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Registering rare haematological tumours: it is time for a breakthrough!

La registrazione dei tumori ematologici rari: è tempo di una svolta!

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Most haematological malignancies (HMs) are rare cancers, and their appropriate characterisation often requires an expert haematologist, a committed pathologist, and the integration of consolidated clinical, morphological, and phenotypic data with the rapidly progressing molecular knowledge. It is conceivable that the forthcoming new World Health Organization's classification will provide further insights in this setting, assigning even more importance to the molecular characterisation of these diseases. However, as the availability of molecular techniques and, more importantly, their standardisation, is not homogeneously applied throughout the country, finding an appropriate balance between accuracy of diagnosis and completeness of case recording will be a major issue for cancer registries (CRs). Indeed, for some HMs, as in the case of fusion genes PML/RAR in acute promyelocytic leukaemia (APL), BCR/ABL in chronic myeloid leukaemia (CML), and adult acute lymphoblastic leukaemia (ALL), FIP1L1-PDGFRA in hypereosinophilic syndromes, and mutations of JAK2/MPL/CALR in myeloproliferative neoplasms (MPNs), molecular biology is already mandatory for diagnosis according to the 2016 WHO criteria. In other situations, for instance mutations of NPM1 and FLT3 for acute myeloid leukaemia (AML), BRAF for hairy cell leukaemia (HCL), MYD88 for Waldenstrom's macroglobulinaemia (WM), and c-KIT for mast-cell disorders, these exams represent, when available, the strongest support for a correct diagnosis and/or a useful tool to stratify patients into different risk groups or to select the most appropriate treatment. Centralising biological samples for molecular analysis at referral laboratories (according to the model employed in other Europen countries) could be a possible solution. In Italy, a national network for CML (Labnet) is currently active and others are developing for MPNs and AML.

Thus, rare haematological cancers should, ideally, be diagnosed in onco-haematologic centres with recognised clinical skills and adequate diagnostic facilities. Diagnosis provided by centres with less expertise and not specifically involved in HMs (e.g., transfusion services and units of general medicine or geriatrics) should be considered with caution, and every effort to have appropriate confirmation should be pursued. As a consequence, reported incidence of some rare HMs might change in the future because of more stringent diagnostic criteria, and this should be taken into account when comparisons are made with previous data.
Another important issue will be the availability of novel agents, many of which, in the last years, have gained (or will soon acquire) a place in the real-world treatment of several HMs, for instance new proteasome inhibitors and IMIDs for multiple myeloma (MM); PI3K and Bruton-kinase inhibitors for mantle and follicular lymphoma; arsenic trioxide for APL; brentuximab-vedotin and anti-PD1 agents for Hodgkin's disease (HD); brentuximab-vedotin for anaplastic lymphoma; JAK inhibitors for PMF and other MPNs; hypomethylating agents for elderly AML; azacitidine and lenalidomide for myelodysplastic syndromes (MDS). In this setting, the most brilliant example is likely to be CML, where recently updated OS curves of patients enrolled in clinical trials show an >90% long-term survival. This is likely due to the availability of novel TK-inhibitors, which have substantially improved the percentage and quality of molecular response in these patients. We expect that such an improvement in survival may be observed in a short time not only in clinical studies, but also in real life. Prevalence of this disease (and that of other rare HMs potentially benefitting from novel therapies in terms of survival) will likely increase accordingly.
Finally, in order to avoid duplications, particular attention should by paid to the possible evolution from an initial HM into other, more aggressive ones, such as AML after MDS or MPN; primary myelofibrosis (PMF) after essential thrombocythemia (ET) or polycythemia vera (PV); aggressive lymphoma after indolent lymphoma; MM after MGUS/asymptomatic myeloma; plasma cell leukaemia after MM; WM after MGUS.
Looking to the near future, some additional considerations are here reported in relationship to specific rare HMs.

MPN. Data on PMF, ET, and PV should be separately reported. In this setting, bone marrow biopsy and driver mutation assessment are fundamental and require expertise in the evaluation. It should also be considered that mast cell disorders include a variety of neoplasms with different characteristics, ranging from indolent disorders to very aggressive forms; this would warrant that they should probably be better defined. More comprehensive data on chronic eosinophilic neoplasms should also be specifically collected.

MDS. A diagnosis of MDS should, ideally, always be performed by an expert haematologist on both marrow aspirate and peripheral blood smears. Though recommended by European guidelines, bone marrow biopsy is not always performed on a routine basis; however, it may be useful and necessary in selected cases. Perls's staining (to identify ring sideroblasts) and karyotype (which has a relevant prognostic value and selects patients eligible for azacitidine – high risk – or lenalidomide – del5q – therapy) should be considered mandatory in most cases and possibly registered, while flow cytometry is not useful for MDS in current clinical practice. It should also be outlined that overall survival of MDS may range from a few months to many years, based on available prognostic

models. Therefore, a more detailed analysis with respect to risk needs to be implemented. Furthermore, while awaiting new WHO criteria, "true" MDS (too simply defined here as «other myelodysplastic syndromes»: they represent the large majority!) should be clearly separated from "mixed" MDS/MPD, as these are disorders with overlapping characteristics based on different genomic abnormalities. Finally, 5q-syndrome is a well defined MDS associated with recognised clinical and morphological features, deletion of the long arm of chromosome 5 (del5q) as single cytogenetic abnormality, low-risk profile, and response to lenalidomide. CR operators should bear in mind, however, that del5q may occur in many other subtypes of MDS (including higher risk MDS), which must not be confused with the 5q- syndrome identified by WHO as a specific entity.

AML. As in MDS, a diagnosis of AML should be urgently performed by an expert haematologist on both marrow aspirate and peripheral blood smears and possibly integrated by flow cytometry. Cytogenetic and molecular data are also critical for risk assessment and guide treatment decision making. With the exception of APL, overall survival in AML is generally disappointing, with less than 20% of patients becoming long-survivors. However, when the analysis is performed by age, it should be noted that long-term survival in younger (15-60 year-old) patients, in whom intensive treatments, including allogeneic stem cell transplantation, can be delivered, is currently 35%-40%. In addition, selected groups of patients with favourable cytogenetic and molecular features may have an even better outcome.

OTHER LEUKAEMIAS. Adult ALL represents another rare HM requiring particular attention, while it would also be of some interest to collect data on blastic plasmacytoid dendritic cell leukaemia, a very uncommon entity currently included by WHO among AMLs.

LYMPHOMAS. Each diagnosis of lymphoma should always derive from an adequate surgical biopsy (preferably an entire lymph node) with appropriate histologic, immune-histochemical and, when required, cytogenetic and molecular evaluation. Core-needle biopsy may be useful in selected situations, while relying on simple fine-needle biopsy to make a diagnosis of lymphoma is not recommended. Lymphoma evaluation should include approaches for clear differentiation between B and T-cell neoplasms (Burkitt's lymphoma/leukaemia should also be analysed separately from T-lymphoblastic/leukaemia), as well as a further identification of aggressive vs. indolent forms. Within aggressive lymphomas, specific subtypes with clinical and biological peculiar characteristics should also be considered; for instance, variants of diffuse large B-cell lymphomas (DLBCL), such as primary mediastinal, leg-type, activated vs. germinal centre, and c-myc positive DLBCL. Among indolent lymphomas, lympho-plasmocytic (WM, if an IgM component is present) and splenic, nodal, and extra-nodal marginal zone lymphomas should be detailed.
Among T-cell lymphomas, anaplastic ALK+ lymphoma should be differentiated from ALK-subtypes. In addition, it should be considered that other T-cell lymphomas (in particular lymphoblastic, angio-immunoblastic, and peripheral T-cell-NOS), as well as NK neoplasms, also have distinctive features, treatments, and survival. Again, they should be analysed separately.

MM. Based on available criteria, symptomatic myelomas, which require treatment, should be well distinguished from asymptomatic/smouldering myelomas, which do not require therapy and have a different outcome; likewise, localised plasmacytomas (bone or extramedullary), as well as primary and secondary forms of plasma cell leukaemia, should be separately detailed. Primary AL amyloidosis should also be considered.
SIE has recently activated an easily accessible IT platform, which provides specialists with timely updated national guidelines for several HMs. In addition, SIE and AIRTUM are closely collaborating in order to define (and refine) the most useful criteria for registering all HMs within cancer registries in Italy, aiming to improve quality and completeness of data and provide a breakthrough in recording. Training of dedicated personnel, identification of new, non-conventional and more appropriate sources (e.g., pharmacies for specific drugs and haematology units for well-documented diagnoses) and integration of central and regional specific haematological expertise within the registering teams will represent the new backbone for the development of these activities.
Last, but not least, following the virtuous example of other registries (e.g., SEER in the US), more accurate registrations of rare HMs could also provide a unique scientific opportunity. Such a qualitative change requires attention to additional data, such as the role of specific clinical and biological prognostic factors, environmental and professional exposures, the role of viral or bacterial infections, and therapies delivered. By depicting as complete as possible a scenario of these tumours in Italy, we aim at carrying out solid population-based studies with numbers not otherwise attainable outside a cancer registry.