05

HOW I TREAT PH+ ACUTE LYMPHOBLASTIC LEUKEMIA

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The greatest improvements in the management of Acute Lymphoblastic Leukemia (ALL) have been witnessed in Ph +ALL patients. The advancements have stemmed from an always more precise genetic characterization at presentation, the use of tailored treatment, the precise monitoring of minima/Measurable Residual Disease (MRD) and, finally, by the inclusion of immunotherapy in the frontline treatment. Prior to the advent of Tyrosine Kinase Inhibitors (TKIs), Ph+ALL was the hematologic malignancy with the worse outcome. The frontline use of TKIs has changed the natural history of the disease. Since year 2000 in Italy all patients enrolled in the GIMEMA multicenter protocols have been treated in induction with a TKI alone (plus steroids) and no systemic chemotherapy. The subsequent advancement has been brought by the addition of the bispecific monoclonal antibody blinatumomab as consolidation, always in the absence of systemic chemotherapy. The results of the GIMEMA LAL2116 (D-ALBA) trial for patients of all ages showed high rates of molecular response following an induction/consolidation treatment with dasatinib and blinatumomab. At 53-months, survival rates of 75%–80% were recorded, with 50% of patients being managed only with a TKI and blinatumomab, without chemotherapy and transplant. Most MRD+ patients were allografted. IKZF-plus patients have a less favorable outcome and should be identified at diagnosis. When possible, they should undergo an allogeneic transplant. In the subsequent phase 3 GIMEMA ALL2820 trial, patients enrolled in the experimental arm and treated with ponatinib followed by blinatumomab showed even higher rates of molecular response, with estimated OS and DFS of 94.9% and 95.6% at 12-months. Of interest, the combination of dasatinib and ponatinib plus blinatumomab, in the absence of systemic chemotherapy, is associated with a marked host immune activation. The MDACC group also reported the effectiveness of ponatinib combined with blinatumomab, though the combination was associated with greater toxicity. For a review on the treatment of adult Ph+ALL see Chiaretti & Foà. The GIMEMA ALL2820 trial will conclusively show how many patients can be spared systemic chemotherapy and transplant. At the interim analysis, only 10% of patients enrolled in the ponatinib + blinatumomab arm have so far undergone a transplant. I have been asked to cover 'How I Treat Ph+ALL', which more appropriately should be 'How Should I Treat Ph+ LL' Based on the 25-year experience gathered through the GIMEMA trials, the optimal algorithm should be: i) Identify the presence of the BCR/ABL gene lesion within one week from diagnosis; ii) During this time treat patients with steroids; iii) Start induction with dasatinib or ponatinib plus steroids, with no systemic chemotherapy; iv) CNS prophylaxis should be carried out; v) MRD should be monitored molecularly at given timepoints; vi) After induction, all patients should be consolidated with multiple cycles of blinatumomab (up to 5 in our protocols); vii) TKI should not be stopped. Through this approach the large majority of patients – of all ages – will become molecularly negative. IKZF-plus patients should be identified on the diagnostic material. Transplant should be offered to patients with an unfavorable genetic profile and/or evidence of MRD. All patients should be closely monitored for MRD during the follow-up. The possibility of offering such a personalized frontline management to all patients – including the elderly – strongly relies on adequate and standardized laboratory facilities aimed at a broad diagnostic work-up and at an accurate monitoring of MRD, as well as an optimal and timely access to the different drugs. In the real life, this is often not possible. Patients should then undergo a TKI (plus steroid) induction associated with mild chemotherapy. Many such patients are offered an allogeneic transplant. The future of patients with Ph+ALL of all ages is looking always more favorable if all the pieces of the puzzle are in place. It is likely that with the advent of the subcutaneous formulation of blinatumomab the long-term outcome will look even better.

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06

WHICH IS THE BEST TREATMENT FOR AML WITH RESTRICTED RESOURCES

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AML itself is one of the worst prognostic hematological malignancies which has to be managed timely, adequately and aggressively to get on top of it. Such, kind of patients will need intensive chemotherapy therapy (3+7, Flag IDA) followed by allogeneic SCT. That is why it is challenging to manage such cases in resource limited setting. Due to constant development of new drugs treatment of such patients with azacytidine and venetoclax have been lot easier. With these drugs we are being able to put patients in remission with less toxicities, and low cost as compared to intensive chemotherapy.

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07

UPDATES ON HODGKIN DISEASE

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Hodgkin Lymphoma (HL) is a B-cell malignancy accounting for approximately 10% of all lymphoma cases and 5% of lymphoma-related mortalities. Incidence increases in younger adults and those above 55-years of age and has a bimodal distribution. Approximately 95% of all HL cases are diagnosed as classical Hodgkin Lymphoma (cHL) and 5% as Nodular

Lymphocyte Predominant B-cell Lymphoma (NLPBL). Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte–rich HL are subgroups of classical HL. Risk Stratification An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. Prognostic models that identify patients at low or high risk for recurrence, as well as the response to therapy as determined by Positron Emission Tomography (PET) scan, are used to optimize therapy. Risk–Adapted Therapy Initial therapy for HL patients is based on the histology of the disease, the anatomical stage and the presence of poor prognostic features. Patients with early–stage disease are typically treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy followed by involved–field radiation therapy, whereas those with advanced stage disease receive a longer course of chemotherapy often without radiation therapy. However, newer agents including brentuximab vedotin and anti–PD–1 antibodies are now standardly incorporated into frontline therapy. Management of Relapsed/Refractory Disease High–Dose Chemotherapy (HDCT) followed by an Autologous Stem Cell Transplant (ASCT) is the standard of care for most patients who relapse following initial therapy. For patients who fail HDCT with ASCT, brentuximab vedotin, PD–1 blockade, non–myeloablative allogeneic transplant or participation in a clinical trial should be considered. The AETHERA study (NCT01100502) shows that Brentuximab Vedotin (BV) improves Progression-Free Survival (PFS) after ASCT in patients with Refractory or Relapsed HL (R/R HL). For patients who relapse after ASCT, BV, and anti-PD-1, monoclonal antibodies were considered incurable, and their outcome is rather dismal, with a median Overall Survival (OS) of 2-years. For Refractory or Relapsed cHL (R/R cHL) patients who have failed both ASCT and BV, Chimeric Antigen Receptor T-cell (CAR-T) therapy offers a new therapeutic option.

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08

HISTORY OF BLOOD TRANSFUSION

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It is not easy to cover the history of transfusion in all its aspects. In the era when blood transfusion was first tried, the indications for blood transfusion were also very different: mental illness, gaining strength, rejuvenation, etc. Blood transfusion process has gone through many dangerous and difficult stages, from obtaining the blood to its safe application in peace, in war, and in the laboratory. This presentation focuses on some stages and developments in the application of blood transfusion. The main developments are summarized in Table 1. The main problems encountered in the history of transfusion can be summarized as follows:

- Blood clotting and preservation could be prevented by the use of 0.2% sodium citrate and dextrose.
- Severe transfusion reactions could mostly be prevented after the ABO blood groups were identified.
- Infection problems that could be partially controlled with antiseptic agents.

In this presentation, various obstacles encountered in the history of blood transfusion and developments regarding their solutions are presented.

Table 1 Important stages in the history of blood transfusion.

1628	William Harwey (GB)	Discovery of human blood circulatory system
1666	Richard Lower (Oxford)	Experiments of blood transfusion beetween animals
1667	Jean Denis (Paris)	Transfusion blood from animals to humans
1818	James Blundell (London)	First blood transfusion from one human to another
1854	J Bovell E Hodder (Toronto)	Cow's milk transfusions was first attempted
1901	Karl Landsteiner (Wienna)	Discovery of ABO blood groups (Nobel Prize in 1930)
1915	Richard Lenwinsohn (NY)	Developing 0.2% sodium citrate as anticoagulant
1921	Percy Oliver (London)	The first blood donor service is established
1932	in the SU and the USA	Cadaveric blood began to be used
1937	Bernard Fantus (Chicago)	The first blood bank
1940	Edwin Cohn (Boston)	A method for fractionation of plasma proteins
1951	Edwin Cohn (Boston)	Developping the first blood cell separator
1971		Hepatitis B surface antigen testing of donated bloods
1982	J Goldstein	Developing universal type O blood by enzyme treatment
1983	L. Montaignier (Paris)	Isolation of the virus that causes AIDS
From 1987 to 2008		A series of tests are developed to screen donated blood for infectious diseases
2010	Seifinejad A et al.	RBCs generated from human induced pluripotent SCs
2020	Ebrahimi M, et al.	Differentiation of human induced pluripotent stem cells into RBCs

SU, Soviet Union; USA, United States of America; RBCs, Red Blood Cells; SCs, Stem Cells.

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09

TREATMENT FOR HODGKIN'S LYMPHOMAS IN COUNTRIES WITH LIMITED RESOURCES

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The incidence and long-term clinical outcome of Hodgkin Lymphoma (HL) vary according to different patient, disease-related factors and geographic location. There have been