Journal Scan

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The goal of this new section in the BJH is to provide a snapshot of pivotal studies published in recent issues of the most important international journals focusing on haematology. Importantly, the selection of the studies discussed here is the sole responsibility of the publisher and was not influenced by third parties. Do you miss an important study, or did you read a hidden jewel that deserves to be shared with your colleagues? Please, let us know (editor@bjh.be) and we will make sure to include it in the journal scan section of the next BJH issue.
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IMPROVED QUALITY OF LIFE AFTER TISAGENLECLEUCEL INFUSION IN CHILDREN AND YOUNG ADULTS WITH RELAPSED OR REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA

The global, single-arm, open-label phase II ELIANA trial could demonstrate that 81% of paediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia achieved overall remission after treatment with tisagenlecleucel. In order to evaluate the patient-reported quality of life in these patients before and after the infusion with tisagenlecleucel, 58 (out of 75) patients, between 8 and 23 years, were included in the analysis. Of those patients, 86% completed the Pediatric Quality of Life Inventory (PedsQL) questionnaire and 83% completed the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS) at baseline. Subsequently, patients were asked to complete the questionnaire at day 28 and months 3, 6, 9 and 12 after treatment. Three months after the infusion of tisagenlecleucel, the mean change from baseline was 13.3 (95%CI: 8.9-17.6) for the PedsQL total score and 16.8 (95%CI: 9.4-24.3) for the EQ-5D VAS in favour of tisagenlecleucel. In total, 30 (81%) out of 37 patients achieved the minimal clinically important difference at month 3 for the PedsQL total score and 24 (67%) of 36 patients achieved this for the EQ-5D visual analogue scale. Together with the activity and safety results, the authors conclude that tisagenlecleucel has a favourable benefit-risk profile in the treatment of paediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukaemia.[1]

LEVOFLOXACIN PROPHYLAXIS IN PATIENTS WITH NEWLY DIAGNOSED MYELOMA

In myeloma patients, around a quarter of patients will experience a serious infection within three months after diagnosis. In a recent edition of the Lancet Oncology, results of the TEAMM study were published in which the potential benefit from antibiotic prophylaxis with levofloxacin was assessed in patients aged 21 years and older with newly diagnosed myeloma. A total number of 977 patients were randomly assigned (1:1) to receive 500 mg levofloxacin orally once daily for 12 weeks or placebo in the same regimen, with dose reduction according to estimated glomerular filtration rate every four weeks. Follow-ups occurred at weeks 4, 8, 12, 16 and after 1 year. After a median follow-up of 12 months, 95 (19%) first febrile episodes or deaths occurred in the levofloxacin group, as compared to 134 (27%) in the placebo group (HR[95%CI]: 0.66[0.51-0.86], p= 0.0018). In de levofloxacin group, 308 (52%) serious adverse events were reported up to 16 weeks from the start of treatment, as compared to 289 (48%) in the placebo group. Tendonitis was reported in five (1%) of 489 patients in the levofloxacin group (*vs.* none in the placebo group) but was mostly reversible. All other serious adverse events were similar between both arms. Overall, the addition of levofloxacin to active

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myeloma treatment in the first 12 weeks of therapy seems to lower the risk of febrile episodes and deaths by 34% without increasing the health care-associated infections. Patients with newly diagnosed myeloma could thus benefit from levofloxacin prophylaxis.[2]

RIVAROXABAN COMPARED WITH STANDARD ANTICOAGULANTS FOR THE TREATMENT OF ACUTE VENOUS THROMBOEMBOLISM IN CHILDREN

The first issue of the Lancet Oncology 2020 featured the results of a randomised, controlled phase III trial of rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in 500 children. Treatment of venous thromboembolism in children is often based on data obtained in adult patients, without direct documentation of the drug's safety and efficacy in paediatric patients. The enrolled children were randomised (2:1) to receive body-weight adjusted rivaroxaban in a 20 mg -equivalent dose or standard anticoagulants (heparin or vitamin K antagonist). The children who had a study treatment period of three months (N= 463) had a median follow-up of 91 days and those with a study treatment period of one month (N= 37) had a median follow-up of 31 days. Four out of 335 children (1%) in the rivaroxaban treatment arm experienced a recurrent venous thromboembolism as compared to five out of 165 children (3%) receiving standard anticoagulants (HR[95%CI]: 0.40[0.11-1.41]). Moreover, rivaroxaban could significantly reduce the thrombotic burden (p= 0.0012). In total, 3% of the patients who received at least one dose of rivaroxaban had a non-major bleeding and no major bleedings occurred. In the standard anticoagulants arm, 2% of the patients had a major or clinically-relevant non-major bleeding. There were no treatment-related deaths and the safety estimates were similar to those of rivaroxaban in adults.[3]

RESPONSE-ADAPTED INTENSIFICATION WITH CYCLOPHOSPHAMIDE, BORTEZOMIB, AND DEXAMETHASONE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

In the randomised, phase III Myeloma XI trial, 583 newly diagnosed multiple myeloma patients were enrolled to the intensification randomisation. All patients were at least 18 years old and completed their induction therapy as per protocol (cyclophosphamide, thalidomide, dexamethasone or cyclophosphamide, lenalidomide, dexamethasone) with a partial or minimal response. After randomisation (1:1), patients received either an intensified regimen with cyclophosphamide (500 mg daily orally on days 1, 8, and 15), bortezomib (1.3 mg/m^2 subcutaneously or intravenously on days 1, 4, 8, and 11), and dexamethasone (20 mg daily orally on days 1, 2, 4, 5, 8, 9, 11, and 12) up to a maximum of eight cycles of 21 days (CVD regimen) or no treatment. After a median follow-up of 29.7 months, the median PFS increased from 20 months in patients without CVD to 30 months in those patients with CVD (HR[95%CI]: 0.60 [0.48-0.75], p< 0.0001) whereas the 3-year OS rate did not change (HR[95%CI]: 0.98[0.67-1.43], p = 0.93). The most common grade 3 and 4 adverse events in the CVD arm were haematological (neutropenia 7%, thrombocytopenia 7%, anaemia 3%). No deaths in CVD arm were considered to be treatment-related. As such, intensification treatment with CVD could significantly improve PFS in newly diagnosed MM patients with a suboptimal response to immunomodulatory induction therapy but did not improve OS. Considering the fact that a substantial number of patients did not enter this trial randomisation following induction therapy, might support the use of combination therapy upfront to maximise response and improve survival outcomes.[4]

POLATUZUMAB VEDOTIN IN RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

In January 2020, the Journal of Clinical Oncology reported on a phase Ib/II trial evaluating polatuzumab vedotin combined with bendamustine and obinutuzumab (pola-BG), and of polatuzumab vedotin in combination with bendamustine and rituximab (pola-BR) versus BR alone in transplant-ineligible relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL). In the phase Ib part of the trial, six patients received pola-BR and six patients received pola-BG whereas the phase II part included an expansion cohort of pola-BG (N=21) and a randomly assigned cohort (N= 80) that compared pola-BR with BR alone (N= 40 in each treatment arm). The primary endpoints of the trial were safety and tolerability (phase Ib) and complete response (CR) rate of pola-BR *vs.* BR (phase II).

In the randomly assigned cohort, a CR rate at the end of treatment of 40.0% was achieved in the pola-BR arm, as compared to 17.5% in the BR-arm (p= 0.026). The median progression-free survival increased from 3.7 months with BR to 9.5 months with pola-BR (HR[95%CI]: 0.36[0.21-0.63], p < 0.001) and the median overall survival increased from 4.7 months to 12.4 months (HR[95%CI]: 0.42[0.24-0.75], p= 0.002). In the phase Ib/II pola-BG cohort (N= 27), a CR of 29.6% and a median overall survival of 10.8 months (with

a median follow-up of 27.0 months) was achieved. Grade 3-4 anaemia (28.2% *vs.* 17.9%), thrombocytopenia (41% *vs.* 23.1%) and neutropenia (46.2% *vs.* 33.3%) were higher with pola-BR than with BR alone but grade 3-4 infections and infestations were similar in both arms (23.1% *vs.* 20.5%). Peripheral neuropathy occurred in 43.6% of the pola-BR patients and was the only reason for polatuzumab vedotin dose reductions (which occurred in two patients, after which the peripheral neuropathy resolved). The authors conclude that pola-BR represents a novel, effective therapeutic regimen to address the unmet need of patients with transplantation-ineligible R/R DLBCL.[5]

PROGNOSTIC VALUE OF MRD NEGATIVITY IN PATIENTS WITH RELAPSED/ REFRACTORY ACUTE LYMPHOBLASTIC LEUKAEMIA TREATED WITH INOTUZUMAB OZOGAMICIN

Minimal residual disease (MRD) negativity after frontline chemotherapy is a prognostic factor in acute lymphocytic leukaemia. The INO-VATE trial (in which relapsed/refractory acute lymphocytic leukaemia patients received inotuzumab ozogamicin or standard chemotherapy) therefore assessed the prognostic value of MRD negativity in the salvage setting. Previously reported results indicated that patients treated with inotuzumab ozogamicin achieved greater remission and MRD-negativity rates than patients treated with standard chemotherapy. Moreover, also the OS improved upon inotuzumab ozogamicin treatment. Recently published results now demonstrate that at the end of treatment, MRD negativity (defined as $<1 \times 10^{-4}$ blasts/nucleated cells) was obtained in 76 out of 164 patients who received inotuzumab. MRD negativity with complete remission/complete remission with incomplete haematologic response (CR/Cri) was associated with a significantly improved overall survival as compared to MRD positive status (HR[97.5%CI]: 0.512[0.313-0.835], p= 0.0009). In addition, a significantly improved PFS was observed (HR[97.5%CI]: 0.423[0.256-0.699]: p< 0.0001). When patients were stratified according to salvage status (S1 or S2), MRD-negativity status has been shown to play a bigger role in the PFS and OS outcomes in patients in S1 as compared to those in S2. Finally, the median OS increased from 7.2 months in the MRD-positive group to 14.1 months in the MRD-negative group. Patients who achieve MRD-negativity at the end of treatment thus have significantly improved survival outcomes versus patients with MRD-positivity. The achievement of MRD-negativity therefore appears to be an important therapeutic goal in the relapsed/refractory setting.[6]

TREOSULFAN PLUS FLUDARABINE AS CONDITIONING TREATMENT BEFORE ALLOGENEIC HAEMOPOIETIC STEM CELL TRANSPLANTATION FOR OLDER AND COMORBID PATIENTS WITH ACUTE MYELOID LEUKAEMIA OR MYELODYSPLASTIC SYNDROME

As the group of older or comorbid patients with acute myeloid leukaemia or myelodysplastic syndrome is growing, improvements in the preparative regimens before allogeneic haemopoietic stem cell transplantation (HSCT) are necessary. *Beelen et al.* therefore evaluated the safety and efficacy of treosulfan plus fludarabine compared with reduced-intensity busulfan plus fludarabine in this patient population. In total, 476 patients were randomly assigned (1:1) to receive either intravenous 10 g/m^2 treosulfan daily applied as a 2-hour infusion for 3 days (days -4 to -2) or 0.8 mg/kg busulfan applied as a 2-hour infusion at 6-hour intervals on days -4 and -3. Both groups received 30 mg/m^2 intravenous fludarabine daily for 5 days (days -6 to -2). The first issue of the Lancet Haematology 2020 published the final confirmatory analysis of this trial. After a median follow-up of 15.4 months for patients treated with treosulfan and 17.4 months for patients treated with busulfan, the 2-year event-free survival was 64.0% in the treosulfan group as compared to 50.4% in the busulfan group (HR[95%CI]: 0.65[0.47-0.90], p< 0.0001 for non-inferiority and p = 0.0051 for superiority). The most frequently occurring grade ≥ 3 adverse events were abnormal blood chemistry results (15% in both treatment arms) and gastrointestinal disorders (11% in the treosulfan arm *vs.* 16% in the busulfan arm). In total, 8% of the patients in the treosulfan arm and 7% of patients in the busulfan arm reported a serious adverse event. Treosulfan was thus non-inferior to busulfan when used in combination with fludarabine for the conditioning for allogeneic HSCT in older or comorbid patients with acute myeloid leukaemia or myelodysplastic syndrome. Moreover, the authors suggest that the treosulfan-fludarabine regimen might have the potential to become a standard preparative regimen in this patient population.[7]

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