HEMATOL TRANSFUS CELL THER. 2022;44(S1):S1–S9

HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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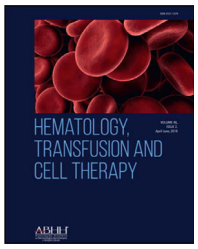

SPEAKER PRESENTATIONS

ADULT SPEAKER PRESANTATION

Sp01

WILL IMMUNE THERAPY CURE ACUTE MYELOID LEUKEMIA?

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There is considerable recent progress in using immune therapy to treat lymphoid including monoclonal antibodies, antibody-drug and -radionuclide conjugates, bi-specific antibodies and chimeric antigen receptor T-cells (CAR-T-cells). Targets of these therapies are B-cell lineage-specific antigens such as CD19, CD20 and BCMA, not cancer-specific antigens. Given these immune therapy advances in lymphoid cancers one might expect similar success using immune therapy to treat acute myeloid leukemia (AML). However, this is not so. There is only one FDA-approved therapy of myeloid cancers, gemtuzumab ozogamicin (Myelotarg®) for AML approved > 10 years ago. Why this discordance? The answer lies in two considerations: (1) lack of a robust AML-specific target antigen(s); and (2) unacceptable adverse effects resulting from non-specificity of lineage-specific antigens such as CD33 and CD124. Also, most data suggest less immune surveillance against myeloid cancers compared with lymphoid cancers. For example, AML cells have an average of 0.28 mutation *per* megabase of DNA compared with 8.15 mutations for lung cancer, 40-fold less. The exception is the anti-AML effect associated with haematopoietic cell transplants, so-called graft-*versus*-leukaemia (G*v*L). However, this effect occurs only in an allogeneic setting and is difficult or impossible to distinguish from graft-*versus*-host disease (G*v*HD). We can envision potential anti-AML immune therapy using two strategies: (1) antibodies; and (2) cell therapies. Synthetic biology may offer a solution to the problem of the lack of an AML-specific target antigens. I discuss the current state of immune therapy of AML and potential future directions. So, will immune therapy cure AML? Stand by.

https://doi.org/10.1016/j.htct.2022.09.1186

Sp02

BRENTUXIMAB VEDOTIN VERSUS CHECKPOINT INHIBITORS: WHICH ONE? WHEN? WHY SHOULD BE PREFERRED?

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About 15% of classical Hodgkin lymphoma (cHL) patients remain refractory to first-line therapy and about one third of the responding patients relapse[1]. The standard of care for relapsed or refractory (R/R) cHL is salvage chemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT)[2]. Three novel agents effective in R/R cHL were introduced; brentuximab-vedotin (BV), anti-CD30 antibody-drug conjugate[3] and the programmed-death-1 (PD-1) blocking antibodies, nivolumab and pembrolizumab[4, 5] has been approved. The optimal line to incorporate these agents is an actual dilemma. BV and PD1-blockers are effective in R/R cHL after ASCT. KEYNOTE-204 study reported that pembrolizumab treatment was associated with significantly longer PFS compared with BV (median:13.2 vs 8.3 months)[6]. In case of durable responses with PD1-blockers, cessation of the treatment may be an individualized decision and high response rates to re-treatment with PD1-blockers is an important advantage[7]. There is not obvious differences in the efficacy and toxicity of nivolumab and pembrolizumab[8]. We can conclude that PD1-blockers could be preferred over BV in patients who relapse following ASCT and who are naïve to BV and PD-1 blockade. For patients relapsing after ASCT with prior BV or PD1-blocker exposure, selection of the agent

that has not been used previously could be recommended[8]. BV and PD1-blockers are incorporated into the pre-ASCT salvage regimens in clinical trials. In the phase II BRaVE study, BV added to DHAP provided a complete metabolic response rate of 81% before ASCT, with a 2-year PFS and OS rates of 74% and 95%, respectively[9]. Similarly, pembrolizumab in combination with GVD provided an overall response rate (ORR) of 100%[10]. BV and nivolumab combination resulted in an ORR of 85%. The 3-year PFS rate for ASCT group was 91%[11]. Regarding these data, the need for ASCT will be an important point of debate in the next years. In case of primary refractory disease, chemotherapy-based salvage regimens remain the standard. Combination treatment with BV and nivolumab resulted in a 21-month PFS of 65% in this group[11], which may be a satisfactory option in the future. Post-ASCT consolidation with BV is now standard of care in patients with risk factors defined by AETHERA trial[12], which is supported by real-world data including pre-treated with and responsive to BV patients[13]. Novel agents are not recommended in the front-line management of early-stage disease. ECHELON-1 study performed on treatment-naïve stage III/IV cHL patients reported 6-year PFS, and OS ratio were 82.3% and 93.9% for BV-AVD cohort versus 74.5% and 89.4% for ABVD cohort[14]. Beside advanced stage cases, BV-based therapies should be considered for elderly, unfit patients who cannot tolerate combination chemotherapies, as they are associated with longer duration of response compared to BV monotherapy[8]. Giving decision about novel therapies, major adverse events, such as neuropathy for BV and immune related events for PD1-blockers. Optimal timing of BV and PD1-blockers and treatment strategies in case of resistance to novel agents are critical questions for the future of cHL management, which hopefully will be answered by the results of clinical trials and real-world data.

https://doi.org/10.1016/j.htct.2022.09.1187

Sp03

TREATMENT OF MANTLE CELL LYMPHOMA IN TRANSPLANT NON-ELIGIBLE PATIENTS

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MCL is a rare but usually aggressive non-Hodgkin lymphoma that most commonly affects the elder population. It is now recognized as a heterogeneous disease with variable biologic and clinical behavior. MCL is considered incurable with current therapies and has historically been associated with a poor prognosis. . Large gains were made in the first decade of the new century when clinical trials established the importance of high-dose therapy and autologous stem-cell rescue and high-dose cytarabine in younger patients and the benefits of maintenance rituximab and bendamustine in older patients. Patients with mantle cell lymphoma (MCL) usually respond to initial combination chemotherapy, but the disease inevitably relapses and often follows an aggressive course. Treatment paradigms have evolved along two lines. Younger, fit mantle cell lymphoma (MCL) patients are generally treated with intensive strategies and older less fit patients with non-intensive strategies. Management of patients with newly diagnosed mantle cell lymphoma (MCL) depends on the age and fitness of the patient. For younger patients, the commonly accepted standard of care is a high-dose cytarabine-based induction chemotherapy followed by autologous stem cell transplantation (ASCT). In newly diagnosed patients with MCL ineligible for intensive therapy and ASCT, the standard-of-care has generally been R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), followed by rituximab, maintenance. In recent years, bendamustine-based therapy has been increasingly adopted for older MCL patients and more recently, vincristine has been replaced by bortezomib in the R-CHOP combination as VR-CAP for previously untreated patients. Traditionally, the treatment of MCL has been determined by patients being deemed “transplant-eligible” or “transplant-ineligible”. In particular, greater depth of understanding of the molecular pathophysiology of MCL has resulted in an explosion of specifically targeted new efficacious agents. In particular, agents recently approved by the Food and Drug Administration include the proteasome inhibitor bortezomib, immunomodulator lenalidomide, and Bruton's tyrosine kinase inhibitor ibrutinib. Newer data suggest more tolerable front-line therapy, including regimens incorporating novel agents, may produce similar outcomes to intensive historical induction regimens. This may in turn preclude fewer patients from autologous stem cell transplant and produce better long-term outcomes in transplant-ineligible patients. In the relapsed/refractory setting, novel agents and combination regimens are improving outcomes and changing the landscape of treatment. New therapies with distinct mechanisms of action, including novel immunotherapeutics, antibody-drug conjugates, and non-covalent BTK inhibitors, have demonstrated great potential for improving outcomes post–BTK inhibitor failure in relapsed/refractory mantle cell lymphoma. Although cBTK inhibitor has transformed the treatment landscape in B-cell malignancies, the majority of patients will eventually experience disease progression or treatment intolerance. There are 2 oral BTK inhibitors approved for use in relapsed MCL: ibrutinib and acalabrutinib. Acalabrutinib, originally referred to as ACP-196, is a novel, irreversible BTK inhibitor that was designed to be more kinase-selective than ibrutinib. Orelabrutinib is an orally administered, potent, irreversible and highly selective BTK-inhibitor being developed the treatment of B cell malignancies and autoimmune diseases. Tirabrutinib irreversibly and covalently binds to BTK in B cells and inhibits aberrant B cell receptor signalling in B cell-related cancers and autoimmune diseases. Zanubrutinib received accelerated approval in the USA on 14 November 2019 for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, based on overall response rate (ORR) seen in phase II and I/II clinical trials. Palbociclib is a specific, potent, oral inhibitor of CDK4/6 capable of inducing a complete, prolonged G1 cell cycle arrest (pG1) in Rb+ MCL cells. Zilovertamab vedotin is an antibodydrug conjugate, which binds specifically to receptor tyrosine kinase-like orphan receptor-1 (ROR-1), an oncoprotein that is pathologically expressed in mantle cell lymphoma and other

malignancies. The development of anti-CD19 CAR T-cell therapy represents a major advance in the treatment of patients with chemorefractory B-cell malignancies.

https://doi.org/10.1016/j.htct.2022.09.1188

Sp04

HOW I TREAT DOUBLE-HIT LYMPHMOMA AND HGBL, NOS

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Introduction: The new world health organization (WHO) classification on lymphoid neoplasms, the WHO-HAEM5, renames the former group that double-hit lymphomas were in as "diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2)". This is mainly to highlight that the presence of MYC and BCL2 rearrangements form a unique phenotype, different than the MYC and BCL6 rearrangements (present in the former classification). Those lymphomas are composed of large or intermediate or blastoid cells, with aggressive clinical course and tendency to be resistant to standard chemotherapy. It's a group ideal for new therapies, such as the bispecifics and CAR T-cells, but lack data to support this since are underrepresented in clinical trials. Retrospective studies, with its inherit bias, consistently points to worst prognosis and poor outcomes with standard RCHOP treatment. How to best approach this hard-to-treat lymphoma is still a matter of debate. **Treatment considerations:** Roughly 65% of patients with DLBCL are cure with 6 cycles of RCHOP. When considering this regimen for HGBL, event-free survival (EFS) has been reported as low as 20% in 3 years. More intensive regimens, like R-DA-EPOCH and R-CODOX/M-IVAC, could increase this response, based on retrospective studies, with EFS 3y close to 80%. The role of autologous transplant as consolidation is controversial, and it's not routinely indicated. However, there are data that patients treated with RCHOP could increase progression-free survival (PFS) with this strategy, perhaps eliminating the difference between more intensive regimens. The lack of a direct comparison in a randomize phase 3 study between RCHOP or more intensive protocols precludes a firm conclusion. In the Alliance/CALGB 50303 study, that compared RCHOP with R-DAEPOCH in patients with DLBCL and PMBCL, there were no differences in 2y PFS between arms. But the number of patients with MYC rearrangement was too small to any conclusion regarding HGBL. Dunleavy et al conducted a phase 2 study with R-DA-EPOCH in 53 patients with MYC-rearranged DLBCL (24 were double-hit). EFS 4y was 71% and overall-survival (OS) 4y was 77%. Although this looks pretty good compared to the historic RCHOP, it's not a randomize study. New therapies have emerged as possible rescue in the relapsed/refractory DLBCL population, a group of patients with a dismal prognosis. The chimeric antigen receptor (CAR) T-cells have become a new standard of care for those patients, when available. Albeit with a small number of patients, the three main products (axi-cell, tisa-cell and lisocell), used for rescue of DLBCL patients, had shown activity against HGBL. That holds true in latter lines and as a first salvage treatment, as the recent trials comparing with autologous transplant. The zuma-12 is a phase 2 study with axi-cell as first-line of treatment with high-risk DLBCL patients, a population enriched with HGBL. Early reports are impressive, with nearly 80% of complete remissions. However, long term follow-up will be necessary to see with the responses are durable. Bispecifics are other very important players on that field, with the first reports of high activity in high-risk DLBCL, even after CAR T-cell failure. **Conclusions:** HGBL is an aggressive form of lymphoma, with tendency of a worst prognosis with conventional treatment. Intensive regimens seem to fare better than RCHOP, although with more toxicity and no randomize studies supporting this indication. New treatments, mainly CAR T-cells and bispecifics, are very promising and possibly will became standard of care for such patients but were in the therapy algorithm is still to be decide.

https://doi.org/10.1016/j.htct.2022.09.1189

Sp05

APPROPRIATE MANAGEMENT OF POLYCYTHEMIA VERA WITH CYTOREDUCTIVE DRUG THERAPY

EUROPEAN LEUKEMIANET 2021 RECOMMENDATIONS

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Classical Philadelphia-negative myeloproliferative neoplasms (Ph-neg MPNs) including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) are characterized by uncontrolled clonal proliferation of multipotent bone marrow progenitors, sustained by acquired mutations in JAK2, CALR and MPL genes. Expansion of the mutated clone triggers an inflammatory response that influences the development of associated vascular complications and disease progression into MF and acute leukemia. This presentation will focus on the recent recommendations by ELN in low-risk PV patients. According to ELN and NCCN patients with PV should be managed by the risk of thrombosis and cytoreductive drugs are recommended in high risk (over 60 y and/or prior thrombosis) while low-risk should be treated with low-dose aspirin and phlebotomy only. These guidelines have been reviewed by international recognized experts in the field of MPN. In January 2021, ELN promoted an international project specifically devoted to updating the clinical indications for using cytoreductive drugs in treating PV. The Expert Panel (EP), the chair and the methodologist were asked to grant the highest quality of the recommendations by adhering to standard methods for developing clinical practice guidelines, namely Grading of Recommendations Assessment,

Development and Evaluation (GRADE) (WHO Handbook for Guideline Development, 2011). These main questions will be presented and discussed. **Question 1** - What benefits should be expected from cytoreductive drugs over phlebotomy in "low-risk" PV patients? **Question 2** - Which "low-risk" PV patients might benefit from cytoreductive drugs? **Question 3** - Which cytoreductive drugs should be preferred in "low-risk" patients? **Question 4** - Which PV patients treated with HU should receive a different cytoreductive 223 drug? The results and recommendations were approved by Delphi consensus rounds and virtual meetings. The EP recommended that PV patients younger than 60 years old and/or free of prior thrombotic events start cytoreductive drug therapy if at least one of the criteria is fulfilled: 1) strictly-defined intolerance to phlebotomy, 2) symptomatic progressive splenomegaly, 3) persistent leukocytosis (> 20.000/mmc), 4) progressive leukocytosis 6) inadequate hematocrit control requiring phlebotomies, 7) persistently high cardiovascular risk, and 8) persistently high symptom burden. RopegIFN or pegylated IFN-alpha-2a was the recommended cytoreductive drug for the above patients. Finally, the EP suggested that either rIFNα or ruxolitinib should be considered for patients treated with hydroxyurea but requiring a therapy change. The purpose of cytoreductive therapy is to obtain hematological responses, since normalizing blood counts with phlebotomy and/or cytoreductive drugs is thought fundamental to reduce the incidence of both arterial and venous thrombosis. However, despite achieving similar hematological responses, it is likely that the various cytoreductive drugs administered both in the first and second line do not have equal antithrombotic activity. In fact, for each of the three cytoreductive drugs currently used in clinical practice (Hydroxyurea [HU], Interferon [IFN], Ruxolitinib [Ruxo]), additional antithrombotic properties are recognized. For instance, HU is thought to have minimal antiinflammatory properties [19], whereas there is evidence that IFN and Ruxo can normalize inflammatory markers, further mitigating thrombotic risk [20, 21]. Unfortunately, clinical trials comparing head-to-head the standard HU with IFN or Ruxo did not provide solid evidence of superiority of the latter in terms of thrombosis reduction. It should be noted, however, that the design of these studies envisaged hematological responses as primary end-points and the trials were not powered to directly evaluate a decrease in thrombosis risk. On the other hand, it is not yet demonstrated that hematological response is a valid surrogate of thrombosis [22-24]. Both the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) recommend a risk-stratified approach to the treatment of an individual patient and in ET and PV patients are [Treatment focuses primarily on mitigation of thrombosis risk and most patients with ET and PV should receive low-dose aspirin As the prognosis for ET and PV varies substantially between patients, both the National Comprehensive Cancer Network (NCCN) and the European Leukemia Net (ELN) recommend a risk-stratified approach to the treatment of an individual patient [4,8]. This is exemplified by two large retrospective studies evaluating prognostic factors and outcomes among patients with MPNs [9,10]. Conventionally, patients age ≥ 60 years or with prior thrombosis are classified as high-risk [4]. However, the association of a higher thrombosis risk with the presence of JAK2/MPL mutations in ET patients is increasingly recognized and included in the validated International Prognostic Score of Thrombosis in ET (IPSET) [5,11]. The impact of other factors such as leukocytosis in PV patients or the influence of co-mutations continues to evolve and is not part of the current guideline recommended approach to treatment selection [5,6,12–14]. Treatment focuses primarily on mitigation of thrombosis risk and most patients with ET and PV should receive low-dose aspirin [4,8,15]. prevention and treatment of major arterial and venous thrombosis in PV and ET with the aim to report: (i) quantitative estimates of major thrombosis incidence; (ii) rates of thrombosis under treatment with cytoreductive drugs; (iii) incidence of thrombosis under aspirin and oral anticoagulants.

https://doi.org/10.1016/j.htct.2022.09.1190

Sp06

VACCINATION AGAINST SARS-COV-2 FOR MYELOMA PATIENTS: DO WE NEED A BOOSTER DOSE AND HOW FREQUENT?

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Patients with multiple myeloma (MM) are at increased risk for severe COVID-19 disease, hospitalization and death. In this context, it is essential to maintain an adequate immune profile. A third (first booster) dose has been offered with priority to patients with MM due to their immunocompromised status and the suboptimal immune response to the initial vaccination schedule against COVID-19. Three important studies that investigate the immune profile following a booster vaccination with a mRNA-based vaccine have been recently published. The first study was published in Blood (2022;139 (9):1409-1412) by Terpos *et al* and included 167 consecutive patients with MM who were vaccinated with the booster BNT162b2. All patients had been fully vaccinated with the 2-dose BNT162b2. Median time between the second and the booster dose was less than 5 months. The booster dose significantly improved the median neutralizing antibody (NAb) response in patients with MM (27.1% before to 96.7% after the third dose $p<0.001$). Importantly, almost half of the patients with suboptimal NAb responses at one month after the second dose of BNT162b2 developed NAb titers of at least 50% at one month after the booster dose. Treatment with anti-BCMA agents emerged as a significant adverse predictive factor for NAb response to the booster shot. None of these patients achieved a NAb level above the positivity threshold. The second study was published in Cancer Cell (2022;40(5):441-443) by Aleman *et al* and included 261 patients with MM with available anti-SARS-CoV-2 spike (S) IgG measurements at least 1 week after the third vaccine shot. Anti-S IgG levels increased significantly after administration of the third dose both in patients with and without prior history of COVID-19 ($p<0.001$), although the depth of humoral response was inferior to healthy individuals. Importantly, 60 out of 68

seronegative patients before the third dose seroconverted with the booster shot. Neutralizing titers against the Omicron variant after the booster dose were detectable in only 54% of MM patients who responded to two doses of the vaccine (they had adequate protection against Wuhan variant) and in none of those who did not respond in the initial vaccine doses. The third vaccine shot significantly increased spike-specific CD4+ T cell-mediated cytokine responses, as well. The third study was published in Cancer Cell again (2022;40(6):587-589) by Enssle *et al* and included 71 patients with MM and 23 healthy controls. The authors observed a 4-fold increase in anti-S IgG levels from a median of 193.2 BAU/ml before to 776.0 BAU/ml after the booster dose in the MM cohort. However, a poor neutralization capacity against the Omicron variant was observed. Regarding cellular immunity, MM patients showed a significant T-cell response against the wild-type virus, the Delta variant and the Omicron variant, although the response was attenuated in the latter case. Overall, the abovementioned studies advocate for prioritizing patients with MM, especially those on anti-BCMA treatments, for additional booster shots, ideally with variant-adapted vaccines, or with the prophylactic administration of monoclonal antibodies against SARS-CoV-2. The standard vaccine seems not to prevent the infection with omicron variant(s) and thus general preventive measures including mask wearing and avoiding crowds remain important for these vulnerable patients.

https://doi.org/10.1016/j.htct.2022.09.1191

Sp07

REDUCED INTENSITY CONDITIONING FOR ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT) IN ACUTE MYELOID LEUKEMIA

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Allogeneic transplantation (HSCT) is an effective curative therapy for high risk acute myeloid leukemia (AML) which account for 38% of the transplants in Europe (1). Prior to HSCT, a conditioning or preparative regimen is administered. The conditioning regimen has 2 components; one target the myeloid system aiming in eradication of the leukemic clones, while the other target the immune/lymphoid system to ensure engraftment and to prevent rejection. Some of the compounds used in the conditioning are more myeloablative in nature for example busulfan or melphalan) 2-4) while others are more lymphodepliting like fludarabine or Cytoxan (5). Traditionally, the pre HSCT conditioning was myeloablative (MAC) and includes total body irradiation (TBI) in combination with cyclophosphamide (CY) (2-3). High-dose busulfan (Bu) is the most commonly used TBI-free-based myeloablative conditioning (2-3). In HSCT from unrelated or mismatched donors the pre transplantation conditioning typically includes serotherapy with anti-thymocyte globulin (ATG) or the CAMPATH monoclonal antibody in order to avoid rejection and ensure engraftment while preventing graft versus host disease (GVHD) (5). However, the MAC is typically associated with significant morbidity and mortality due to the toxicity of the preparative regimen, GVHD, and the immune-deficient state that accompanies the procedure (2,5-6). This is especially true in patients above the age 55-60 years old and in patients with comorbidities which are the majority of AML patients. Extensive research, including pharmacokinetic and pharmacodynamics studies has been directed therefore towards the development of safer and less toxic conditioning regimens for HSCT, optimizing the conditioning allowing its applications to elderly patients and patients with comorbidities (2,5-6). These modern conditioning regimens which are based in part on the immune-mediated graft versus leukemia (GVL) effect are in principle low-dose, less toxic and tolerable conditioning regimens termed reduced intensity (RIC) with different immunosuppressive and myelosuppressive properties (5-7). These regimens combine immunosuppressive agents (such as fludarabine with or without serotherapy or targeted therapy with agents with moderate myelosuppressive effects or novel agents. However, they typically result in higher relapse rate especially in patients undergoing HSCT while not in remission and in patients with high risk leukemia including patients with adverse cytogenetics, high risk mutations and patients with positive measurable residual disease (MRD) at time of transplants. The optimal regimen is thus the one with intensive anti-leukemic activity, but with limited toxicity-the so called reduced toxicity regiments (RTC). These novel regimens are mostly fludarabine based and incorporate drugs like melphalan; thiotepa; treosulfan and clofarabine (8-11). Other protocols are the so called TBF protocol that include two alkylating agents like busulfan and thiotepa(9,11) and the FLAMSA protocol that includes fludarabine, cytarabine, and amsacrine (11).The RIC and RTC regimens enable HSCT in elderly patients and those with comorbidities reducing drastically transplant related mortality and organ toxicities in combination with improved anti leukemic effect. Efficient safe pre transplant conditioning protocols are continuing to be developed. Future protocols will most probably incorporate specific anti leukemic targeted novel compounds as well as monoclonal and radiolabeled antibodies.

https://doi.org/10.1016/j.htct.2022.09.1192

Sp08

LESSONS FROM THE EUROPEAN AND ISRAEL NATIONAL MDS REGISTRY

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On behalf of the Israeli MDS working group and EUMDS Registry/ XIII Eurasian Hematology Oncology Congress (EHOC) 2022. The myelodysplastic syndromes (MDS) are a group of clonal stem cell diseases with cytopenias and a tendency to transform to leukemia. Despite the progress, there is still lack of real world data about the disease. In 2008, top European experts

launched the EUMDS Registry. In this project, including 19 countries and 150 sites, epidemiological, clinical and lab data on newly diagnosed MDS patients, are collected and analyzed. As of today, 3300 patients have been recruited. In 2012, the Israel MDS group joined the project. We have contributed data on 360 patients, # 4 in the contributors. This project led to more than 100 abstracts in international meetings and 40 publications in first line journals. We will mention some of these studies. de Swart et al. summarized data on the first 1000 patients, validated the IPSS-R prognostic classification, showing its superiority on IPSS (de Swart L. BJH 2015). Another study, focusing on Quality of life (QoL) of LR-MDS patients revealed that these patients suffer from depression, anxiety, pain, discomfort and mobility difficulties, compared to controls (Stauder R, Leukemia 2018) The effects of Erythroid Stimulating Agents (ESAs,) was evaluated: Garelius et al. showed that ESA administration delays RBC transfusion dependency (Garelius HK. J Intern Med 2017). Since in most countries ESA is given to transfusion-dependent MDS patients, it might change the paradigm. Recently, we demonstrated that ESA treatment, is associated with improved outcomes and overall survival (Garelius HK. EHA 2022; submitted). Since prognostic factors are often determined at disease presentation, it was important to develop dynamic parameters. We showed that a rapid decline > 25% in the platelet count within 6 months is an adverse prognostic marker (Itzykson R. Bl Adv 2018) A study focusing on the mutational status was presented at ASH 2021 showing that LR-MDS patients can be grouped into 3 clusters, with a correlation to the clinical status (Malcovati L. ASH 2021) The Israeli group, independently and as a part of the EUMDS, was involved in several projects. Oster et al. suggested a non-invasive calculator to assess the probability of or excluding MDS diagnosis, based on patient characteristics, avoiding BM examination (Oster HS. Bl Adv 2021). We also investigated the correlation between Hb level and QoL. This correlation was found to be partial, and the decrease in QoL was not linear. This suggests that other factors other than Hb might play a role in determining QoL (Haring Y. ASH 2021). We recently presented data on lymphoid aggregates in BM biopsies, suggesting a possible association with poor prognosis (Book-Rabinowitz. Int MDS Symposium, Toronto 2021; submitted). **In summary**, the EUMDS registry is a platform of a scientific project, and an example of international collaboration. Such projects, especially in relatively uncommon diseases, allow collection of enough data to allow meaningful conclusions that might change paradigm and improve patient care. We call all participants of this meeting to join us and improve the quality of this wonderful important project.

https://doi.org/10.1016/j.htct.2022.09.1193

Sp09

EMERGING DATA FOR CANCER ASSOCIATED THROMBOSIS TREATMENT

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Venous thromboembolism (VTE) is a common complication in patients with malignancies,resulting in deep vein thrombosis, pulmonary embolism and central venous catheter VTE, and is responsible for high morbidity and mortality (1). The prevalence of cancer-associated thrombosis is increasing because of multiple factors, including longer patient survival, anticancer therapies, increased detection of incidental VTE during surveillance imaging, and wider use of central venous catheters. Anticoagulant therapy with low-molecular-weight heparins (LMWHs) was the standard of care for the treatment of cancer-associated thrombosis, with vitamin K antagonists providing a secondary treatment option, until direct oral anticoagulants (DOAC) emerged as alternative first-line treatment options in 2016 (2). Rivaroxaban, Edoxaban and Apixaban are recommended as initial treatment in patients with cancer-associated thrombosis who are not at high risk of gastrointestinal or genitourinary bleeding (3). LMWHs and Fondaparinux are still recommended for prophylaxis of VTE in medically-treated patients with cancer. Rivaroxaban and Apixaban can be used selectively for thromboprophylaxis in patients with malignancies at high risk of VTE, for example in patients with pancreatic cancer or myeloma (4,5). Anticoagulant choice should incorporate a personalised medicine approach that considers cancer type, VTE and bleeding risk factors, drug–drug interactions (DDI), and patient preferences. Patients with cancer often experience narrow therapeutic index polypharmacy and undergo treatment for several simultaneous comorbidities. In this setting the risk of DDI is high in particular during therapy with tyrosine kinase inhibitors (6). Concerns on DDI management include decreased efficacy and bleeding risk. In general, DOAC use is not advisable in combination with drugs that are strong inhibitors of both P-gp and/or CYP3A4 for high bleeding risk and in combination with strong inducers of Pgp and/or CYP3A4 that could markedly reduce DOAC plasma levels. Routine use of plasma level measurements for DOAC, only available in few laboratory centres, is not currently recommended (7). Nevertheless it has recently become increasingly clear that clinicians need to assess the anticoagulant status of a patient receiving anticancer therapies. The global coagulation Test of thrombin generation (TGT) a sensitive method to assess the anticoagulant therapy, provides a global measure of anticoagulant effect by measuring the inhibition of formation of thrombin (FIIa), a common endpoint for both LMWH and FXa inhibitors (8). Furthers studies are warranted to better define the future role of this coagulation test in this subgroup of patients.

https://doi.org/10.1016/j.htct.2022.09.1194

Sp10

VASCULAR DISEASES IN PNH

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PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A)

gene in bone marrow stem cells, 1,2 resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis, 3. Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release4 . Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure5 . Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems6 . Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma7,8,9. Platelet activation, complementmediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH. 10 Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.11 The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion) has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.12,13 Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.14,15 Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.16,17

https://doi.org/10.1016/j.htct.2022.09.1195

Sp11

HOW WE (WILL) TREAT PNH?

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Clinical signs arising from intravascular hemolysis, hemolysis-related transfusions and thrombosis are indications for treatment initiation in paroxysmal nocturnal hemoglobinuria (PNH), whereas clone size *per se* is not. Eculizumab prevents intravascular hemolysis and reduces significantly thromboembolic risk resulting in a five-year overall survival of >90%. Hemoglobin value, LDH and reticulocyte count are used to define treatment response. Residual intravascular hemolysis is mainly caused by an incomplete C5 blockage and can lead to continuous low–grade hemolysis or transient breakthrough hemolysis episodes in 10-15% of PNH patients. Additional complement–amplifying conditions such as infections, surgery or pregnancy may overcome efficient therapeutic levels of Eculizumab and therefore require dose adjustments. *C3–mediated extra–vascular hemolysis* represents the main reason for residual anemia during anti–C5 treatment. Patients with an inherited C5-variant lack response to Eculizumab and have been directed (in past) towards allogeneic HSCT. Transplantation has an overall mortality of up to 30%, with a higher risk in patients with previous thrombosis. A plethora of novel therapeutic agents are reported to impact on both; residual intravascular hemolysis and C3–mediated extra–vascular hemolysis. The new C5 inhibitor Ravalizumab with an eight–week i.v. dosing interval showed non-inferiority to Eculizumab. Crovalimab, binding on the single missense C5 heterozygous mutation is injected s.c. monthly; two large phase III trials are ongoing as add on- and mono-therapy. Others, such as Pozelimab, injected subcutaneously on a weekly basis after an initial IV loading dose or Tesidolumab are still under current investigation. Currently investigated proximal inhibitors are acting towards: (i) the C3 complement; (ii) complement factor D or (iii) the complement factor B. They are aiming in particular to prevent C3–mediated extra–vascular hemolysis. Pegcetacoplan is a PEGylated version of compstatin which binds to C3 and is injected s.c. in monotherapy 4 weeks after initial concomitant therapy with Eculizumab. In a recent phase III trial, pegcetacoplan showed superiority to eculizumab in hemoglobin change from baseline and is now approved by the FDA for patients with PNH who are either treatment–naive or switching from anti–C5 monoclonal antibodies. Danicopan is an oral first–in–class factor D complement alternative pathway inhibitor and decreased significantly transfusion requirement, as shown in a phase II trial (phase III ongoing). BCX9930, another FD inhibitor in early development is given orally and demonstrated initial clinical efficacy both as add–on therapy in patients with inadequate response to eculizumab as well as in monotherapy in treatment–naive patients. In conclusion, novel proximal and distal complement inhibitors with different application modalities, in part as add-on or monotherapy seem to improve significantly intra- and extra–vascular hemolysis in PNH, resulting in a better hematological benefit. Before choosing specific treatment, hematologists have to assess hemolysis, thrombosis and patients‘ bone marrow function. Future studies will help to explore long-term efficacy and safety of these novel agents.

https://doi.org/10.1016/j.htct.2022.09.1196

Sp12

THE THEN, NOW, & FUTURE OF ENGINEERED T-CELL THERAPEUTICS FOR HUMAN APPLICATION

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Since the 1990's, we have conducted clinical trials of gene modified T cells. Chimeric antigen receptor (CAR) T cells independent of HLA and targeting CD19 on B cells leukemias and lymphomas have induced durable complete responses in patients who are relapsed or refractory to all other available treatments. New designs for genetically modified T cells include switches and potency enhancements that will be required for targeting solid tumors. In one such approach, a decoy receptor is inserted into CAR T cells to thwart a tumor immunosuppressive mechanism. Another improvement shortens ex vivo manufacturing, along with the addition of an anti-tumor cytokine to increase in vivo potency. Determining the critical quality attributes, dose, potency, and anticipating pharmacokinetics of a living, dividing drug presents unique challenges. Improving patient access to advanced cell and gene therapies entails not only on scientific progress in targeting, gene modification and cellular manipulation, but also on meeting automation, engineering, clinical site onboarding, and health policy challenges.

https://doi.org/10.1016/j.htct.2022.09.1197

Sp13

FROM ALLOGENIC TRANSPLANTATION TO PRECISION IMMUNE THERAPY

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Allogeneic stem cell transplantation (ASCT) represents a model for immune cellular therapy leading to Immune Precision Medicine. *The pioneers* Georges Mathé in Paris and E. Donall Thomas (Nobel Prize in 1990) in Cooperstown, New York, pioneered ASCCT in the clinical field. In 1958, the first 4 survivors were seen in patients after accidental exposure to lethal or near lethal dose of TBI, in Paris. However, they were subsequently shown to have autologous recovery. Understanding of ABMT immune support begun in 1954 with 1980 Nobel Prize Jean Dausset. The first ABMTs were performed in severe combined immunodeficiencies with the first success observed in 1968 (syngeneic donor), followed in 1973 by unrelated donor ABMT in London. This was also the time of the initiation of registries. *Development time in hematological malignancies* The first success of ABMT in acute leukemia was observed in 1976 in Seattle with a related donor and in 1976 with an unrelated donor. Thereafter, the evolution will take place within the framework of the risk-benefit balance with reduction of the intensity of the conditioning regimen, the graft versus leukemia (GVL)/graft versus host disease (GVH) balance and the donor extension with umbilical cord blood and more recently the haplo-identical allogeneic ASTC. Autologous SCT was introduced at the beginning of the 80s to amplify reduction in tumor mass, particularly in lymphoid malignancies. *Stem cell transplantation as an immune therapy platform* Whatever the autologous or allogeneic context, the hematopoietic SCT is an exceptional platform for combining, modulating immunotherapy. In an allogeneic context, by modifying lymphocyte subpopulations, such as the supply of cytotoxic T-cells, the modulation of Tregs, the addition or activation of NK cells have an impact on GVH/GVL balance. The enhancement of anti-tumor cytotoxicity can be brought about using monoclonal antibodies (moAb), the addition of cancer vaccines. In an autologous context, there are some windows of opportunity, in the aplasia period due to the accessibility to stressed cancer cells, and cytokine burst approximately at D15, to add cell-drugs such as NK, $\gamma\delta$ T-cells or anti-cancer moAbs, or to associate chimeric antigen receptor (CAR) immune cells such as CAR-NK, as well as immune checkpoint inhibitors depending on the risks. This paves the way for a real dynamic personalized medicine and should cause the methodology for developing these therapeutic strategies to be rethought. Obtaining an optimization of the clinical efficiency which must be preceded by a reflection of biological efficiency can be helped by mathematical models or AI. We have thus developed a mathematical model for the optimization of the use of anti-IL-6. There is a modeling of use of cytotoxic cells. In cellular therapy, the concept of cell-drugs orients towards non-MHC dependent allogenic cells such as NK and $\gamma\delta$ T-cells, as well as obtaining them in large batches to reduce production costs. We are entering a new medical era, with new notions such as dynamic, globalized vision, the use of new tools resulting from the digital revolution, new targeted therapies, immunotherapy, the combination of strategies for better efficiency: the Immune Precision Medicine.

https://doi.org/10.1016/j.htct.2022.09.1198

Sp14

EUROPEAN EXPERIENCE FROM BARCELONA – IN-HOUSE PREPARATION AND CLINICAL RESULTS

XIII EHOC 2022 / CELLULAR THERAPY: CAR T-CELLS IN HEMATOLOGICAL MALIGNANCIES

Manel Juan & a team of more than 200 professional

Servei d'Immunologia. Hospital Clínic de Barcelona (HCB). Plataforma de Hospital Sant Juan de Déu-HCB. Barcelona – Spain

ARI-0001 [systematically named Varnimcabtagene autoleucel (var-cel), a second generation anti-CD19 chimeric antigen receptor (CAR) T-cell] granted local use authorization (under the rule of "hospital exemption", HE) by the AEMPS (Spanish drug agency = *Agencia Española de Medicinamentos y Productos Sanitarios*) and just a little more than half-year ago (December 2021) PRIME (*Priority Medicine*) designation by the EMA (*European Mediciness Agency*) for patients >25 years old with relapsed or refractory (R/R) B cell acute lymphoblastic leukaemia (B-ALL). The authorization is based on the results of a phase 1 clinical trial (NCT03144583), but additional patients (already reimbursed by Spanish Health System), new clinical trials or compassionate uses with ARI-0001, have been produced and infused in our Hospital Clínic de Barcelona or our

pediatric partner, Hospital Sant Joan de Déu. Although HE for adult ALL patients and compassionate uses (next to indicated commercial products that authorized our center) allow us to use CART19 therapy for treating our patients (our real aim of this development), the good clinical results, and petitions of different centers all around the world (specially from places where commercial products are not available) encouraged us to consider how we should proceed to extend our product to other patients. Our Academic proposal is the result of the work of a multidisciplinary team, a point-of-care (PoC) procedure based on a well stablish protocol in a commercially available bioreactor and our home-developed lentivirus. All the elements of our proposal follow the GMP standards, strictly controlled by the AEMPS and the regulations for Advanced Therapy Medicinal Products (ATMPs) of the EMA; although the product could be developed in our clean-rooms at Barcelona, our aim is to share procedures to allow production as a real PoC product, looking for partners that can reproduce all steps next to the patient. This multi-site cell production has been already accomplished with success in several clinical trials, while for a homogeneous lentiviral production, we decided (by now) to use facilities centralized in our university hospital. We expect to obtain first local authorization for this multicenter production in Spain, and later by EMA and other regulators (India). In fact, this experience is also supported by developing a clinical trial with 60 multiple myeloma patients under the treatment of a new own CART-BCMA (ARI-0002h). We are convinced that it is a possible model, although most of the huge number of rules are mainly thought for pharma-companies and are not easily implemented by Academic entities. But if we want to have the best treatments for our patients, to find solutions with real options for Academic ATMPs developments is the only way to arrive where the commercial companies, the health systems and in general countries will not be able to arrive for different reasons (difficult recover of investments by complex reimbursement, low level of patients, no-sustainable expenses and procedures for economic and ecologic reason, ...).

https://doi.org/10.1016/j.htct.2022.09.1199

Sp15

USA EXPERIENCE: IN-HOUSE PREPARATION: PROSPECTS AND PROBLEMS

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Adoptive Cellular Therapy (ACT) is transitioning from experimental to standard of care. Limited specificities of chimeric antigen receptor T cells (CAR-T) are licensed drugs, with commercial products selling for ~400,000 USD. Tumor infiltrating lymphocytes (TIL) can target multiple cell surface and intracellular tumor antigens. TIL have not been commercialized, due to complex logistics and cost. Our objective is to leverage a single standardized platform (Miltenyi Prodigy) for in-house ACT. We currently manufacture CD19 CAR-T under an FDA IND and are developing a virtually identical TIL protocol minus the lentiviral vector. TIL are manufactured from malignant pleural effusions rich in immune infiltrates. CD4+ and CD8+ cells are enriched and activated with anti-CD3/CD28 beads. CAR-T are transduced, and both CAR-T and TIL are expanded (IL-7/IL-15) for 5 days. The product is infused fresh, avoiding losses associated with cryopreservation and thawing. Developing and validating release tests (absence of replication competent virus, vector copy number, chimeric antigen receptor expression, endotoxin testing) posed an initial challenge. Having completed assay development, our manufacturing process, including release testing, can be performed for less than 1/10 the cost of commercial CAR-T. We expect that the platform that we have validated will be easily transitioned to new chimeric antigen receptor designs and specificities and will likewise be adaptable to TIL manufacture for the wide variety of cancers that metastasize to the pleura of peritoneum. Standardized in-house ACT manufacture may greatly reduce the cost of cellular immunotherapies, making it more widely available to patients.

https://doi.org/10.1016/j.htct.2022.09.1200