Sp06

Treatment Of Classical Hodgkin Lymphoma: The State Of The Art

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WHERE WE ARE?

Patients with advanced-stage classical Hodgkin lymphoma (cHL) have a good prognosis. In most countries, the first-line treatment has been, for at least a couple of decades, the ABVD protocol. Depending on several factors such as age, presence of *bulky* disease, or extranodal involvement, around 75-80% of patients are cured with this regimen[1]. However, there are now new treatment recommendations for advanced-stage cHL. After 6 years of follow-up, the ECHELON-1 study showed overall survival (OS) benefit for brentuximab vedotin with AVD versus the standard ABVD[2]. This has never happened in previous direct comparative trials. Although the BV+AVD was already approved for first-line treatment of advanced-stage cHL patients, based on the gain of progression-free survival (PFS) published a couple of years ago, a benefit in OS makes a much stronger case. Peripheral neuropathy was a special concern, with about 2 out of 3 patients treated with BV+AVD experiencing some form of symptom. Mainly it was grades I 1 and 2, and the symptoms did resolve or improved in almost 90% of cases[2]. But the BV-AVD reign has already been challenged. The SWOG1826 study is a randomized, multicenter, phase 3 trial, that compares the combination of nivolumab with AVD (nivo-AVD) versus BV-AVD[3]. This is a large trial, with almost 1000 patients, that included patients between 12 and 83 years. The 1-year PFS rate was 94% versus 86% (HR 0.48, 99%CI 0.27-0.87; p=0.0005), in favor of Nivo-AVD. OS was similar (99% vs 98%), with a short median follow-up of 12.1 months. Interesting that both arms of this study were for a limited number of 6 cycles, something different that is normally done with checkpoint inhibitors (usually until the progression of the disease, unacceptable toxicity, or up to 2 years). So, a longer follow-up will be paramount to see if this advantage for nivo-AVD will hold in time. The toxicity profile was largely as expected and no new safety signals in both arms. On the other hand, the HD21 study looked at the association between BV and a similar backbone of the escalated BEACOPP (eBEACOPP), known as BrECADD[4]. This new regimen was compared in a multicenter, randomized, phase 3 non-inferiority trial, with the standard eBEACOPP. Using a PET-adapted strategy, where interim PET negative patients completed 4 total cycles versus 6 total cycles in PET positive, BrECADD was non-inferior to eBEACOPP. The 3y-PFS rate was 94.9% versus 92.3%, with a median observation time of 40 months. These impressive results compare favorably with BV-AVD in the ECHELON-1 study (6y PFS of 82.3%) and with Nivo-AVD in the SWOG study (1y PFS of 94%), but with all the restrictions of comparing different trials.

WHAT TO EXPECT FOR THE FUTURE?

Clearly, in one of the lymphomas with the best overall prognosis, the treatment landscape evolved. There are now at least 3 new options for the treatment of advanced-stage cHL in the first line, with better results than ABVD, the standard for a long time. As we continue to improve efficacy, toxicity remains an important issue. Longer follow-ups will be needed to see if we can have great results without impact in our patient's quality of life.

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Sp07

MDS 2023: State of The Art

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The myelodysplastic syndromes (MDS) are clonal bone marrow (BM) stem cell disease(s), characterized by abnormal hematopoiesis, with anemia (95%) and/or other cytopenias. The pathogenesis is based on genetics and inflammation of aging (inflammaging). The median age of onset is 74yr, with increasing incidence with age. Patients are classified as having a lower (LR-MDS) or higher risk disease (HR-MDS), and leukemic transformation occurs in 20%-60%.

We will cover new aspects like quality of life (QoL), novel genetic information, will briefly touch the emerging field of inflammaging, describe new tools for (early) diagnosis, the new classifications, and finally will address MDS treatment. We will skip aspects such as epidemiology, clinical picture and cytogenetics.

Over the last decade QoL has become important in MDS, to study and improve – we will show some data. Genetics is an integral part of evaluation, with at least one mutation in 90% of MDS patients, but as more information is obtained it has become clear that the field is quite complex. The pathogenesis is carefully investigated and inflammation of aging (inflammaging) appears to play an important role.

Diagnosis of MDS has been recognized as a challenge. The introduction of new tools, such as genetic and digital medicine improve the process, make it more accurate, less invasive, and hopefully may identify individuals at risk.

Several new MDS classifications (and guidelines) have been proposed over the last couple of years. We will focus on the new IPSS-Molecular model, and will summarize the 5th WHO and ICC classifications.

RBC transfusions and erythropoietin (EPO) remain the 1st line treatment for anemia in lower-risk MDS. EPO is safe and might delay the need for RBC transfusions. A recent EUMDS study suggests a prolonged survival with EPO. Lenalidomide remains effective for MDS with del(5q) (50% response), but also somewhat effective (27%) in non-del(5q) patients. Luspatercept appears as an effective second-line (maybe 1st ?) agent. Several experimental agents are investigated, including oral azacytidine, imetelstat, a pyruvate-kinase activator and roxadustat. For thrombocytopenia two agents, romiplostim and eltrombopag, were shown to be effective. However, due to safety concerns their development has been stopped.

Treatment of higher-risk MDS is still based on hypomethylating agents (HMA) as the standard 1st line treatment, but attempts are ongoing to overcome the barrier of 50% response rate and less than 2 years response duration. Younger patients may respond to antileukemic treatment with or without transplant. Ways to improve the HMA effect include treating the HMA-related complications; modified HMA formulation; combinations of HMA with other agents (venetoclax appears to be the frontrunner), novel agents and targeted molecules.

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Sp08

Blastic Plasmacytoid Dendritic Cell Neoplasm BPDCN

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy with an aggressive clinical course and poor prognosis. BPDCN is most often characterized by its presentation with cutaneous lesions which are often asymptomatic, can be solitary or multiple lesions, can be distributed widely, and may range from bruise-like lesions to plaques or nodules. Bone marrow involvement, central nervous system (CNS) infiltration, lymphadenopathy, splenomegaly, and/or cytopenias are also seen to varying degrees.

The nomenclature has changed many times over the years, making descriptions of the epidemiology more challenging. It was first described in 1995 as acute agranular CD41 natural killer (NK) cell leukemia. In the most recent WHO 2022 classification, BPDCN is classified under dendritic cell and histiocytic neoplasms along with plasmacytoid dendritic cell proliferation associated with myeloid BPDCN is more common in older men, with a sex ratio of 3:1 to 5:1 and a median age of diagnosis between 60 and 70 years. A bimodal age distribution was recently described, with higher incidence in patients aged ,20 and .60 years.

BPDCN cells characteristically express CD123, CD4, CD56, CD303, TCF4, and TCL-1, whereas certain specific lineage markers such as CD14, cCD3, CD19, and MPO are not expressed.

Genetic mutations implicated in the pathogenesis of BPDCN include inactivating tumor suppressors (ie, TP53, RB1, CDKN1B, and CDKN2A), activating oncogenes (ie, NRAS, KRAS, FLT3, RUNX2, and HES6), activated NF-κB pathway, mutated RNA spliceosomes (ie, ZRSR2 and others), immune response gene dysregulation (IFNGR, TGFB, CLEC4C, and IFNA cluster), and epigenetic dysregulation (ie, IDH1, IDH2, TET1, TET2, and ASXL1).

Historically, BPDCN treatments have been based on multiagent chemotherapy regimens for lymphoma, acute lymphoblastic leukemia, and AML. In addition, acute leukemia regimens achieve high complete response (CR) rates ranging from 40–90% and allogeneic hematopoietic cell transplantation (allo-HCT) can result in durable remission in some patients. However, their rarity and heterogeneity make it difficult to determine the most effective therapeutic strategies.

Owing to recent advances in molecular biology and genetics, targeted treatment strategies have been developed. In 2018, the FDA approved tagraxofusp, a firstin-class CD123-targeting therapy for treatment- naïve or relapsed/refractory BPDCN.However, unfit, relapsed, or refractory patients continue to require effective therapeutic strategies.

Besides CD123 Targeted therapy; many other modalities are considered e.g. Venetoclax-based therapy, Transplantation and many new potential therapeutic targets under investigation.

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Sp09

Sustained Remission and Decreased Severity of CAR T-Cell Related Adverse Events: A Pivotal Study Report of CNCT19 (inaticabtagene autoleucel) Treatment in Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia (R/R B-Cell ALL) in China

Lv Lulu

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A B S T R A C T

CNCT19 (inaticabtagene autoleucel) is an autologous CD19-specific chimeric antigen receptor (CAR) T-cell product. The patent protected CAR structure of CNCT19 contains a unique CD19 scFv, HI19a, which is different from commonly used FMC63. Together with using 4-1BB co-stimulatory domain in the CAR structure, CNCT19 is expected to reduce the severity of treatment-associated cytokine release syndrome (CRS) and neurologic toxicities (NT) while maintaining a stronger and longer durable anti-tumor effect.

CNCT19 has been granted Breakthrough Therapy Designation by China National Medical Products Administration and Orphan Drug Designation by the U.S. FDA for the treatment of ALL.

The trial of CNCT19 in adult Chinese patients with R/R B-cell ALL (NCT04684147) is a single-arm, open-label pivotal study conducted at 10 centers in China. The primary endpoint was the overall complete response rate (OCR) of complete response (CR) and CR with incomplete hematological recovery (CRi) within 3 months and at the end of Month 3 after CNCT19 infusion by central assessment.

All 39 patients diagnosed with B-cell ALL were refractory and relapsed to multiple lines of prior therapy. Among the 39 patients 32 (82.1%) had reached MRD-negative OCR within 3 months after CNCT19 infusion, The median duration of response and OS have not been reached. 25 patients (64.1%) remained on CR (51.3%) or CRi (12.8%). at the end of Month 3 after CNCT19 infusion These patients had sustained long-term remission regardless of whether subsequent allo-HSCT treatment was done or not. The most common CNCT19-related adverse events (AEs) were CRS and NT and there were