Artificial intelligence and related technologies enabled nanomedicine for advanced cancer treatment

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“AI and related technologies may be used to select the right nanomedicine combinations as well as to maintain optimum drug level in the blood or target site to improve treatment output. It is further believed that AI-enabled nanomedicine would bring down the translational bench to bedside gap.”

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Cancer nanomedicine

Nanomedicine, a combination of nanotechnology and medicine to diagnose, monitor and treat diseases, has significantly improved the treatment outcome of highly complicated and deadly diseases by maintaining therapeutic dose at the target site [1–6]. The regulatory approval of injectable liposomal preparations such as Doxil[®] (AIDS-related Kaposi's sarcoma and cancer of the ovaries), Myocet[™] (metastatic breast cancer), DaunoXome[®] (advanced HIV-associated Kaposi's sarcoma) and nanoparticle formulations like Abraxane[®] (metastatic breast cancer, advanced non-small-cell lung cancer, metastatic pancreatic cancer) by the US FDA shows the transformation of nanomedicine-based products from the laboratory to the bedside. Recently, injectable liposomal irinotecan (Onivyde[™]) for treating metastatic pancreatic cancer and injectable liposomal cytarabine and daunorubicin (Vyxeos[®]) for acute myeloid leukemia has also been approved by the FDA and others are in various phases of clinical trials. Nanoparticles and liposomes particularly coated with navigating ligands can enhance accumulation highly at the tumor site. For example, doxorubicin-loaded liposomes further overcoated with an analog of blood clotting factor XIII significantly (40-fold) increased drug accumulation at the tumor site [7]. Prescribing more than one drug is a common approach used to treat diseases like AIDS, cancer, diabetes, inflammatory disorders and asthma. Drug combination provides drug synergism and improves efficacy and safety when compared with monotherapy. Research has been focused recently on multifunctional nanoparticles to simultaneously deliver both diagnostic and therapeutic substances. These multifunctional nanomedicines are expected to overcome the challenges associated with conventional cancer therapy. For example, theranostic liposomes containing docetaxel and quantum dots were prepared and decorated with RGD-TPGS for brain imaging as well as cancer therapy. The results showed that the therapeutic effectiveness of theranostic RGD-TPGS-decorated liposomes was much better than Docel[™] and also significantly reduced reactive oxygen species (ROS) production without causing edema or brain damage [8].

Artificial intelligence in medicine

Artificial intelligence (AI) discusses the simulation of human intellectual processes by machines, particularly computers which includes speech recognition, learning, reasoning, problem solving, learning from past experience and self-correction without being specifically programmed for a particular action. AI has wide applications in medicine and is useful in diagnosis, particularly to detect small variations from the baseline, to identify pandemic disease outbreaks at an early stage and imaging diagnostics. AI in medicine, for example, IBM Watson for use in

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oncology, helps oncologists to provide the most suitable and personalized therapy to their cancer patients. IBM Watson collects data from the expertise of the leading oncologist, medical journals, textbooks and clinical data as well as analyzing patients' medical records and provides treatment options based on this information. The oncologist can use the data along with their expertise to find out the best treatment options [9]. Microsoft's Hanover project and Google's DeepMind are to name a few other platforms which are also working on AI in medicine.

AI & related technologies enabled nanomedicine for cancer

Optimizing drug combinations can facilitate drug synergism to enhance clinical efficacy of cancer treatment. But optimization still remains a difficult task because it requires selection of the right combination of drugs, dose and dosing frequency to enhance the effectiveness while reducing unwanted toxicities. Further, drug combinations may produce unexpected toxicities due to biological systems complexities. Even though particularly multifunctional nanomedicines have improved the therapeutic efficacy, they also face the same optimization difficulties. Hence, a combination of AI and nanomedicine can overcome the challenges and improve the efficacy of cancer therapy [10]. In a recent study, Wang *et al.* developed feedback system control, a widely used platform for both unmodified and nanotechnology-modified therapeutic optimizations. The authors used AI to standardize drug dose combinations that would produce maximum cytotoxicity. The combinations used were nanodiamond-doxorubicin, nanodiamond-mitoxantrone, nanodiamond-bleomycin and unmodified paclitaxel and the combinations were studied on many breast cancer cell lines. The results showed that the nanomedicine drug combinations, optimized using AI, gave a better performance when compared with randomly selected nanomedicine combinations, AI-optimized unmodified drug combinations and nanomedicine-modified and -unmodified monotherapies [11]. In another study, Weiss *et al.* used streamlined feedback system control to optimize multiple drug combinations to inhibit the viability of renal adenocarcinoma cell line 786-O. The renal cell carcinoma, usually chemotherapy and radiotherapy resistant, treatment mainly depends on the use of targeted drugs. The authors used ten drugs with broad spectrum of activities and found that the optimal combination containing axitinib, erlotinib, dasatinib and AZD4547 showed better synergistic activity while minimizing the effect on nonmalignant cell types [12]. Rashid *et al.* developed a quadratic phenotype optimization platform (QPOP) to find out an optimal combination from a pool of 114 FDA approved drugs, including dactinomycin, decitabine (Dec), mechlorethamine and mitomycin C (MitoC) to treat bortezomib-resistant multiple myeloma. QPOP can be used to overcome the problems related with the designing of drug combination as well as optimization, selection of ideal combinations of drug and ideal doses. QPOP uses experimental data to a deterministic model which is independent of molecular mechanistic assumptions. The AI-guided optimization revealed that the combination of Dec and MitoC was the superior two-drug combination while Dec, MitoC and mechlorethamine was the superior three-drug combination to treat bortezomib-resistant multiple myeloma [13]. Recently, Pantuck *et al.* developed CURATE.AI, an AI platform based on a phenotypic response surface correlation, which was validated clinically and was used to standardize therapy of tuberculosis patients with liver transplant-related immunosuppression. CURATE.AI was used in one study to guide a patient receiving combination therapy consisting of ZEN-3694 (a bromodomain and extraterminal inhibitor) and enzalutamide (an androgen receptor inhibitor) to treat metastatic castration resistant prostate cancer. The CURATE.AI was used to modify the ZEN-3694 and enzalutamide doses with the patient's response to the treatment. The CURATE.AI-guided treatment reduced prostate-specific antigen and halted disease progression [14].

Conclusion

Despite enormous advancements in cancer research, it is still the second leading cause of death after cardiovascular diseases. The introduction of AI and related technologies in nanomedicine gives a lot of hope for early diagnosis of cancer as well as treating cancer in the advanced stages in an effective manner. AI and the related technologies can play a vital role, starting from drug development all the way through to the clinic. The application of AI may overcome low responses and failures of clinical trials due to inappropriate (sub-optimal) selection of drug combinations, hence helping to increase the number of drug approvals. Nanomedicine has been used to improve drug targeting at specific sites in order to maintain drug synergism. But the drug concentration required at the target site may vary from one patient to another. Further to this, the drug synergism produced by a particular dose to one patient may produce antagonistic effects to another patient [15]. The drug synergism, during treatment, may also be transformed into antagonism to the same patient [10]. AI and related technologies may be used to select the right nanomedicine combinations as well as to maintain optimum drug level in the blood or target site to improve treatment output. It is further believed that AI-enabled nanomedicine would bring down the translational bench

to bedside gap. However, AI-enabled nanomedicine would gain wider acceptance and come into general practice if it proves its supremacy in terms of efficacy, safety and improving treatment outcomes over the conventional cancer nanomedicine therapies. Finally, it is important to address the regulatory concerns.

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