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REVIEW ARTICLE

Artificial intelligence and chimeric antigen receptor T-cell therapy

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Abstract

Therapy with the use of chimeric antigen receptor T-cell (CAR T-cells) is one of the most modern medical technologies in hemato-oncology, using, thanks to the advances in molecular biology, natural anti-cancer immune mechanisms. Nowadays, it is an extremely effective complement to conventional treatment and hematopoietic cell transplantation. Ongoing clinical trials show the enormous potential of this treatment beyond hemato-oncology. We discuss in this paper the potential use of Artificial intelligence (AI) in this setting. AI has been at the cutting edge of science in recent years. It has spread from computer science to areas like medicine, economics, finance and business. The use of and research into AI in medicine have become prominent due to its versatility and capabilities.

Key words: artificial intelligence, machine learning, CAR T-cell therapy

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Artificial intelligence — introduction

In recent decades, the topic of artificial intelligence (AI) has been on the cutting edge of science. It has spread from computer science to areas including medicine, economics, finance and business. With ever-improving technology year-on-year, its uses and applications have significantly expanded. However, to evaluate the use of this technology in CAR T-cell therapy, it is crucial to present an overview of the technology. Currently, there is no scientific consensus on a singular definition of AI, due to its broadness and complexity.

For the purposes of an overview, the 'Oxford Dictionary of Phrase and Fable' definition is sufficient: "the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages". AI can be categorized into general AI and narrow AI, with the former being able to mimic human intelligence and its ability to adapt and solve an arbitrary problem and the latter being specialized in performing a specific task (IBM Cloud Education, 2020, https://www.ibm.com/cloud/learn/what-is-artificial-intelligence). Currently, general AI has not been achieved, while narrow AI is being actively utilized. AI can be, and is, used without employing machine learning algorithms, and this subtype is categorized as Symbolic Artificial Intelligence or Good Old Fashioned Artificial Intelligence (GOFAI); however, machine learning algorithms have become more prevalent in medical applications. Machine learning is a technique in artificial intelligence characterized by the use of algorithms and statistics that allow the self-improvement of a program. A subset of machine learning is neural networks, which are structures based on interconnected **neurons** or **nodes** in a layered structure comprising an input layer, hidden layers, and an output layer. These nodes pass information from one to another through weighted connections based on activation, or lack of it, in the previous layer. By manipulating

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the activation thresholds of nodes and weights associated with each connection, the network can be optimized to achieve greater accuracy. A further subset of neural networks is deep learning algorithms, defined as neural networks with more than three layers.

Neural networks allow for the processing of unstructured data, making them more autonomous and allowing the use of data such as images or text (IBM Cloud Education; 2020, https://www.ibm.com/cloud/learn/neural-networks; Kavlakoglu E., AI vs. Machine Learning vs. Deep Learning vs. Neural Networks: What's the Difference? 2020 https://www.ibm.com/cloud/blog/ai-vs-machine-learning-vs-deep-learning-vs-neural-networks). These machine learning algorithms can be further divided into four types: supervised, unsupervised, semi-supervised, and reinforcement learning. The first three are defined according to the training data used, where supervised learning utilizes labeled datasets, unsupervised learning utilizes unlabeled datasets, and semi-supervised learning uses a combination of the two. The use of labeled training data allows the machine learning algorithm to check its output against the correct answer, although it is limited by the cost and time required to label the dataset by experts. Nevertheless, this is the most commonly used type in medical imaging [1].

In contrast, unsupervised machine learning trains on unlabeled data and utilizes methods such as clustering to find parallels between elements in the dataset and group them (Delua J., Supervised vs. Unsupervised Learning: What's the Difference? 2021, https://www.ibm.com/cloud/blog/supervised-vs-unsupervised-learning). Semi-supervised learning is a method that uses both types of data, possibly improving the algorithm's accuracy on a smaller set of labeled data, overcoming the limitations of supervised learning. This method is of particular interest in medical imaging where labeled datasets are expensive to produce, although employing unlabeled datasets may result in decreasing the accuracy of the algorithm [2]. Reinforcement learning is a method based on trial and error, where desired outcomes are rewarded or reinforced. It is characterized by states embedded within an environment, in which certain actions are allowed, and based on the interaction with the environment-specific actions on specific states are rewarded allowing improvement with repeated trials. Due to the sequential nature of the algorithm, it is used in dynamic treatment strategies, where the state of the patient has to be periodically evaluated and adjusted [3, 4].

Artificial intelligence in medicine

The use and research of AI in medicine have become prominent due to its versatility and capabilities.. One of the areas with the most promising use of AI is radiology, due to the image processing capabilities of neural networks. Rajpurkar et al. [5] have developed a neural network, CheXNet, that is more accurate at diagnosing 14 thoracic diseases than expert radiologists, although in the study neither CheXNet nor the radiologists had access to patient history.

Machine learning algorithms are also being developed and tested in genome-wide association studies (GWAS), where they show promise in finding causal genes in cardiovascular disease-associated loci [6]. Moreover, AI has also shown possibilities in real-time treatment applications in the treatment of sepsis with the development of a Targeted Real-time Early Warning Score (TREWS) algorithm, which identifies patients with sepsis significantly quicker than competing warning systems, allowing earlier treatment and potentially improving patient outcomes [7].

Artificial intelligence in CAR T-cell therapy

Therapy with chimeric antigen receptor T-cell (CAR T-cells) is a modern, technologically advanced method of cancer treatment based on adoptive cellular immunotherapy. The treatment process uses the patient's own autologous T-cells, which are genetically manipulated *ex vivo* to express the tumor antigen-specific CAR receptor. T lymphocytes reprogrammed in this way, after intravenous administration to the patient, expand, recognize cancer cells, and destroy them. The antigens used so far as targets for modified T lymphocytes are CD19 on B lymphocytes and BCMA (B-cell maturation antigen) on plasmocytes, which allowed the registration of CAR T-cells products for the treatment of B-cell lymphomas, B-cell acute lymphoblastic leukemia and multiple myeloma [8–13]. Nowadays, this is an extremely effective complement to conventional treatment and hematopoietic target transplantation. Ongoing clinical trials show the enormous potential of this treatment, going beyond hemato-oncology.

Chimeric antigen receptor T-cells can produce durable remission in hematological malignancies not responding to standard therapy. Recently published and ongoing studies indicate high efficacy of the treatment in early disease phases, depending on the diagnosis. The treatment is associated however with a unique profile of toxicities that may limit its use [14]. On the other hand, CAR T-cells therapy is a very expensive treatment, and additionally requires the time and involvement of the latest technology to produce it [15]. Therefore, it seems that both the qualification for CAR T-cells therapy, as well as monitoring and possible interventions after the treatment, should be very precise.

From a clinical point of view, Artificial Intelligence could be used to combine biomarkers associated with CAR T-cells' response to built robust prognostic/predictive models. One challenge is that building robust models using AI requires the creation of large datasets, hence the need to aggregate data from multiple institutions to avoid overfitting.

Deep learning could contribute to determining the radiomics signature correlated with survival.

Several simple factors have been proven to be relevant to predict response to CAR T-cells therapy: Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH), C-reactive protein (CRP), and platelet (PLT) number. With AI, analysis of more sophisticated parameters is possible: tumor mutational burden; alteration in antigen presenting pathways; downregulation or tumor antigen loss; tumor microenvironment; and exhausted (senescent) phenotype. This data could be helpful in appropriate qualification to therapy, response prediction, relapse risk and timing (early vs late relapse) [16].

Deep learning could contribute to determining the radiomics signature correlated with survival.

Due to the availability of routinely performed imaging studies, and correlations of images with underlying biological processes, radiomics may serve as a new predictive tool in immune-oncology in the near future. Apart from the non-invasive identification of potential responders to therapy, addressing resistance mechanisms as well as the visualization of drug distribution and of the tumor microenvironment are major goals of radiomics in immune-oncology. Radiomics is based on common imaging modalities such as computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). It aims to extract a large number of quantitative features from medical images using data-characterization algorithms. These features, termed 'radiomic features', have the potential to uncover tumoral patterns and characteristics that fail to be appreciated by the naked eye. This may be useful for predicting prognoses and therapeutic responses for various cancer types, thus providing valuable information for personalized therapy.

Perspectives of AI in CAR T-cell therapy

AI offers potentially endless possibilities in CAR T-cells therapy:

- creating virtual models to analyze safety;
- creating virtual models to analyze efficacy;
- developing a lymphodepleting treatment that ensures safety and efficacy by influencing the expansion of CAR T-cells;
- novel cancer-associated antigens;
- the possibility of designing new molecules.
- The medical community should however always bear in mind the potential hazards of AI.

Authors' contributions

LG, MG — equal.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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