ductive agents have been added to achieve hematocrit control in patients at high risk for thrombosis. Thus PV has lagged behind other hematologic malignancies in the implementation of novel and targeted drug therapy. This has changed recently with the development of novel therapies for this disease, a number of which have received regulatory approval internationally.

Ruxolitinib has been approved as second line therapy for PV patients intolerant of or resistant to hydroxyurea on the basis of the RESPONSE trial. In this study 222 patients were randomized to receive ruxolitinib or best available therapy (BAT) in the second line setting. At 5 years 60% of the ruxolitinib patients versus 19% of the BAT patients maintained hematocrit control without need for phlebotomy. Reduction in spleen volume was also more frequent among ruxolitinib patients (89 vs. 49%). There were decreases in *JAK2* V617F allele burden in both groups but complete molecular remissions were rare. Importantly, herpes zoster infections occurred among ruxolitinib treated patients.

Interferon has become an important drug in the treatment of PV with the publication of interim and final results of a number of studies of pegylated versions of interferon. The Myeloproliferative Disorders Research Consortium (MPD-RC) 112 and MPD-RC 111 randomized studies previously treated and untreated patients respectively. Good clinical responses with manageable toxicity were attained and further follow up is awaited. The 3 year results of the combined PROUD-PV and CONTINUATION-PV, randomized, phase 3 trials comparing ropeginterferon (a novel, long-acting, mono-pegylated proline interferon) to hydroxyurea in newly diagnosed PV patients show improved complete haematological response and reduced *JAK2* V617F allele burden with ropeginterferon. The drug is also under study in patients with low-risk PV in whom hematocrit levels at or below 45% compared with those who received monthly phlebotomy alone were more common according to interim findings from the ongoing LOW-PV trial.

Novel agents for PV include MDM2 inhibitors, nutlins. MDM2, an inhibitor of *TP53* is up-regulated in PV CD34+ cells and exposure to a nutlin induced *TP53* and selective stem cell depletion in preclinical models. Early trials of idasanutlin, an oral MDM2 antagonist demonstrated a 58% overall response rate and median duration of response of 16.8 months in high-risk PV patients after failing prior therapy. Idasanutlin is being evaluated in a multinational phase 2 trial.

A unique approach to controlling the hematocrit in PV by targeting iron metabolism is currently in early testing. Hepcidin is the major physiologic regulator of iron metabolism. PTG-300 is a first-in-class synthetic hepcidin mimetic that is in phase 2 clinical trial development. The agent reduces iron available for erythropoiesis and in a preliminary study was able to maintain the hematocrit at <45% without need for phlebotomy in a small number of PV patients all of whom were previously phlebotomy dependent.

These novel agents and others will likely change treatment paradigms in PV.

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SP 27

New drugs for low grade lymphoproliferative diseases

Argiris Symeonidis

For asymptomatic patients with low-grade lymphoproliferative disorders and low tumor burden, watchful waiting represents a rational approach. For symptomatic patients or for those with high tumor burden, initial treatment is usually chemoimmunotherapy with an anti-CD20 monoclonal antibody (mo-Ab), most commonly Rituximab or Obinutuzumab plus an alkylator, such as bendamustine or chlorambucil and/or a pourine analog, such as fludarabine or cladribine. For the Refractory/Relapsed (RR) setting treatment options depend on patient's background, initial PFS and on various prognostic parameters. Newer anti-CD20 mo-Abs, such as Ublituximab appear equally effective, but have not yet been tested comparatively with the previous ones. Radioconjugates such as 90Y-ibritumomab tiuxetan and 131I-tositumomab are no more in broad use due to unpredicted myelotoxicity. The newer 90Y-epratuzumab tetratexan appears safe as consolidation following R-CHOP in DLBCL patients. Polatuzumab vedotin, Pinatuzumab vedotin and Tafasitamab targeting CD19 have mainly been used, combined with an anti-CD20 mo-Ab to treat RR-DLBCL with success, which render them candidates for indolent lymphomas also. BTK inhibitors represent one main treatment option, either as initial treatment or in the RR setting. Ibrutinib, the first in class drug, is used either alone or in combination with Mo-abs and/or alkylators. Acalabrutinib, already approved for CLL/SLL and MCL, is now being tested for other B-cell malignancies. Zanubrutinib, a newer analog not exhibiting some of ibrutinib's AE, has been approved for RR-MCL and is currently being evaluated alone or in combination with Mo-Abs, lenalidomide and other agents. Idelalisib, the first PI3K-inhibitor, the second family of highly used targeted agents, has been approved for CLL/SLL and FL. Duvelisib, Copanlisib and Umbralisib are newer agents coming up and are currently being tested usually in combination with mo-Abs or other agents. Bimiralisib, a dual PI3K/mTOR inhibitor is a promising agent still in phase I. Hepatotoxicity, the major AE of this class, is reversible and dose-dependent. The BCL2 inhibitor venetoclax, alone or combined with mo-Abs and/or bendamustine (BRVen) or with Ibrutinib (ongoing trial), is a breakthrough approach, being tested in several disease entities with impressive results. Bispecific antibodies engaging CD19 (Blinatumomab) or CD22 (Inotuzumab ozogamycin) to a T/NK-cell surface antigen have received approval for more aggressive B-cell lymphomas. Lenalidomide combined with Rituximab (R2) has demonstrated impressive results as initial treatment in FL and the newer cereblon-modifier Avadomide is now being tested in combination with Obinutuzumab in RR B-cell lymphomas of all types. Lenalidomide with Blinatumomab is also tested in an ongoing study. mTOR/NF-κB inhibitors (temsirolimus, everolimus) are not so effective as single agents but can be combined with various targeted and/or cytotoxic agents and construct synergistic regimens. Tazemetostat a novel EZH2 inhibitor recently received accelerated approval by FDA for patients with RR-FL and EZH2 gene mutations, following the

results of a phase-II study. Combinations of this drug with other agents are also expected. Immune check point inhibitors (Nivolumab, Pemprolizumab, Atezolizumab) are promising as third line treatment and beyond. Other agents under investigation include the inhibitor of nuclear export selinexor, the SYK inhibitor entospletinib, the dual SYK/JAK inhibitor certulatinib and the CDK inhibitors flavopiridol and dinaciclib.

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SP 28

Which aggressive B cell lymphoma should not be treated with RCHOP?

Christian Gisselbrecht

The standard treatment of high-grade B cell lymphoma with RCHOP did not change yet despite the description of the biological heterogeneity. With an overall survival rate superior to 80%, patients with an IPI score 0–2 define a good prognosis group and there is no need to modify this approach if chemotherapy still remain the main tool. How can you characterize high risk aggressive B cell Lymphoma? Important progress has been made in our understanding of the biology and immunology of the group of diseases now included within DLBCL, and now there is an expanding list of active, targeted options. The integration of molecular, genetic, and metabolic imaging studies is essential for clinical trials involving the rational assembly of drugs with various mechanisms of action and immunologic properties. Several adverse factors have been described, closely related to the technology used. In a first historical approach DLBCL can be biologically isolated in GCB and non-GCB subtype with a different outcome, Double hit Myc, Bcl2 translocations, or double expressors Myc, Bcl2 are associated with a poor prognosis. Attempts have been made to elaborate a new classification that integrate next-generation sequencing. In this heterogenous high risk lymphoma, RCHOP needs to be improved. Several targeted agents have been added to RCHOP however none of these new regimens were able until now to improve the outcome in randomized study. Another approach is to detect earlier patients still not achieving a satisfactory response. The percentage of is close to 30% and reflects the heterogeneity of the disease. Detecting early failure of response can be done by incorporating an evaluation with PET scan at diagnosis with the metabolic tumour volume and after two or four cycles for the quality of response. What can we propose for this population? Salvage chemotherapy and stem cell transplantation is the most common practice. Several studies have showed an improvement of survival for the patients with pet positive after two cycles. However, half of the patients will not be eligible for transplantation due to ineffective salvage treatment, and the other half will relapse after ASCT. There is clearly a need for new drugs that improve salvage efficacy. Impressive results have been reported with CAR-T cell engineering with a high response rate in refractory patients lasting over two years at the last report. This new approach will revolutionize the treatment of lymphoma.

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SP 29

How can we estimate early relapsed follicular lymphoma and how can we treat?

Ozan Salim

FL is the most common indolent non-Hodgkin lymphoma, generally with favorable outcomes (median overall survival [OS] >20 years). The median age at diagnosis is 65 years. Treatment options, both in the front line and in the relapse setting, are observation, immunotherapy and chemo-immunotherapy. The addition of rituximab to standard chemotherapy has significantly improved the OS. However, current treatment options for FL is not curative and a subgroup of the patients has a more aggressive clinical course (early progression, histologic transformation). Histological transformation of FL occurs at a risk of 2% per year. At the time of diagnosis, the FL international prognostic index (FLIPI) and tumor grade are used to distinguish low-risk from high-risk patients. Median progression free survival (PFS) by the FLIPI risk group was 84, 70, and 42 months for low, intermediate, and poor risk disease, respectively. POD24-PI and m7-FLIPI scores are also investigated to predict progression free survival (PFS) in a large cohort of patients receiving first-line chemo-immunotherapy. At the time of relapse, the best available predictor of poor survival is the duration of remission following initial treatment. Relapse of FL within 24 months of chemo-immunotherapy (POD24) occurs in approximately 20% of patients. POD24 was significantly associated with inferior OS at 5 years (50% vs. 90%). The FLIPI, m7-FLIPI, and POD24-PI have been evaluated to identify POD24 patients. Sensitivity and specificity of these prognostic indices in POD24 are 70–78% and 56–58% for high risk FLIPI, 43–61% and 79–86% for high risk m7-FLIPI, 61–78% and 67–73% for high risk POD24-PI, respectively. Furthermore, gene expression profiling and circulating tumor/cell-free DNA are other emerging methods for predicting POD24. However, there is no standardized method to prospectively predict POD24. Patients with relapse FL should undergo an excisional biopsy before initiating next therapy to confirm relapse and exclude histologic transformation. Because no treatment modality has been shown to be superior to another in this situation, POD24 patients should be encouraged to participate in clinical trials whenever possible. If a patient is not a candidate for a clinical trial, treatment options include chemo-immunotherapy (such as bendamustine plus obinutuzumab(O) or O-CHOP) and targeted therapies (such as immunomodulators and PI3K inhibitors). For fit patients age <65 years without an appropriate clinical trial option consolidative autologous stem cell transplant should be considered to induce prolonged remissions and improve prognosis. Nevertheless, there is an unmet need for better identification and treatment of POD 24 patients.

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