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Review Article

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Chemotherapy Overview: Treating Cancer and Overcoming Resistance

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Abstract

Chemotherapy has been the most used approach in cancer treatment. It can be used alone or as adjuvant therapy in order to prevent tumor reoccurrence in association with radiotherapy or surgery. Nevertheless, certain cancers can development of Multi Drug Resistance (MDR) the remains a major challenge in the treatment of cancer. The present review aims to elucidate most commom cancer treatments, as well as explain the leading drug resistance mechanisms and key strategies to overcome it. Although there are many mechanisms that seems to be a potential in overcoming MDR, such ABC transporters, synthetic and natural chemosensitizers and epigenetic therapy, the use of these approaches and the possible interactions is not yet fully understood, therefore further studies aiming at understanding this dynamic are necessary.

Keywords: Chemotherapy, Multidrug Resistance, Chemosensitizers

Introduction

Cancer figure among the leading worldwide health problems, with approximately 20.3 million new cases and 13.2 million deaths expected for 2030 [1]. The most common sites of cancer occurrence can differ for men and women. Among men, lung, prostate, colorectum, stomach, and liver cancer were the most diagnosed in 2012, while among women were breast, colorectum, lung, cervix, and stomach cancer (WHO**,** 2017). Given its broad occurrence and harmful consequences treating cancer has been the aspiration of researches worldwide [2]. The central goal of cancer treatment is to cure or significantly extend the life of patients, guaranteeing the best potential life quality to survivors [3]. There are numerous kinds of cancer treatments, depending on the type of cancer and on its developmental stage [4]. The traditional approach to cancer patients' treatment is the combination of chemotherapy and radiotherapy, besides surgical resection [5]. Additional therapies can be used, including immunotherapy, targeted therapy and hormone therapy [6].

Chemotherapy has been the most used approach in cancer treatment aiming at stopping or reducing the growth of cancer cells that usually display higher growth and division rates [7], Chemotherapy can shrink tumors before surgery or radiation therapy (neoadjuvant chemotherapy), destroy remaining cancer cells after treatment with surgery or radiation therapy (adjuvant chemotherapy), enhance other treatments and exterminate cancer cells that are returning or spreading to other tissues [8]. However, chemotherapy does not solely kill or slow the growth of cancer cells, it also act on healthy cells, promoting undesirable side effects on hair follicles, bone marrow and gastrointestinal tract cells, among others [9].

Cancer chemotherapy is the most used treatment against cancer, aiming to decrease the number of cancer cells with minimum toxic side effects [10]. Nevertheless, chemotherapy alone can be effective only for few cancer types, such as haematological neoplasm (lymphomas and leukemia) [11] and gastric cancer [12]. Similarly solely surgery and sometimes radiation can only be effective for small and located tumors, displaying the need to combine different treatments [13]. Additionally, chemotherapy can be used as adjuvant therapy in order to prevent tumor reoccurrence and, in association with radiotherapy, can be used as neoadjuvant therapy so as to shrink tumor size before surgical proceeding [14].

Nevertheless, certain cancers can eventually develop resistance to the chemotherapy treatment [15]. There are several mechanisms underlying this process such as cell signaling reprogramming, DNA damage and repair and epigenetic regulation [16-18]. In this context, better therapeutic approaches have been proposed in order to improve drug efficiency and inhibit resistance mechanisms [19]. Therefore, the present review aims to elucidate most commom cancer treatments, as well as explain the leading drug resistance mechanisms and key strategies to overcome it.

Chemotherapy

Initially, the development of cancer chemotherapy drugs was based on cytotoxicity assays using cells lines derived from neoplasias with a phenotype of fast growth [20]. The first drugs

developed can act, predominantly, through inducing DNA damage in the tumor cells that show increased replication rate and inadequate repairing mechanisms [5]. Although efficient these drugs have numerous side effects reported, such as increase incidence of secondary tumors and high toxicity levels for healthy cells [21]. In order to reduce the side effects new drugs appeared, with increased specificity and targeting specific intermediaries of oncogenic signalization pathway [20].

Chemotherapy drugs can be categorized as: alkylating agents (i.e., cyclophosphamide, ifosfamide, melphalan, busulfan), antimetabolites (i.e., 5-fluorouracil, capecitabine, methotrexate, gemcitabine), antitumor antibiotics (i.e., daunorubicin, doxorubicin, epirubicin), topoisomerase inhibitors (i.e., topotecan, irinotecan, etoposide, teniposide), and mitotic inhibitors (i.e., paclitaxel, docetaxel, vinblastine, vincristine) [22]. Chemotherapy drugs can be given as injection into the bloodstream (usually through a vein), drip (intravenous infusion) into the bloodstream and as tablets or capsules [23]. Although chemotherapy drugs are normally administered intravenously, 25% of them can also be administered orally, offering patients convenience and superior life quality [24]. Among the benefits of oral chemotherapy it is worth to mention: fewer interferences with work and social life activities, avoidance of hurting injections and extended infusion times [25]. Moreover some types of oral chemotherapy (i.e., topoisomerase I inhibitors and fluoropyrimidines) can offer prolonged drug exposure when compared to parenteral therapy, being a more effective delivery choice [26]. Nevertheless, it is important to consider oral chemotherapy drugs and food interactions that can contribute to increase treatment-related toxicities [27]. Although chemotherapy has been advance in recent years, its efficacy is limited by multidrug resistance that remains a major hurdle to the successful treatment of various types of cancers [28].

Multidrug Resistance

Despite all efforts to improve chemotherapy drugs' delivery and concentration there is an emergent concern regarding multidrug resistance [29]. Multidrug resistance (MDR) to chemotherapy, is the process whereby cancer cells develop resistance to the cytotoxic effects of numerous structurally and mechanistically unrelated chemotherapeutic agents [30], leading to the failure of chemotherapy in about 80% of cancer patients [31]. There some potential mechanisms of MDR currently reported: ABC transporter family, apoptosis induction, autophagy induction, cancer stem cell regulation, hypoxia induction, DNA damage and repair, and epigenetic regulation [19].

The most extensively studied mechanism of MDR is the overexpression of ABC transporter pumps, which are located on the cytoplasmic side of the resistant cell membrane, leading to removal of a large amount of chemotherapeutic agents from cells thus decreasing their intracellular accumulation [32].

The process of drug-induced apoptosis involves the upregulation of pro-apoptotic factors as well the modulation of cell survival factors. The deregulation of one or more of these factors may give rise to a failure of drug-induced apoptosis leading to chemoresistance [33]. The autophagy is upregulated in response to cancer treatments and has a cytoprotective in cancer effect by degrading the drug molecules helping cancer cells evade apoptosis. Cell populations that respond to drugs by inducing autophagy are more drug-resistant and will recover after the withdrawal of the chemotherapeutic agents [19,34]. The hypoxia can also modulate apoptosis and autophagy mechanisms contributing to MRD. In hypoxia, the hypoxia-inducible factor-1 (HIF-1) can change the drug-induced apoptosis and authophagy and reduce drug-induced senescence in response to drugs. The inhibition of HIF-1 re-sensitises cells to drug treatment [35].

In normal cells the DNA damage activate checkpoint pathways, which cause an arrest in cell cycle unless DNA is repaired, but in cancer cells efficient repair of DNA will contribute to drug resistance. Moreover, in response of dysfunction of one DNA repair pathway can be overcome by another compensatory pathway, which could contribute to the resistance to chemotherapy [36].

The cancer stem cells (CSCs) have the ability of self-renewal and asymmetric division, which, is responsible for giving rise to differentiated daughter cells which make up the bulk of the tumor. These cells contributed to initiation and progression of cancer [36]. In addition, stem cells are involved in MDR by several mechanisms, such as the expression of multiple transport proteins of the ABC family, resistance to DNA damage and apoptosis, and the ability to make the epithelial transition to mesenchymal [37,38].

The epigenetic mechanism such us DNA methylation histone modifications and variation on miRNA expression can work gene expression and can also be involved in drug resistance [39-41].

However the MDR phenotype is usually the synergistic result of a combination of different MDR mechanisms, thus inhibiting only one contributor to cellular resistance is usually insufficient to overcome all mechanisms of cancer-cell resistance to chemotherapy [42]. In order to overcome MDR oncologists and researchers came up with certain alternatives, for example finding analogs of regularly used chemotherapeutic agents, which would have wider activity and lower toxicity. However, few analogs become clinically useful, due to reduced anticancer activity and high risk of toxicity [43]. Additional strategy was to administrate MDR modulators, known as chemosensitizers in combination with anti cancer drugs, these modulators can block the efflux pumps of the ATP-binding cassette (ABC) transporter family, however in many cases they are toxic at the concentration capable of inhibiting MDR [44]. In this context better drug delivery strategies are being developed, such as the ones citied bellow.

Metronomic Therapy

Cancer chemotherapy customarily employs the highest tolerated drug dose that a regular patient can take, leading to the need of prolonged time intervals between treatment cycles to allow for normal tissue recovery from the cytotoxic effects of the treatment [45]. This approach is useful in tumors that are less genetically complexes, like acute lymphoblastic leukemia (ALL) in children [46], gestational choriocarcinomas, certain germ-cell tumors [47], testicular cancer [48], Hodgkin disease

[49] and B-cell non-Hodgkin lymphomas [50]. However in tumors that are more genetically complexes, for example sarcomas, breast, prostate, pancreas and lung cancers, this sort of treatment is less effective [51].

A plausible explanation for the failure of treatments that use the highest tolerated drug dose followed by the intervals between treatment cycles is that during treatment drugs stimulate weak endothelial cell damage [52]. During the intervals these endothelial cells are able to repair themselves and recover, and since they can support tumor growth, their regrowth generates tumor resistance, which reinforce the hypothesis that more condensed or accelerated schedules of drug administration, using smaller individual doses, would be more effective and less toxic to patients [53].

Instead the metronomic chemotherapy uses a cytotoxic agent at a lower, less toxic dose given at regular, more frequent time intervals [46]. Benefits of this type of treatment includes less gastrointestinal disorders, such as vomiting, nausea, and mucositis, resulting in fewer supportive care procedures, like prophylactic growth factors and intense antiemetic schedules [54]. Finally, oral chemotherapy (i.e. capecitabine, vinorelbine, cyclophosphamide, methotrexate) can be used, reducing the inconvenient of altering to a greater extend the patient lifestyle, since it makes home therapy possible and reduce costs due to the lower dosage [55].

Nonetheless, the metronomic therapy solely could hardly perform overall effects against the disease, introducing the possibility of combining metronomic drugs and regular chemotherapy, in a treatment called “chemo switching”, in which patients go through a short-term conventional chemotherapy followed by a long-term maintenance metronomic chemotherapy, eventually combined with targeted therapies [56].

Chemo sensitizers

Chemosensibilization is a process capable of increasing tumor sensitivity to chemotherapy, through agents that can be synthetic or natural [57]. The natural bioactive agents are safer and showed several mechanisms of action, such as efflux protein modulation, upregulation of apoptotic proteins and downregulation of antiapoptotic proteins to reverse drug resistance and increase drug sensitivity [27]. Additionally these natural agents are not harmful to healthy cells and interfere with multiple signaling cancer pathways, leading to cell death besides chemosensitizing tumor cells [58]. Examples of these chemosensitizers include: nanoparticles [9], food bioactive compounds [59], drugs with epigenetic targets [60].

Nanocarriers

Nanotechnology was able to prevent MDR by encapsulating, attaching, and conjugating drugs or therapeutic biological products to nanocarriers, that can comprise small molecules such as lipids or polymer nanoparticles that target the therapeutic cargo to tumors or tumor cells [61]. One mechanism used by these nanoparticles is known as the enhanced permeability and retention (EPR) effect and it is generally referred to as ‘passive drug targeting’ [62]. The EPR consists in improving the circulation time of the entrapped or conjugated chemotherapeutic agents by relying on the pathophysiological properties of solid tumors, which tend to present a leaky vasculature, in contrast to the vasculature of healthy tissues, allowing the nanoparticles with sizes up to several hundreds of nanometers to accumulate in solid tumors over time [63].

In this context Doxil™ is one of the best examples of nanomedicines that work through EPR, it is coated with a hydrophilic polymer called PEG which attenuates the uptake of particles by macrophages and monocyte members of the reticuloendothelial system, enhancing efficient targeting of tumors, Doxil™ is commonly used to treat breast cancer [64]. Further examples of passive targeting nanomedicines approved for clinical use are: Myocet™, DaunoXome™, Genexol-PM and Marqibo™. Although these nanoparticles have great therapeutic effects, EPR effect heterogeneity within and between tumors is an obstacle, since there is a wide spectrum of possible responses, even tumors without EPR [65].

In order to overcome the EPR heterogeneity scientists developed the “active drug targeting”, that consists in active bind to specific receptor in cancer cells. Among other mechanism, nanoparticles can: bind to extracellular matrix adjacent to the tumor, bind with high affinity and specificity to a particular cell surface receptor and recognize and bind to target cells through ligand-receptor interactions [66]. Some examples of drugs with active targeting are: Rituxan™, Herceptin™ and Avastin™.

Carbon Nanotubes

Although particularly effective, nanomedicines have its shortcomings, such as production multiple steps process, including the fabrication of the nanoparticle itself, the addition of a layer compatible with the target, derivatization for functional groups, addition of the functional group and ultimately drug loading step. This complex process involves a purification procedure for each step, resulting in an ineffective process, which is inconvenient for large-scale synthesis [67]. Therefore, more resourceful delivery agents are needed, such as carbon nanotubes, which are allotropes of carbon with a cylindrical nanostructure with distinctive properties, such as high aspect ratio, surface area, and simple drug loading mechanism [68].

Carbon nanotubes have already shown interestingly uses in the biomedical field, due to its capacity to absorb and convert electromagnetic radiation, like the near infrared, into heat or sound energy, they can be effectively employed in photothermal therapy [69] and in photoacoustic therapy against cancer cells [70]. Regarding their application in drug delivery, carbon nanotubes have already been used in carrying various therapeutic agents, such as chemotherapeutic drugs, showing great efficiency [71]. However, there are some concerns regarding carbon nanotubes, since *in vitro* studies showed that they are toxic at concentrations of 5-10 mg/mL, due their ability to activate multiple cellular pathways (Mattheolabakis, Rigas & Constantinides 2012). Nevertheless ***In vivo*** studies suggest that they are safe at similar or higher concentrations [72].

Bioactive Compounds

Bioactive compounds are essential and non-essential food compounds (e.g., vitamins or polyphenols) that occur in nature that can have significant effects on human health [73] both in preventing cancer and improving chemotherapy efficiency [74]. Among these compounds genistein, resveratrol and curcumin can act as chemosensitizers of anticancer drugs [59]. Genistein decreased cell growth and apoptosis when administered in combination with cisplatin, docetaxel, doxorrubicin or gemcitabine in prostate, breast, lung, pancreas and ovary cancer cells [75]. Moreover, Genestein was also able to intensify the gemcitabine effect through inhibition of NF-kB and AKT in osteosarcoma and pancreas cancer [76]. Similarly, genestein restored cell sensitivity in ovary cancer that was resistance to cisplatin, docetaxel and gemcitabine through inhibition of NF-kB pathway targets (c-IAP1, Bcl-2, Bcl-xL) and surviving [75]. Resveratrol also sensitized cells from several cancers, when administered in combination with doxorubicin, cytarabine (AraC), actinomycin D, taxol and methotrexate, by increasing the apoptosis rate and decreasing survivin expression, aside from acting in cell proliferation through inhibition of inflammatory pathways involving NF-kB e STAT-3 [77]. In association with docetaxel, resveratrol showed synergetic effect inducing apoptosis in cells with overexpression of HER-2 in breast cancer [78]. Furthermore, when resveratrol was associated with cisplatin it showed increase average surviving time among animals with breast cancer, due to reduction of cell proliferation [79].

Curcumin was able to increase the sensibility of tumors to different drugs such as doxorubicin, 5-FU, paclitaxel, vincristine, vinorelbine, melphalan, cisplatin, oxaliplatin, celecoxib, gemcitabine, etoposide, sulfinosine and thalidomide in both solid and haematological tumors [75]. When associated with cisplatin, curcumin reduced drug resistance by acting on the signaling pathways of NF-kB, STAT3, Akt, Notch and inhibiting DNA repair [80]. Similarly in association with carboplatin, curcumin displayed synergetic effect on cell invasion and migration, through inhibition of MMP2 and MMP9 activity [81]. This evidence suggests that the bioactive compounds can act as powerful agents against MDR by increasing chemotherapy efficiency [74].

Epigenetics

Epigenetic alterations are structural modification in genomic regions that alter the gene expression without alterations in the DNA sequence [82]. These modifications can be involved in the carcinogenesis process in all stages [83]. The most common described epigenetic mechanisms are: DNA methylation histone modifications and variation on miRNA expression [84].

DNA methylation is the most extensively studied epigenetic modification [85] and refers to the covalent addition of a methyl group to the nucleotides in the cytosine located next to guanine (dinucleotide CpG), these dinucleotides are often enriched in certain genomic regions known as "CpG islands" **[84]**.The main forms of aberrant methylation are global hypomethylation, responsible for generating genomic instability, and site-specific hypermethylation, which is related to the silencing of tumor suppressor genes [86]. DNA methylation is mediated by a family of DNA methyltransferase enzymes (DNMTs). High levels of DNMT1 expression have been reported in cancer patients who are not responsive to cancer chemotherapy [39].

In addition, the modification of histones are involved with MDR and plays a key role in the regulation of chromatin structure [73] and are involving in chromatin condensation, DNA accessibility and transcriptional activity [86], the changes caused will depend from which residues are modified and the type of modifications present [85]. Histone modifications can be of different types including acetylation which is regulated by histone acetyl transferases (HATs) and histone deacetylases (HDACs) [87]. Abnormal expression of these enzymes can contribute to carcinogenesis [88].

Another important mechanism in chemosensibilization involve miRNAS, small non-codifying RNAs that are capable of regulating genetic expression through binding to the 3' region of the target messenger RNA, modulating its stability and/or transduction [89]. miRNAs can act either in oncogenes as well as in tumor suppressor's genes, depending on its target genes. They have been considered important circulating biomarkers due to it stability in the circulation and specificity in tissue expression [90].

Recent studies have indicated that this epigenetics mechanism can be used on the chemosensibilization of chemotherapy drugs [40,91]. Preclinical data with numerous cancer cell lines showed that the combination of HDAC inhibitors with a variety of chemotherapy drugs have synergetic or additive effect [92]. The HDAC inhibitors, especially SAHA and TSA, downregulated the expression of multidrug resistance protein 2 (MRP2) in KBV20C cells. In addition, this downregulation of MRP2 is associated with synergistic increase in paclitaxel-induced G2/M arrest and apoptosis [93]. When administered together, decitanine and vorinostat, is a potent inhibitor of HDAC activity [94], the synergetic effect results in increased apoptosis in colon carcinoma cells [95].

Drugs with epigenetic mechanisms can be effective in sensitizing tumor even before chemotherapy begins [60]. In an experiment in which patients with lung cancer were treated with azacitidine (demethylating agent) and entinostat (histone deacetylase inhibitor) [96], exhibiting better chemotherapy subsequent response [97].

Certain miRNAs, such as miR-520 , miR-519c , miR-328, miR-181a and miR-487a were identified as being able to regulate expression of ABCG2, gene associated with chemoresistance, therefore sensitizing diffenrents tumor cells to the chemotherapy treatment [98]. The high levels of miR-30c, that is a prognostic marker for breast cancer in humans, resulted in a significant decrease in survival of chemo-resistant MDA-MB-231 breast cancer cells to paclitaxel and doxorubicin at even low doses. Elevated miR-30c also sensitized the drug response of a second breast cancer cell line BT-20 to paclitaxel and doxorubici, and increased the apoptotic sub-G1 population of these cancer cells upon paclitaxel and doxorubicin treatments [99]. The association between gefitinib and miR-34a inhibited cellular growth and induced apoptosis and tumoral regression [100]. ***In vitro*** and ***In vivo*** breast cancer studies showed that the combination of 5-fluorouracilo with adenoviral vector, which express the tumor suppressor miR-145, exhibited

anti-proliferative effect in comparison with treatment using 5-fluorouracilo alone.

There is a controversy in the literature regarding miRNA role improving chemotherapy drug efficiency [14]. Although there is evidence that support the improving efficiency and activity that miRNAs exerts on these drugs [98] there are also studies that show miRNAs can increase MDR [101-103]. Therefore more studies are needed in order to fully understand the miRNAs effects in MDR [104].

Conclusion

The chemotherapy is the main cancer treatment; unfortunately a long-term use causes MDR and decrease the effectivity of drugs. Several different approaches have been developed to sensitize tumors such as ABC transporters, synthetic and natural chemosensitizers, nanocarriers and epigenetic therapy. Although this mechanism seems to be a potential in overcoming MDR, the use of these approaches and the result of their possible interactions in the long term is not yet fully understood, therefore further studies aiming at understanding this dynamics are necessary.

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