THE TIME TO TARGET AND TERMINATE THE THREAT OF PTCL

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Whenever professional interest is directed towards this particular type of lymphoma, some terms are evidently present more than others: heterogeneous, aggressive, dismal prognosis, standard treatment not established, poor outcome..., something that does not make any hematologist very happy. If some breakthroughs in hematology in the past two decades brought smiles to our faces, this area of expertise is certainly not among those.

Let's have a look at the definition of Peripheral T cell Lymphomas.

Although the term “peripheral” could associate to “not central”, or “distal”, in means of occurrence, localization of the disease, or eventually to the zone in the lymph node where it develops and/or grows, that is not what it refers to. Peripheral is an attribute for the T cells, aiming to explain that the essence of these lymphomas is the mature T cell, one that has been introduced to its destined functions in the human organism. If it had been still immature, and taken a turn towards malignant proliferation, the result would be a lymphoblastic lymphoma (only approximately 10% of these are of B lineage origin), or an ATLL. In a smaller proportion, these lymphomas can have their origin in a subset of lymphocytes of the natural killer type.

In explaining the previous, we have also established that the pathognomonic substance of these neoplasms are the T lymphocytes.

The last of the terms simply delineates that these disorders are inevitably of malignant nature, lymphoproliferative neoplasms, very aggressive, fast growing, quite resistant to known therapies, and very frequently fatal.

The final word in labeling these neoplasms belongs to the pathologist, regardless whether only morphology is going to be decisive, or immunophenotyping, molecular analyses and/or genetics are going to be included in the process of establishing the diagnosis. Many problems lie in the path for the pathologists. Firstly, due to the not clearly distinct clinical manifestations, parallel to the aggressive and rapidly advancing disease course, the pathologist might not even receive any substrate for examination, only leaving the opportunity for establishing the diagnosis following autopsy. When substrate is available, the problems arise from the growing number of entities that are introduced to this segment of pathology in the successive classifications of lymphoproliferative disorders, which becomes the basis for naming this group of disorders heterogeneous, diverse and complex. In such a situation, when not so many cases of PTCL are scattered around the World, and are being classified in a growing number of distinct categories, the suffering end is the level of concordance in pathologist’s opinions. Even in the vast field of B-cell lymphomas pathologists have a certain level of disagreement regarding final diagnoses, but it has been observed that the accord, confidentiality and reproducibility levels decline for around further 10% in the area of PTCL. Utilizing contemporary available lab techniques gives rise to the possibilities for precise diagnosis of a certain type of PTCL, but characteristics obtained by these are not attributable to all subtypes. Therefore, for some types of PTCL, molecular analyses of immunophenotype or genetic distinctions can be the decisive factor, but for others it will still remain a matter of professional opinion.
the small overall number of PTCL cases definitely handicaps progress in managing this area of hematology. Prospective randomized studies have since long ago become the verified basis for advances in the field of establishing successful treatment options for any kind of disease. When PTCLs are in question, not much success is observed. According to different reports, the whole segment of PTCLs account for not more than 12-15% of all lymphomas, which, when distributed to the existent and growing number of hematology centers, hardly comprise patient populations sufficient for randomized studies. Even more, this option is made more implausible, because of the rising number of agents that are introduced as therapeutic possibilities for PTCLs. In summary: too few cases, too many centers, too many treatment alternatives ... not a fruitful field for randomized studies. The conclusion is inevitable: progress can be achieved only through multicentre investigational programs and protocols, such as is the International PTCL project.

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At present, the number of entities comprising the circle of PTCLs is a result of joint efforts of the WHO classification and the International PTCL project consortium. Some of the entities are better characterized and firmly established, and a minor number are labeled as provisional entries. There is a total of 22 entities, T-cell and NK-cell derived neoplasms, distributed in several groups (Table 1).

A few of the entities are diagnosed with great confidentiality, based solely on morphology, especially the cutaneous types of PTCL, since clinical presentation patterns and characteristics contribute considerably to the process. Immunophenotyping, whether performed by immunohistology or flow cytometry, can aid the categorization, but also of a certain number of entities, and maybe help in distinction of certain subtypes. Since we have largely entered the era of genomics, efforts are introduced to utilize this methodology in better characterizing the PTCL’s also, but definite genetic associations in the area of PTCLs are still anecdotal. This is why most of the diagnosed PTCLs are framed in the category of “not otherwise specified”.

Some of the entities are definitely associated with the presence of the HTLV-1 virus, in particular the Adult T-cell leukemia/lymphoma type. Since this virus is much more frequently present in the population of the Far East, the Caribbean and the Middle East, chances for acquiring a consequent PTCL of this particular type range from 2-4%, but by no means does it state that a person with the HTLV-1 will certainly develop a PTCL. Considering the Asian region again, the intestinal PTCLs on that continent are far more frequently associated with an EBV infection. On the other hand, some PTCLs are associated with other disorders, as is the enteropathy associated TCL, which arises more frequently in individuals with celiac disease, making it more prevalent in Northern Europe. Therefore, the PTCLs also have, to some extent, a particular geographical pattern of distribution.

Considering most of the previously stated, it is not a surprise at all, that the largest number of PTCLs are categorized as NOS, a wastebasket that encircles all the diagnosed PTCLs, with no specific morphological, immunological, genetic, clinical or prognostic feature. This simply leads to the conclusion that we have still not found the common denominator for a large proportion of these disorders. It also reveals that, not being able to distinguish any differences between them, the designated treatment approach for all of those would be the same.

When we come to the point of treatment, we must once more emphasize that a total relatively small number of cases denies possibilities for performing successful randomized studies. Small numbers deny the analyzes the statistical power to prove a hypothesis, and they also demand greater differences in order to assign the attribute of significance to the findings.

Nevertheless, clinical experience has come to some revelations. It is now well established that the subset of anaplastic lymphoma kinase protein (ALK) positive ALCL (which can be T-cell or NK-cell derived) have a better prognosis with today’s “standard” treatments, i.e. with chemotherapy alone, even better than cases with DLBCL: ~70% for 5-y OS. Also, it is almost without exceptions shown that the cutaneous forms of PTCLs tend to have a better outcome and vital statistics.

Worldwide, CHOP chemotherapy regimen is still recognized as the “standard” first line treatment option for all PTCLs, everywhere quoted as producing results that are not even close to those obtained in B-cell neoplasms. With the exception of ALK+ ALCL, all other PTCL subtypes have OS rates below 50%, some expressed as 5-y rates, but some as only 2- or 3-y rates. In some types, PFS and/or OS are expressed only in months, when first-line treatment is analyzed. The dismal prognosis becomes even shorter, and finally inevitably fatal, in virtually all relapsed patients.

When one tries to improve on treatment results, there are two basic options: a. increase treatment intensity by elevating drug dosage or by shortening the intervals of chemotherapy administration, or b. expand the “coverage” area of chemotherapy by adding drugs to the regimen. Most such efforts have been performed by the Nordic and the German Lymphoma Study Group, resulting in the CHOEP (adding of Etoposide) regimen, and eventually in the Mega-CHOEP (dose escalated) regimen, now standard treatments for PTCLs by their guidelines. Many investigators would recommend HyperCVAD as the more aggressive chemotherapy regimen. Others have tried, or would prefer EPOCH, ICE, DHAP, ESHAP, or similar combinations.

The issue of “standard” treatment is completed by the wide acknowledgement and recommendation that all PTCL cases, except the ones with low risk disease, if remission is achieved, continue to
high dose chemotherapy followed by autologous PBSC rescue. Although the transplant issue is still not with a high level of evidence support, this is the current "general" recommendation. As for the issue of allogeneic SCT in PTCLs, it is still quite debated, controversial and hampered by the low number of cases and the wide variety of subtypes submitted to such treatment.

Of the newer agents, several are more widely explored, while others are confined to single center attempts or incidental observations. Common for the newer agent reports is that almost all of them express results with an emphasis on response rates, not remission rates, which most often is derived from shrinking in tumor size as the measurable effect, regardless of how short-lived that effect had been. As is the case with most of the new drugs, investigations have started dominantly in relapsed patients. The obtained results in such cases have led to the approval by relevant authorities for some of the drugs to be utilized in the setting of relapsed disease. Side effects, in some instances very detrimental, further hamper the successful prospects of such drugs.

Pralatrexate, a folate antagonist similar to methotrexate, is the first agent approved for relapsed PTCL patients, based on the results of the phase II PROPEL study. The observed ORR was 28%, with a median duration of 9.4 months and a median OS of 14.7 months.

Many reports are released on the use of Romidepsin, a novel bicyclical HDAC inhibitor. Based on results as second line therapy, it has approvals for PTCL since 2011: ORR = 26%, CR = 13%. In subsequent trials, the ORR has risen to 34%, with as many as 15% CR's, and around 10% having longer lasting (48+ months) uninterrupted responses. Romidepsin has also been tried in the setting of maintenance for good responders to initial treatment.

The other agent approved for the relapsed setting in the US is vorinostat.

PTCL cases that express the CD30 antigen have been treated with considerable success with an agent, initially tested on patients with HD: brentuximab vedotin. Used as third line therapy, and in a cohort of 72% ALK negative ALCCL, it produced an 86% ORR, but with a median duration of 12.6 months. The CR rate observed was 57%, but again the duration of it only 13.2 months. Another such agent is iratumumab.

No doubt that hematologists would be extremely happy to know that a new antibody, probably named T-Rituximab, has been synthesized. Unfortunately, no such news are emerging on the scientific horizon. Nevertheless, some of the PTCLs (AITL) express CD20 on the surface of some of the cells involved, which favors adding Rituximab to the treatment. However, desirable results are limited to individual cases.

Following this line of investigations, other antibodies and conjugates have been employed in the quest for better management of PTCLs: alemtuzumab, CCR4 antibody, siplizumab, zanolimumab, denileukin diftitox, bevacizumab, etc.

In view of the somewhat encouraging results with the newer drugs, further attempts to improve efficacy in PTCLs are represented by many tests of combinations of newer agents with “classical” chemotherapy regimens: Pral-CHOP, Romi-CHOP, Bren-CHOP, However, new “standards” are not emerging.

Some well known agents have been explored for treatment of PTCLs also: Lenalidomide, Bendamustine, Belinostat (HDAC inhibitor), MLN8237 (Aurora kinase inhibitor). As a specific type of a virus associated PTCL, treatment of HTLV-a associated T-cell lymphoma/leukemia has been attempted with AZT (sometimes in combination with IFN).

Emergence of new drugs in other fields of hematology and/or oncology, inspires clinicians and researchers to try them in new areas, with the hope that a certain signaling pathway can be crucial not only in a single disorder, but maybe in different settings as well. Such a “modern” approach is challenging the PTCLs with Dasatinib (TKI). Research evidence prompted attempts with JAK-STAT inhibitors (Ruxolitinib and others) as well. Others have been investigated also, some as a primary option, but mostly in the relapsed or refractory settings: Bexarotene (retinoid), Bortezomib (proteasome inhibitor), Sunitinib, Sorafenib, nucleoside analogs, signaling inhibitors, etc.

Clinical research has made attempts to categorize patients with PTCL in risk categories, establishing prognostic criteria, scores and indexes. It is important to acknowledge that most of these systems have been based on relatively small, often selected populations of PTCL patients, and treated with various regimens. They have certainly contributed to delineating patients with low risk, who
would benefit even from “standard” treatment, as well as those with high risk, who would need to receive treatment designed for patients with poor prognosis. Nevertheless, categorization is mostly made difficult by the enormous number of agents, so far explored in the treatment of comparably variable PTCL’s subtypes, which impedes general, universal conclusions.

In conclusion, a hematologist cannot be very satisfied with what we have learned and achieved so far regarding patients with PTCL. It is one of those areas that does not bring a smile to our faces, nor does it show the light at the end of the tunnel for our patients. I believe that we would all love to ultimately witness another revolution in the management of the serious diseases which comprise our everyday professional life, as we have seen with Hairy-cell leukemia, non-Hodgkin’s lymphomas, and especially with Chronic myelogenous leukemia. I am a believer in targeted therapy. A hematologist has no alternative options in his work, but to be an irrevocable optimist, posing the only possible question: not “if”, but WHEN the dream will become reality?

References


