The Journal of Liquid Biopsy 1 (2023) 100008

Contents lists available at ScienceDirect

The Journal of Liquid Biopsy

journal homepage: www.sciencedirect.com/journal/the-journal-of-liquid-biopsy

Liquid biopsy, big data and artificial intelligence as a new global clinical trial model in targeted therapy

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ARTICLE INFO

Keywords:
Liquid biopsy
Fase III
Targeted therapy
Big data
Artificial intelligence

ABSTRACT

To this day, the phase III trial continues to be, as it was more than 60 years ago, the standard for the incorporation of new treatments in oncology. We currently have new tools such as NGS, Liquid Biopsy (LB), Big Data (BD) and Artificial Intelligence (AI) that will allow us to move towards faster and more universal research. This article analyzes the important weaknesses of phase III trials, the importance and current status of targeted therapy, and the contributions to LB decision-making and the knowledge of what happens in real life (RWD) that we facilitates BD and AI. Finally, what could be a clinical trial model that would take advantage of all these tools is proposed.

For more than 60 years, a Phase III clinical trial has been the requirement for the approval of most new treatments [1,2]. In our opinion, this approach has obvious weaknesses that may be questionable at the present time. First, patients in the control arm of the trial (usually 50%) are harmed by not receiving the presumed most beneficial treatment. In addition, it takes approximately 5 years to obtain mature results and subsequent approval of the treatment by regulatory agencies. During these 5 years, thousands of patients do not receive the best treatment for their disease while awaiting approval, while new drugs and strategies are being developed that surpass the results of the study [3–5] .

On the other hand, the development of new cytostatic drugs has been abandoned. Currently, the main objective in most translational research studies is the discovery of target molecular alterations and their applicability through targeted therapy treatment. Despite the progress made, this personalized treatment only reaches approximately 6.5% of patients (NCCN Guidelines 2023). These reflections lead us to ask ourselves some questions: Do all these new targeted drugs really require comparative studies? Could this be an obstacle to rapid progress towards their approval in new indications? Do only 6.5% of our patients present target alterations in their tumor? In a short personal experience using liquid biopsy, two out of six patients with colon cancer presented potential targets that are unknown for this specific disease but with approved target therapies in other tumors. (non-published data).

New era, new tools

The detection of mutations in circulating tumor DNA (ctDNA) has been postulated in recent years as an alternative to classical tumor biopsy. The presence of DNA fragments in the blood was first described in 1948 [6]. But it was not until 1994 that the presence of specific mutations in ctDNA, particularly N-RAS, was described in patients with pancreatic cancer and acute leukemia [7,8]. Since then, ctDNA has emerged as a tool with great potential in oncology. In the last decade, the implementation of highly sensitive sequencing technologies has allowed the development of ctDNA-based liquid biopsy as a promising technique in the diagnosis and treatment of cancer.

The concept of Big Data (BD) [9] refers to collections or combinations of data whose size (volume), complexity (variability), and growth rate (speed) make it difficult to capture, manage, process, or analyze using conventional technologies and tools (relational databases and conventional statistical or visualization packages) in the time required for them to be useful. BD also allows us to achieve knowledge based on Real-World Data (RWD), and through its analysis, access to potential medical results in the usual clinical practice (Real-World Evidence), not reflected in clinical trials whose population is always highly selected.

Artificial intelligence (AI) algorithms have revolutionized the classification of radiological, anatomopathological, and dermatological images thanks to the application of deep learning (DL), which has demonstrated superior performance compared to that of clinical experts [10–12]. Similarly, AI with Machine Learning subfields based on statistical methods and DL can provide us with a fast and accurate evaluation of the results obtained in BD.

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https://doi.org/10.1016/j.jlb.2023.100008
Received 6 September 2023; Accepted 15 September 2023

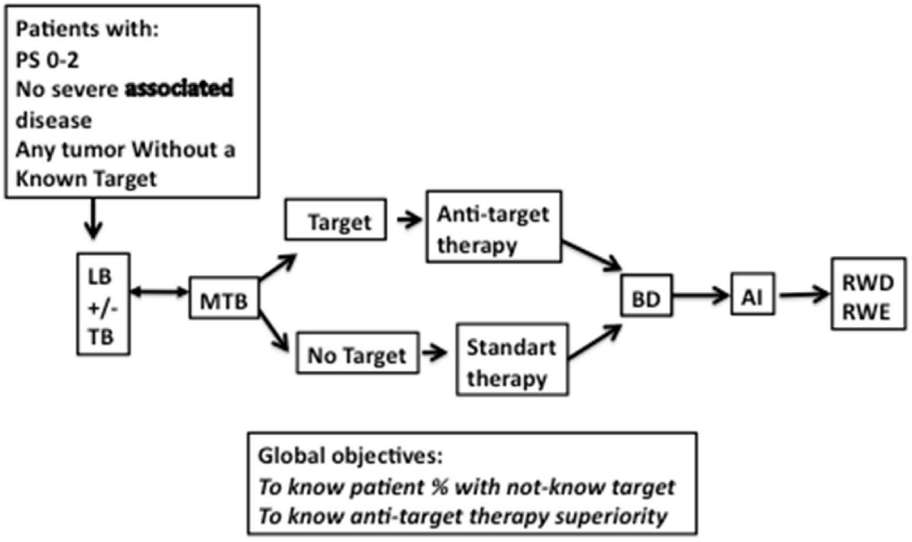

Fig. 1. LB: liquid biopsy; TB: tumor biopsy: MTB: molecular tumor board; BD: big data; AI: artificial intelligence; RWD: real world data: RWE: real world evidence.

Taking into account that much of the clinical research in oncology aims to evaluate the efficacy of targeted drugs and considering the tools offered by the Internet era, we propose a model of a first-line clinical trial for advanced cancer based on LB, RWD, and AI. To achieve the results of the clinical trial and those obtained by RWD in parallel, we propose the following inclusion/exclusion criteria: 1) Functional status of the patient, PS 0-2; 2) Severe associated diseases that would not allow treatment in daily clinical practice; and 3) Any tumor histological type without a known molecular target. In all patients, an LB analysis would be performed as part of the screening, which would be completed with a tumor biopsy under the proposal of a Molecular Tumor Board (MTB) in case of doubt. The results of the plasma and histological molecular study would be evaluated individually within the MTB. Patients with an actionable molecular alteration would be treated with the corresponding targeted drug regardless of tumor type. Patients without a target would be treated with standard therapy. Treatment would be maintained until disease progression or toxicity. Data would be collected in a large database (DB) and analyzed by AI in the shortest possible time (in the time needed to be useful).

This model provides both clinical trial results and RWD. It provides insight into the percentage of patients without a molecular alteration requiring tailored therapy and whether targeted therapy is globally superior to standard therapy. It can be designed as an open-label study in which new drugs with proven activity from phases I and II clinical trials are gradually added. Its main strength should be the speed in obtaining results provided by the BD, as well as the dynamism in terms of the incorporation of new targeted drugs.

We understand that there are significant weaknesses and difficulties in developing a trial of these characteristics, such as the requirement for a large number of participating sites to obtain results through BD in a short space of time, adequate computer and technological resources, as well as acceptance by the oncology community. In any case, we believe that this proposal should be a starting point, a provocation, to consider the importance of optimizing the design of current clinical trials in order to be more efficient and increase the availability of new drugs to the maximum number of potential patients.

Author contribution

Conception and Design: Albert Abad.
Manuscript Writing: All Authors.
Final Approbal: All Authors.

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Albert Abad.
Consulting Flomics Biotech S.L.
Joana Vidal.
Personal fees from Merck, Amgen, Sanofi, Bristol Myers Squibb and Pierre Fabre outside the submitted work.
Laura Layos.
Santiago Viteri.
Personal fees from Merk, MSD, Roche, Ose Inmunotherapeutics, BMS, Takeda, Astra Zeneca, Ipsen, Abbvie.
Personal fees from AstraZeneca, Merck, Roche and Pierre Fabre.
Cesar Morcillo, and Izar Achaerandio.
No disclosures.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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