Natacha Bolaños – Global Alliances Manager & Regional Manager, Europe, Lymphoma Coalition



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The Lymphoma Coalition's Natacha Bolaños outlines the fundamentals of the lymphoma patient experience today, the growing number of innovative new treatment options available, and the issues surrounding their integration as earlier lines of treatment.

Can introduce Lymphoma Coalition to our international audience and tell us about your role within the organization?

Although the Lymphoma Coalition was formed in 2002, it was not until 2010 when it was incorporated as a non-profit organization. The idea behind the Coalition is to have a central hub of consistent and reliable information and share resources and best practices with lymphoma patient organizations.

Today we work alongside 83 member organizations in 52 countries serving patients and families with all lymphoma subtypes including chronic lymphocytic leukaemia (CLL). Our current strategy is focused on ensuring impact within two main pillars: information and evidence-based advocacy, to help patient organizations stay on top of the most pressing issues and ensure that patients can receive and benefit from information on the latest treatment research and disease management practices.

Every year 735,000 people around the world are diagnosed with lymphoma. There is a lot of misinformation about the disease and a great deal of discrepancy and variability in the quality of information, treatment, and access. Our aim is to ensure these issues are raised to build awareness about where the gaps and disparities are and where the focus should be to provide better care to patients.

We want to create more equal access to lymphoma care, diagnosis and medical treatment, but we focus on the holistic concept of care, recognizing not only the clinical gaps but also the patient meaningful outcomes. For instance, we address problems of fatigue and fear of relapse, alongside other patient-centred concerns, based on facts and research.

We work together with the medical community to help them understand the patient experience from their point of view. Every two years, we run a global patient survey to take the pulse on the current issues that patients and caregivers are facing. The survey has a high participation level; the 2020 edition received almost 12,000 responses. With that information, we can identify the primary medical issues affecting the wellbeing of patients, the most pressing psychosocial issues and how adverse effects can be persistent over the years. We try to bring all that information together not only to help the medical community to understand the patient experience but also to inform at a decision making, regulatory and policy level. Additionally, we work with the European Medicines Agency (EMA) to provide scientific advice, review patient leaflets, or provide input on the assessment of clinical trials or new medicines. We also work with HTA bodies at a country level to give patients the opportunity to be part of the discussions.

As you mentioned that 735,000 people are diagnosed with lymphoma every year, has science kept pace when it comes to lymphoma?

It is firstly important to note how lymphomas are classified. Traditionally, lymphomas are divided on Hodgkin and non-Hodgkin, but we are trying to change the language because grouping almost all lymphoma statistics under the non-Hodgkin umbrella is not helpful.

There are more than 80 different subtypes, so we try to classify the lymphomas into low-grade or chronic lymphomas where the cancer cells grow slowly, and high grade, aggressive or acute lymphomas where the cancer cells grow and spread quickly.

Curiously, aggressive lymphomas have better cure rates as chemotherapy and immunotherapy can effectively kill the cancer cells. However, low-grade lymphoma patients often have to go through a

remission and relapse cycle and, because these lymphomas generally affect older patients, there is a higher risk of death from other factors. Many patients also have comorbidities; therefore, we must consider the quality of life needs and not only how long the remission could be.

In aggressive lymphomas, the challenge is to predict the percentage of patients whose lymphoma did not respond well to first-line treatments and could benefit from a second-line treatment that is going to offer them long term remission.

In recent years, we have substantially improved not only in terms of diagnostic tools but also in treatment options. The introduction of CAR-T cell therapy has proved to be an innovative approach to treating high-risk lymphoma patients and could offer a curative approach in the future. There is, however, a lack of efficient methods to predict the patients whose lymphoma will not respond to the therapies available, and that is where we should make greater efforts. If we know how to identify the patients that will not get any benefits from a given therapy we could spare them the suffering and toxicity of a treatment that at the end of the day will not bring them any benefit and focus on bringing new therapies for those patients and get them to remission.

How do you assess the potential for new innovative approaches to be used as an earlier line of treatment impacting the standard of treatment and care?

This is an area where research could make a difference. There is a consensus on first-line therapy for most lymphomas. However, when it comes to second-line therapy it is not as clear.

Let’s take diffuse large B cell lymphoma (DLBCL) as an example. Between 25 to 33 percent of patients will fail to achieve a complete remission after first-line treatment and will either develop primary refractory disease or relapse. Currently, we have several treatment approaches for relapsed or refractory diffuse large B cell lymphoma patients including CAR-T, bispecifics, immunomodulatory drugs, immune checkpoint inhibitors, monoclonal antibodies, antibody-drug conjugates, molecular pathway inhibitors, and epigenetic modifying drugs among other options.

The challenge now is how to predict which should be the best second-line therapy for each patient understanding benefit as longer survival together with better quality of life. Some of these treatments could provide longer survival, however, they diminish the quality of life, and that is a big issue because in most cases only patients that have zero to one ECOG performance status are offered the option to participate in a clinical trial.

Patients with worse functional status and comorbidities are commonly excluded from research, but those are the patients who represent the best real-world patients. When a clinical trial is run following certain criteria, the approval of the treatment follows the same criteria. This means that if the criteria for the clinical trial was an ECOG zero to one, then when payers are discussing who should get the therapy and who they are open to pay for they will follow the criteria of the trial. Those patients that are excluded from research are also excluded from reimbursement. That is why we advocate for changing eligibility criteria for pivotal studies, it should be re-examined, as it may be excluding patients who may benefit from innovative treatments.

Likewise, we need to bring treatments to first-line that could provide better clinical outcomes, and if not cure, at least put patients in complete remission for a long time with a good quality of life. Hopefully, soon we will be able to better understand the biology of the disease and find a way to predict the best line of treatment and approach for each patient depending on their disease.

CAR-T was first introduced as a treatment option amid a great deal of stakeholder excitement and optimism. How has it been received by the lymphoma community?

CAR-T in the context of lymphoma is often presented as the last option to patients with advanced disease. At that point they have accumulated toxicity, their quality of life may be diminished, and their performance status may not be optimal. The primary aim of the treatment is patient survival, and when CAR-T became available it was presented by the media as a curative option, There was a significant amount of excitement and enthusiasm surrounding CAR T-cell therapy for lymphoma, specifically Diffuse Large B Cell Lymphomas (DLBCL), but at the beginning, the outcomes were less clear. . It is true that in the case of leukaemia the outcomes were pretty amazing in the real world, however, we should also measure other aspects of health such as functional status, cognitive function, psychosocial concerns, even financial toxicity.

In addition, there are important barriers to accessing CAR-T therapy, starting with the fact that it is not administered in every hospital but rather in specialised centres (for good reasons) adding logistics challenges to overcome. Even though CAR-T therapy is very promising it is important to inform patients about realistic outcomes, explaining the risks and the benefits and complexity.

In general, by the time a patient is presented with CAR-T as an option they are exhausted after undergoing several lines of treatment. Even if you have a patient that is eligible, the manufacturing process can present hurdles. For example, there is a window of time for that manufacturing process to happen, and after modifying the cells and bringing them to infusion if the patient is in a

very aggressive stage of the disease and it is progressing rapidly the window for infusion might be lost.

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It seems like even from a clinician perspective it might be a difficult choice to go for CAR-T as the recommended therapy.

It is a difficult decision for a doctor; they must consider many things, and most importantly if there is a time window for the patient to undergo the treatment without the decease turning more aggressive. If the clinician is working in a hospital without CAR-T accreditation, they must consider logistical issues as well. If a patient meets the criteria for CAR-T they have to find a hospital nearby that could provide the therapy, the patient would have to travel with a caregiver and stay in the area close to the hospital for between 30 to 45 days. Moreover, that is only in case if CAR-T is approved and reimbursed in the patient's home country; in some countries CAR-T is only approved for certain indications and in some others such as some in Eastern Europe or those in Latin America, with the current price-setting and the financial burden on healthcare systems, it is not even available yet.

When it comes to bringing a therapy like CAR T to earlier lines of treatment, what do you think are the main obstacles?

If you analyse trials and research, most of them are planned for relapsed refractory settings. It is very challenging to move a first-line therapy because there is a lot of real-world data; it is known what is going to happen, how to manage the toxicity and that a significant number of patients will benefit from that therapy. Bringing a new therapy to front line is challenging and it cannot be done while thinking about only a small minority of patients.

If we could predict the patients who would not benefit from a certain therapy, then we could focus on the characteristics of those patients and try to bring therapies that are probably now approved as further lines of treatment and try to move them to earlier stages.

In your view, what would need to change to administrate CAR-T therapy earlier in the treatment regime?

We need more real-world evidence. Clinical trials are relevant of course, but real-world evidence is even more relevant considering that patients out there are not necessarily the ones with the inclusion/exclusion criteria that were mapped for the clinical trial. On top of that, in the context of CAR-T (at least with the first clinical trials) a big effort to capture clinical data was done, but they were not so efficient when it came to capturing the quality of life data or patient-reported outcomes.

If we think about moving CAR-T to earlier lines of treatment we should have a transparent discussion on sustainability, pricing, and reimbursement strategies, including associated costs of pre- and post-care for CAR T-cell therapies as these costs are reimbursed insufficiently. because health systems, in general, won't be sustainable with the current prices of innovative therapies. Combined with the expected expansion of indications, the financial burden on healthcare systems will increase substantially with a direct impact on patient access to these treatment options. We also need more hospitals with the experience and the availability to deliver the therapy.

Which stakeholders should assume the responsibility for collecting the real-world data needed to truly assess the value of CAR-T therapies?

In the context of CAR-T, I think that the EMA has done a good job in making data collection mandatory. Every patient needs to have a follow up of at least 15 years. My hope would be to expand that data collection window, because 15 years (depending on the age of the patient) may not be enough if you consider children for example. After 15 years of collecting their data, we would need to continue the follow-up.

I would also hope for a collection of data not only in terms of clinical outcomes, but also in the quality of life and patient-reported outcomes and other parameters as, for instance, associated cost of care, resources allocation, or variability in clinical practice. That is why the GoCART Coalition came to be. It is a strategic partnership between the European Haematology Association and the European Society for Blood and Marrow Transplantation (EBMT) to advance in the field of cell and gene therapies. The idea behind it is to be a pre and post-authorization registry, to monitor product manufacturing, safety, efficacy, harmonize data collection and support patient access to

these novel gene and cell therapies and overcome barriers in regulation.

Patients are also part of the GoCART Coalition; the idea is to gather data sets, different cohorts from all over Europe with everybody reporting in the same format in order to build a big platform. GoCART is working not only to ensure that these data sets are built correctly, but also that the analysis of the data is done correctly. This will create a better understanding of where the gaps are and ensure that patient outcomes are not overlooked.

What would be your final message to pharmaceutical companies?

There is a misalignment of research and development efforts with persistent unmet clinical needs. I want to recognize the efforts that have been made in recent years to engage patients and to bring patient inputs into clinical trial design much earlier. However, there is still so much to be done, and the pharmaceutical industry needs to make a bigger effort when it comes to designing clinical trials. The inclusion-exclusion criteria need to be modified or we will keep leaving patients out of research. I think many resources in research and development are being wasted, not only because the gaps in the design of the trials but also because of the amount of bureaucracy associated with clinical research.

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