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Personalized Treatment for Hematologic Diseases in Europe: An EHA Position Paper

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Personalization of hematologic therapies is made possible by novel diagnostic methods and precisely targeted treatments. For Europe-wide routine implementation of personalized therapies for all patients with hematologic diseases some major technological, regulatory and access challenges have to be overcome. We provide a status quo analysis and solutions for the near future which reflect the common thoughts of healthcare professionals *and* patients actively engaged in developing this topic.

Introduction

Isn't it a good thing that we are thinking more and more on the level of the individual patient, as scientists and doctors in hematology had to do "in the early days" when they designed and developed allogenic bone marrow transplantation and HLA matching? Increasingly, the questions we ask are: "What is the problem in this individual patient?" "What is the defect in his/her DNA?" "What has happened with the proteins in the tumor cell of this patient?" *Personalized medicine* (PM) refers to treatments which take into account all factors that characterize the differences between patients, including: sex, age, comorbidities, expected toxicities, tumor subtype and targetable molecular characteristics. *Precision medicine (PrecM)* is targeted therapy with a clearly identifiable target and its respective inhibitor, targeting antibody or cellular therapy.

Personalization is now possible because of advances in diagnostics, particularly by improved molecular and genetic diagnosis.[1] In addition, an increasing therapeutic armamentarium, including targeted therapies, has paved the way to individualization. In hematology and oncology, companion diagnostics for a rapidly increasing portfolio of small molecule inhibitors, monoclonal antibodies and cellular therapies are available. A PM approach is still regarded as experimental in many settings but will be introduced more and more into clinical practice in the near future. A major setback remains the lack of appropriate clinical trials.

Individualization is not new in hemato-oncology. Differences in treatment response and toxicities have been noted between sexes and patients with different body mass indices. As an example, serum levels, pharmacokinetics and clinical response to monoclonal antibodies in lymphoma have been clearly linked to both factors and prospective clinical trials have shown the utility of higher antibody doses in men. Such findings have never really been implemented in clinical practice. Targeted "designer" drugs, such as the BCR-ABL inhibitor, Imatinib, have been given on the basis of genetic findings since the 1990s. More recently, cellular therapies such as CAR-T[2,3] and other T-cell modifications have been developed. This is a beautiful evolution in cancer research and treatment.

We are now entering a new era, in which not only single changes at the genetic or protein level are used to guide precision treatment. Sequencing of the whole genome or large parts of it open the possibility of off-label use of drugs which target specific pathways. This has implications for clinical trial planning (Fig. 1).[4]

As opposed to classical randomized trials, where one new treatment is compared to the current standard-of-care (SOC) or placebo, or to "basket trials", where one drug is tested in various diseases with the same genetic aberrations, we now have the possibility to find the right targeted treatment amongst a large number. This is achieved by extensive genetic or functional diagnostics. In this case, patients also serve as their own "control." The first successful PM clinical studies for late-stage hematologic malignancies have been conducted.[5–7] Despite many individual success stories, there are still a number of challenges which have to be tackled during the next few years in order to scientifically evaluate the place of PM:

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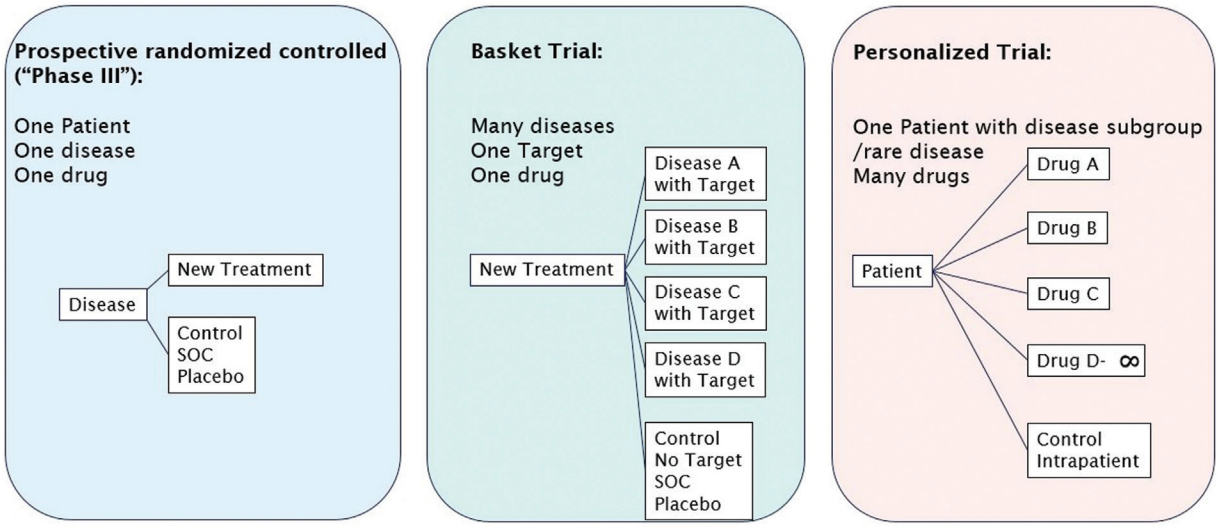

Figure 1. Types of clinical trials.

1. A clear and internationally accepted definition of the terms "personalization," "individualization" and "precision medicine." In this position paper, we use the definitions mentioned above.
2. Better access to innovations for all patients in Europe, since many of these treatments are currently confined to high-level academic institutions.
3. New regulatory requirements to define the way clinical trials are conducted and to ensure potential use of non-licensed drugs in patients in whom a targetable tumor lesion has been identified.
4. Rational decision-making processes in tumor boards supported by artificial intelligence.
5. Establishment and translation of novel diagnostic tests which predict the response to treatments and the development of rational mono-therapeutic and combinatorial strategies.

These items are on the agenda of patient organizations, EHA, the European Society for Medical Oncology (ESMO), the International Consortium for Personalized Medicine (ICPerMed), the European Commission and EMA. They must be a priority for all policymakers and regulators responsible for healthcare and pharmaceuticals, at the European and national level.

The current status of advanced diagnostics and access to treatments

The first advances in *PrecM* were made through the detection of antigens on the surface of tumor cells. With novel methods of immunohistochemistry or flow cytometry, these cells can be identified down to at least levels of $1/10^4$ cells. This information is used to deliver specific monoclonal antibodies to the right subgroups of patients and to avoid unnecessary treatment if the tumor is negative for this antigen. With the advent of molecular diagnostics at the DNA, RNA or epigenomic levels, mutations have been identified which can either be directly targeted or define signaling pathways that can be targeted, particularly by a small molecule inhibitor. Methods have been established to detect the sensitivity of a tumor to certain drugs or to predict response. This had been tried for many decades but has now reached a level of practical implementation.

While these diagnostic methods are available to various degrees and at reasonable prices in specialized centers, they are still not available to all patients in Europe. We propose two strategies to improve access:

1. Dissemination to small centers. This facilitates early local access, but is hampered by low sample numbers with higher unit costs and less specialized diagnostic quality/experience in analytic and bioinformatic evaluation.
2. Centralized diagnostics for samples from local/regional centers on central reference diagnostic platforms. This facilitates specialized/experienced diagnostics and minimizes unit costs, but poses logistic challenges in preparation and transport of material and data.

Our proposal: Centralize what is needed (from both treatment and research perspectives), decentralize what can be done reliably and cost-effectively locally.

The current status of personalized therapy

A large number of targeted treatments (antibodies and small molecules) have been licensed for many indications and have been linked to companion diagnostics, only some of which can be carried out in all treating centers (e.g., through immunophenotyping or immunohistochemical diagnostics). For advanced diagnostics, there is a still a lack of in-depth knowledge and access to these methods, which hampers access to targeted drugs for patients. In addition, accumulation of big data poses difficulties for doctors in making the right treatment decisions. Artificial intelligence – while still far from perfect – can help physicians distil the right information and improve the quality of decision making. The creation of tumor boards consisting of geneticists, biologists, pathologists, molecular pathologists and bioinformaticians is not possible in smaller institutions, and large numbers of patients cannot be discussed.

The current status in clinical trials

Proof of safety and potential therapeutic benefit of drugs comes from phase 1 to 3 trials. However, the potential of advanced diagnostics and other possibilities of better response prediction

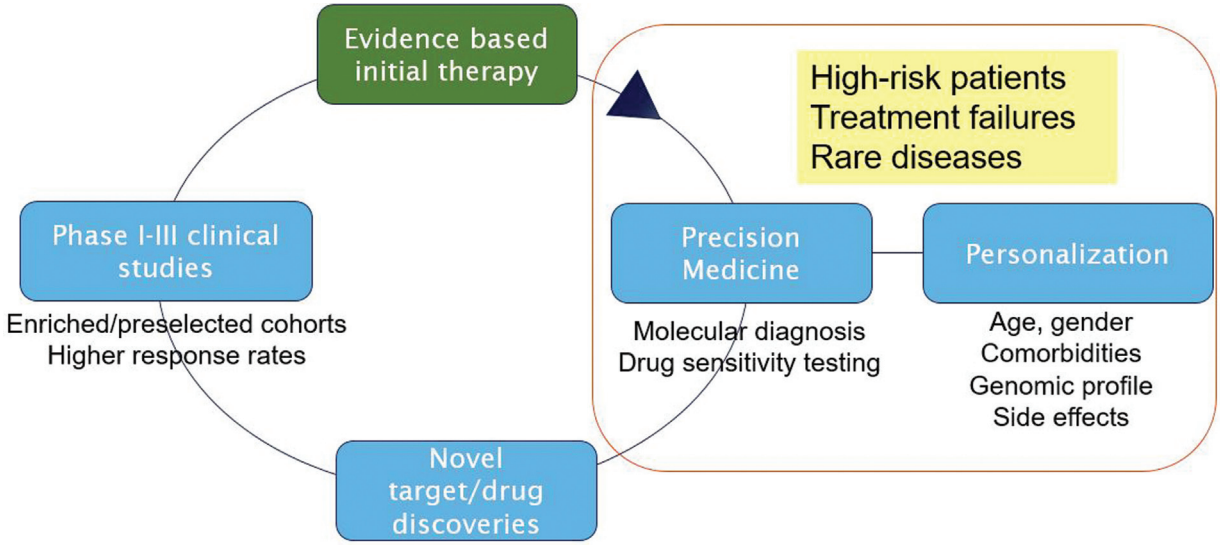

Figure 2. The state of precision and personalized medicine.

are not fully implemented in current clinical trial models (Fig. 1). At relapse, response and survival rates drop dramatically for most malignant diseases. High-risk patients should be identified earlier and with greater precision and should be given the possibility to participate in experimental treatments, including precision or personalized medicine trials (Fig. 2). Waiting for relapse is often too late to start identifying personalized targets, so diagnostic prediction of those most likely to relapse, in order to prepare innovative second-line treatment if and when it becomes necessary, is attractive (on condition that the targets are stable between diagnosis and relapse). This will create a learning loop resulting in higher response rates.

To achieve the best outcome for individual patients, we collect information on treatment response and toxicities through registries or the comparison of small cohorts within networks, in order to define subgroups of patients with certain molecular lesions responding to a specific treatment. High-quality data collection and data analysis, resulting in rapid and precise information, are at the basis of better treatment decisions. The collection of big data at a pan-European level is being pioneered by the HARMONY IMI2 project, in which EHA is a partner.[8]

There have been a few PM trials in oncology yielding positive or negative results, illustrating the problems of implementation and correct clinical trial planning. Data from oncology trials suggest that 40% to 50% of patients with relapsed disease have an actionable target; 27% to 43% receive targeted treatment with an 11% to 36% overall response rate.[9–11] The number of patients with hematologic malignancies with actionable targets seems to be higher (up to 82%),[12] with response rates of up to 88% in patients with refractory disease who have already received several lines of treatments.[6] It is clearly possible to reach better results for the individual patient than with the traditional, statistical approach.

New models and solutions

To evaluate the impact of PM on the outcome of patients, we have to address legal, ethical and regulatory issues.

- Data sets provided by institutions and healthcare providers, such as the HARMONY[8] or EHDEN[13] programs, will help to collect information on rare entities or exceptional treatment attempts which have not been systematically published. AI will help us to mine the data.
- A new group of trials will have to be initiated within an innovative regulatory framework. PM or PrecM trials represent a paradigm where the patient is at the center and could be treated with a choice of over 200 or 300 drugs (Fig. 1). Every patient could become a trialist, even if it is currently hard to foresee the treatment modalities and combinations and appropriate trial design. It also poses a problem for tumor boards, because they will have potentially applied complex algorithms based on multiple clinical, imaging and laboratory parameters in order to decide which drug a patient will get in a given trial.
- Availability of targeted drugs for an individual patient might be limited by participation of pharmaceutical companies or financial restraints in institutions or countries. This creates access problems for patients and health care professionals. PM networks between European health authorities, academia and industry need to overcome this. Regulations need to be changed for unresponsive patients with an unmet medical need. European medical societies, individually or within concerted actions such as the Biomedical Alliance in Europe,[14] are essential actors in this process.

To conclude

PM is the logical evolution for patients with hematologic diseases. We have the techniques to start treating patients based on their individual situation: “This patient, with his or her defect, at this moment, will have this (combination of) drug(s) based on drug response prediction.” PM has not yet been perfected, but patients need informed doctors prepared to act now. Everything starts with a patient with an unmet medical need – a relapse and a failing protocol. Adaptation of protocols, regulations and drug reimbursement is a prerequisite. The attendant costs of saying YES are often clear and calculable. The hidden costs of saying NO are unacceptably high.

Patients and hematologists call for the creation of regulations, networks and structures that provide a solid basis for performing specific controlled PM and PrecM trials, which will vastly increase access to promising new treatments.

Key messages for policymakers and stakeholders

Europe-wide routine implementation of personalized therapies – made possible by novel diagnostic methods and precisely targeted treatments – for all patients with hematologic diseases requires dedicated data and regulatory frameworks as well as rational, concerted decision-making on availability and affordability.

Specifically, the following is needed:

- To improve access to advanced diagnostics, centralize what is needed and decentralize what can be done (reliably and cost-effectively) locally.
- To advance personalized therapy:
  a) High-quality data collection and data analysis, resulting in rapid and precise information and better treatment decisions;
  b) A new group of PM or PrecM trials, centered around patients with an unmet medical need, within an innovative regulatory framework;
  c) PM networks between European health authorities, academia, industry and – crucially – medical societies to optimize regulatory and access strategies. Patient advocates need to be integral and full partners in decision making.

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