that this construct works against CD37- and CD19-expressing targets, which gives hope that this kind of construct can suppress and treat antigen loss variants.

The novelty of CD37 as an antigen for CAR T cells extends beyond simply not being CD19. As an important adjunct, this antigen is also expressed on some T cells and in peripheral T-cell lymphomas. T-cell malignancies in pediatrics have high remission rates with chemotherapy, but relapsed T-cell disease has a poor prognosis.9 The field of immunotherapy has struggled with how to target T-cell malignancies with T-cell therapies, because the issue of fratricide, on the surface, seems to be quite formidable. The advent of gene editing technologies such as TALEN and CRISPR has given cellular therapists tools to delete the target antigen from the CAR T cells, but this approach only kicks the can down the road.10 If you have CAR T cells targeting a developmental T-cell antigen such as CD2 or CD5, how will the patient recover normal T-cell function? How long do you need to have CAR T cells present to be cured? How can you be sure you eliminate all the CAR T cells with a suicide gene? One of the attractive features of CD37 described by Scarfò et al is that it is present on peripheral T-cell malignancies but does not seem to result in fratricide in CD37 CAR T cells. Finding an antigen that discriminates a malignant T cell from a normal T cell, at least in a subset of T-cell diseases, challenges researchers to look harder for these targets.

In summary, the article by Scarfò et al exemplifies 2 areas at the heart of innovation in cellular therapy for cancer: multiantigen targeting and smart antigen selection. The next phase is testing the CD37 CAR for safety and hopefully moving the combination CD37 and CD19 CAR to the clinic soon thereafter. The family of the second patient we treated generously agreed to let us study her leukemia in the laboratory so we could learn why antigen escape happens and work to prevent it from happening to other children. After reading the article by Scarfò et al, I want to determine whether her leukemia had CD37, even though CD37 is rare in immature B-cell malignancies. Maybe it did and maybe it did not, but there is now a reason to hope that we can target CD19 escape variants or better yet, prevent them in the first place.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Downloaded from http://ASHPublications.org/doi/pdf/10.1182/blood-2018-08-868117 by guest on 03 November 2021