REVIEW ARTICLE

THE CONTEMPORARY CONTRIBUTION OF BIOTECHNOLOGIES IN DIAGNOSTIC AND THERAPEUTIC DEVELOPMENTS DURING MALIGNANT HEMOPATHIES.

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Abstract: Hematology is a medical discipline which studies, among other things, cancers of the blood, bone marrow and lymph nodes, has benefited from great advances both in the field of pathophysiological knowledge of malignant blood diseases, and in the therapeutic field to the development of biotechnologies.

These biotechnologies have enabled the development of cytogenetic with the use of in situ fluorescence, that of flow cytometry with flow cytometers at 8 and 10 colours, allowing increasingly precise immunophenotyping of malignant cells, that of molecular biology with the discovery of numerous oncogenes and tumor molecular markers by "Polymerase Chain reaction" (PCR) and more recently with the use of sequencing (Next Generation Sequencing NGS). These diagnostic methods have also made it possible to develop therapeutic strategies, such as targeted therapy, immunotherapy with monoclonal and bispecific antibodies, hematopoietic stem cell transplantation, as well as CAR-T cells. Finally, the post-therapeutic evaluation of hematological malignancies has gone from the stage of complete clinical remission to undetectable molecular complete remission. This work aims to show the progress made in malignant hematology during the last century and this century.

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Conflicts of interest

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Introduction:

Hematology is a medical discipline that studies, among other things, cancers of the blood, bone marrow and lymph nodes, an improvement of the great advances both in the field of pathophysiological knowledge of malignant blood diseases, and in the therapeutic field, thanks to the development of biotechnologies. This progress has made it possible, in part, to fine-tune and update the classifications, which are constantly renewed [1-3], as well as the emergence of new nosological entities [4-5] and, on the other hand, a very significant increase in survival times [6-7]. This type of general review work of hematological malignancies aims to summarize their management, both from a diagnostic point of view, as well as from a therapeutic and evolutionary point of view during this 21st century.

Contribution of biotechnologies in the field of diagnostics:

Cell immunophenotyping by flow cytometry:

The study of blood cells, first by optical and then electronic microscopy and today by flow cytometry, has made it possible to qualitatively and quantitatively identify the various normal and pathological blood cells [8]. Currently, the diagnosis of acute or chronic leukemia as well as that of all lymphomas is easily made thanks to increasingly precise immunophenotyping [9-10]. This examination, more and more technically improving (cytometer with 8 and 10 colors) makes it possible to identify with certainty currently the origin of the circulating cells of the blood and also makes it possible to follow the evolution of the cell populations in time, in response to treatments or diseases.

Cytogenetic and the FISH technique:
In addition, the study of blood cells by cytogenetic and the FISH technique has made it possible to establish a hematological karyotype and to search for specific and/or recurrent cytogenetic abnormalities, such as translocations, deletions, abnormalities in the number of chromosomes and thus to define new distinct nosological entities, which has made it necessary to establish classifications of these hematological malignancies on the cytogenetic level [11-12].
Molecular biology:
Biotechnologies have now made it possible to develop very fine techniques for analyzing the genome of pathological cells in search of oncogenes in hematological malignancies. The techniques used are the "Polymerase Chain reaction" (PCR) or RT-PCR [13-14], qualitative and quantitative, and more recently, Next Generation Sequencing (NGS) techniques, which have made it possible to evaluate the genetic sequencing of pathological cells, thus allowing the discovery of many tumor oncogenes and molecular markers, and to prepare a future therapeutic targeting of isolated defective genes [15].

Contribution of biotechnologies in the field of classifications and staiging:
Biotechnologies, in particular, flow cytometry, molecular biology (PCR and NGS) as well as cytogenetics (FISH), have made it possible to establish increasingly fine classifications that are increasingly adapted to the pathophysiology of malignant hemopathie. Thus, there are numerous nosological classifications relating to lymphomas [16-17], acute myeloid or lymphoid leukemias [18-19], myeloproliferative syndromes [20], myelodysplastic syndromes [21], lymphoproliferative syndromes [22]. Some of these classifications relate to the “staiging” of hematological malignancies, others to therapeutic and/or prognostic indications.

Contribution of biotechnologies in the field of prognosis:
Once the diagnosis of malignant hematological disease has been established, it is important to prejudge its evolution. Thus, the prognosis can now be assessed by calculating the tumor mass or volume (imaging by computed tomography, Pet-Scanner) [23-24] or by the presence of cytogenetic abnormalities [del 17p, t(9;22), t(15;14)] and/or molecular (FLT3 mutation, BCR-ABL transcript, IgVH status, JAK2 mutation, etc.) negative effects on the therapeutic response [25-26-27-28] or evolution by measuring residual disease, by CMF, by molecular biology and/or cytogenetics [29-30]. All the resulting prognostic scores [31-34] are currently established using mathematical modeling based on artificial intelligence [35-36].

Contribution of biotechnologies in the field of treatment:
Targeted therapy and targeted immunotherapy:
Biotechnologies have greatly contributed to the evolution and therapeutic progress in hematological malignancies during the 20th and 21st centuries. The most striking example is that of chronic myeloid leukemia (CML), which paved the way for targeted therapies in onco-hematology, through the development of inhibitors (chemical agents) of tyrosine kinases (TKIs) [35- 36].
The approach was made "easy" by the discovery of the chromosomal translocation t(9;22) in cytogenetics, then the discovery of the BCR-ABL chimeric gene by molecular biology, then research from the pharmaceutical industry, has developed an inhibitor of its cell proliferation function by ITKs. Subsequently, targeted therapy was extended to almost all malignant hemopathies with "immunological" inhibitors (monoclonal antibodies), example of FLT3 in AML [37], of CD30 in Hodgkin's lymphoma and lymphomas T [38], BRAF in Tricholeukocyte AL [39], Chekpoint inhibitors [40], etc…. Similarly, the appearance of so-called “bispecific” conjugated antibodies, such as Blinatumumab in ALL B[41], associated with TKIs (LAL Ph+) or anti-BCMA in multiple myeloma [42].

Hematopoietic stem cell transplantation:
Hematopoietic stem cell transplants have also evolved in large proportions. Nearly 50,000 transplants are performed each year worldwide (60% autografts, 40% allografts) [43]. Most stem cells (80%) are now collected by cytapheresis from the peripheral blood, whereas bone marrow was the preferred source in the 20th century. Advances in hematological resuscitation as well as pre-transplant conditioning, which in most cases are attenuated

conditioning, have made it possible to significantly reduce the mortality linked to the transplant. Furthermore, it has become possible to find a donor for practically every indication for transplantation, thanks to the international file of unrelated voluntary donors and above all thanks to the recent possibility (since 2005) of carrying out transplants from haplo-identical intra-family donors, which makes transplants more and more to be intrafamilial [45]. However, today the future of transplants is under constant discussion in the face of the development of increasingly effective and highly innocuous targeted therapies (CAR-T cells) and no one can predict with clarity the place they will have retained in the future

CAR-T cells:

CAR-T cells (Chimeric Antigen Receptor=CAR) is an immunological therapeutic procedure using an anti-CD19 protein that is very effective in malignant type B cell proliferation [46-47]. There are two types of CAR-T cell preparations, autologous or allogeneic. It is therefore an immunological treatment technique, derived from allografts or autografts, which consists of targeting CD19. This therapeutic method is less toxic than the allogeneic cell allograft, with little or no graft versus host reaction (GVH) and zero post-infusion morbidity and mortality apart from toxemic lysis syndrome. CAR-T cells are on the way to becoming an essential therapy in the management of hematological malignancies in first intention and should replace cell transplants in the more or less short term.

Contribution of biotechnologies in the field of evaluation:

Today, post-therapeutic evaluations are mainly carried out in biology, by cytogenetics or molecular biology or flow cytometry and secondarily by imaging (Pet-Scanner) during hematological malignancies. The most discriminating parameter is currently the measurement of the residual disease or MRD [48-49], both in hematological malignancies such as acute or chronic leukemia, and in lymphomas, by measuring the residual tumor volume. Thus, patients are continuously monitored depending on whether residual disease (MRD) has been detected or not, and the objective that was yesterday to obtain complete cytological remissions (CR) is now replaced by the need to obtain molecular CR without detectable residual disease called “MRD negative” CR. This new approach in the evaluation of hematological malignancies has made it possible to develop new therapeutic strategies, such as therapeutic de-escalation during lymphomas [50] or even more, discontinuous treatments [51] or discontinuation of treatments during CML for example [52].

Conclusion:

Formerly, formidable by their constantly fatal evolutions, malignant hemopathies have today become for some of them chronic affections (CML, Myeloma, Lymphomas), while others are currently totally curable with new procedures and innovative therapies.

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