Chemotherapy and radiotherapy: Could they contribute to the development of new tumors and metastases?

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Abstract

Objective: Both chemotherapy and radiotherapy have demonstrated high effectiveness as the best mechanisms in the fight against cancer; however, various studies seem to confirm that they could also favor the development of other unwanted effects of great importance for the patient. The main objective of this study is to find out the possible existence of this type of links. Method: This is a systematic literature review that seeks to find out which and how long cases of late interactions related to chemotherapy and radiotherapy treatments have been known. The bibliographic review was carried out based on references published in the last five years. Results: Various studies confirm the possible relationship between chemotherapy and radiotherapy treatments with the development of new undesirable side effects, especially as a consequence of the hepatotoxicity generated in the case of chemotherapy and radiation in radiotherapy. However, in this last type of treatment, the problems raised are really few. Conclusions: The existence of a risk of suffering new unwanted side effects after different types of treatment seems to have been demonstrated, especially in the case of chemotherapy. In the case of radiotherapy, adverse effects are practically non-existent, although they are no less important.

Keywords: Chemotherapy; radiotherapy; tumor; cancer; metastasis; hepatotoxicity; radiation
Background

In 2005, we found a study that related the side effects caused as a consequence of treatment with radiotherapy and chemotherapy, where the risks of the possibility of developing second tumors as a consequence of late toxicities were already discussed [1]. However, there currently seems to be evidence that identifies chemotherapy as a double-edged sword where its effectiveness on the primary tumor could be counteracted by a series of reactive tumor/host responses that would end up supporting the survival and dissemination of subpopulations of cancer cells [2]; In fact, an increase in preclinical and clinical observations seems to indicate that near-death cells could cause induced metastasis as a consequence of chemotherapy treatment [3]. The problem of cardiotoxicity is another aspect that also usually appears after chemotherapy, especially with fluorouracil, indicated in patients with locally advanced or metastatic gastric cancer [4]; an adverse effect, which often also seems to occur in patients diagnosed with breast cancer and who have also been treated with chemotherapy [5]. It is known that metastasis is the main cause of cancer-related mortality, but it is also said that the existence of a mechanism induced by this type of treatment and mediated by the host could promote a remodeling of the extracellular matrix, ultimately facilitating the seeding and metastasis of cancer cells [6].

Method

This is a qualitative systematic review study carried out through a synthesis of different research articles based on the appearance of important adverse effects as a consequence of treatments such as the possible development of tumors or metastases derived from chemotherapy or radiotherapy treatments. The following search engines were used: Pubmed, Regional Portal of the VHL (Virtual Health Library), and CISNE of the Complutense University of Madrid; In addition, searches were also carried out in various sources such as Google Scholar in order to collect more information related to the study that was being carried out. Regarding the search strategy, a search was carried out that related this problem to both chemotherapy and radiotherapy, for which the following keywords were used: chemotherapy-induced metastases and radiotherapy-induced metastases. All searches were conducted in English. The results that contained one or both of the keywords used were as follows:

Pubmed: 180; VHL Regional Portal: 235; Google Scholar: 742; Swan. Complutense University of Madrid: 185. The prism diagram is in Supplementary Material 1.

Results

Chemotherapy

Chemotherapy is an important means of treating malignant tumors. The main role of chemotherapy drugs is to induce cell death; However, the apoptotic pathways of many tumor cells are often severely affected, leading to failure of apoptosis induced by this type of treatment. Apparently, tumor stem cells attached to the tumor microenvironment are closely related to tumor recurrence and metastasis [7].

Tumors through acquired drug resistance often overcome the cytotoxic effects of chemotherapy. Recent studies have even linked the cytotoxic effects of chemotherapy with the development of a new prometastatic tumor process [8]. Also metastasis is one of the main reasons that cause of death in cancer patients. However, it is thought that chemotherapy could also induce the development of these metastases [9], and this is why it happens. Apparently the natural aging of cells is activated in response to the use of chemotherapy in order to prevent the spread of future cancer cells; However, recent studies seem to have shown that this type of response is not always definitive and that there are populations that could use this same mechanism as an adaptive way to restart proliferation, thus becoming more aggressive [10].

Another problem is related to the hepatotoxicity that this type of treatment can generate; Apparently, liver injury induced by chemotherapy is quite common in patients diagnosed with cancer who have been subjected to this type of treatment [11, 12]; an induced hepatotoxicity that should be taken into account in order to avoid possible errors in the detection of future liver metastases; The use of magnetic resonance images seems to have proven to be a useful tool for resolving possible false negatives that could occur after treatment with chemotherapy [13]; It is also known that those patients who have inoperable disease are usually treated (whenever possible) with aggressive chemotherapy in order to reduce the disease; However, this type of action can also end up favoring liver injury [14], which has also established a relationship of this type when the postoperative result after an open liver resection has not been as expected [15]; On the other hand, it seems that there are atypical patterns that can pose difficulties in some diagnoses, especially in patients who have been treated with chemotherapy, among which they are known as cavitating metastases [16].

Tumors often overcome the cytotoxic effects of chemotherapy through acquired or environmentally mediated drug resistance; Furthermore, signals from the microenvironment hide the beneficial effects that it offers, potentially facilitating progression and metastatic dissemination; Apparently, the seminal mediators found in the metastases induced by this type of treatments seem to be a wide range of hematopoietic, mesenchymal and immunogenic cells that originate in the bone marrow [17]. However, there are also treatments in which combined chemotherapy therapy with other compounds is quite effective, as in the case of cisplatin, which has become an important adjuvant therapy in patients with bladder cancer [18]. Also, exosomes, a class of extracellular vesicles derived from tumors secreted by cancer or stromal cells, can confer drug-resistant anticancer traits to cancer cells since promoting chemoresistance makes them an attractive vehicle for the delivery of anticancer drugs [19]. There are even studies, in which the targeted inhibition of proangiogenic deubiquitinasases whose objective is to search for associated treatments that attempt to control the degradation of proteins given the implication that these represent in the development of cancer and resistance to chemotherapy [20].

Regarding breast cancer, its mortality appears to be almost exclusively the result of tumor metastasis and resistance to therapy. Chemotherapy routinely used to treat this type of disease appears to induce extensive tissue damage, provoking an inflammatory response that could apparently hinder efficacy and promote metastatic relapse [21]. Regarding neoadjuvant chemotherapy, that which is applied as the first treatment option and which generally seeks to reduce the size of the tumor for subsequent surgery and/or treatment with radiotherapy) is a standard component of breast cancer treatment. Despite everything, recent studies seem to suggest that chemotherapeutic drugs could promote metastasis through mechanisms that are not yet well-defined [22]. It is for this reason that in chemotherapy-induced liver disease, which includes a wide variety of hepatic parenchymal and vascular changes, CT MR imaging is important since there is the possibility that diffuse or focal liver disease may occur (i.e. hepatitis, steatosis, fibrosis, pseudocirrhosis, or sinusoidal obstruction); changes that could also profoundly alter the liver parenchyma on images, leading to false-negative and false-positive diagnoses of liver metastases; which can lead to possible errors regarding management strategies in this type of patients [23].

Radiotherapy

Radiotherapy is a very effective means to achieve especially local control in a wide range of primary tumors. However, there seems to be some evidence (fortunately scarce but no less important) that seems to be related to the existence of some risks as a consequence of complex changes generated by radiation in the tumor environment, thus reducing its long-term effectiveness, of the treatment [24]. It has been proven that in pancreatic cancer, dying cells after irradiation could promote the repopulation of cancer cells that have survived, which would lead to tumor recurrence [25]. These acquired metastases and

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invasion of cancer cells during radiotherapy appear to be due in part

to the induction of epithelial-mesenchymal transition and cancer stem
cell properties that are mediated by TGF-β signaling [26]. Despite
everything, and although the development of secondary malignant
neoplasms related to irradiation treatment is not common, on some
occasions (as in some childhood malignancies), it seems that they
could have favored the development of a sarcoma different from the
primary tumor [27]. A higher risk of malignant neoplasms induced by
radiotherapy has been observed, especially in cases of patients with
Li-Fraumeni or Li-Fraumeni Like syndrome [28].

Discussion

Various studies have linked the cytotoxic effects of chemotherapy with
the creation of a tumor microenvironment that apparently could end up
favoring the development of possible metastases; all of this, either
as a consequence of the cytokine storm facilitated by the
chemotherapy itself or by the direct effects of the compounds used on
the stromal and/or immune cells; Because, in addition to killing tumor
cells, chemotherapy treatment may also increase intravasation,
clusters of cells known collectively as the tumor metastasis
microenvironment (TMEM) that appear to serve as gateways. Entrance
for tumor cells entering the vasculature [29]. It has been
demonstrated that chemotherapy selects clones of cancer cells that are
resistant to chemo, inducing clones of cancer cells mutated for
metastasis, favoring prometastasis in the microenvironment of the
primary tumor, thus facilitating cancer metastasis to distant organs
[30]. It has also been proven that the widespread use of multiple
chemotherapeutic agents has favored the recognition of different
patterns of hepatotoxicity associated with specific drugs, although the
underlying mechanisms involved in this type of condition remain
poorly understood [31]. Regarding breast cancer, chemotherapy has
also been and is an important factor in the treatment of this type of
patient. However, paradoxically, it also seems to induce cancer
progression [32]. The liver has been seen as the organ most affected
by this type of treatment, so its monitoring and control should be of
great importance; For this reason and as a control mechanism for
chemotherapy, radiological control seems to play a very important
role, a very important aspect to take into account since this type of
treatment favors a series of effects with a great influence of surgical
moribundity on this organ [33].

Regarding radiotherapy, fortunately, and despite some references
that also raise problems of possible metastases, its frequency does not
represent an incidence as worrying as with chemotherapy; although
this aspect does not mean that it is not a matter of concern and that,
therefore, its surveillance and control must continue.

However, perhaps most important are some questions that have
arisen from all this information; as Dr. Joan-Ramon Laporte Roselló,
honorary professor at the Autonomous University of Barcelona and
former senior official of Health, the Spanish Medicines Agency, the
European Agency, as well as the WHO [34], says in an interview
comments that “the difference between a medicine and a poison lies
in the dose” [35]; If this is so, could it be that the doses used in the
treatments are higher than they should be? Would it be advisable
to assess the possible degree of toxicity that the patient could present
before a new treatment?

We know that before starting this type of treatment, the patient
is informed of the possible adverse effects that they entail, but in the
document that is given to them to sign the consent, this possible
adverse effect that we have seen does not usually appear. Should it be
considered? Is it mandatory to inform patients of this possible risk? Do
patients have the right to be informed about “all” the possible risks
that appear especially about those in which, instead of improving,
they could even make them seriously worse? Would the corresponding
professional have the obligation (at least from an ethical point of
view) to warn the patient about the latest (verified) studies that could
make their situation worse as a result of the treatment they are going
to receive? It would be necessary to carry out more research with a
certain urgency that could, to a certain extent, clarify (as far as
possible) this probable risk to which these types of patients are usually
exposed.

Conclusion

The existence of a risk of worsening the treated disease after different
types of treatment with both chemotherapy and radiotherapy seems to
have been demonstrated (although, in this case, it is more unlikely).
Another important aspect (at least from an ethical point of view)
would be the need for the consent form given to the patient, in
addition to explaining (as it already does) the entire procedure in a
sufficiently clear and easy-to-understand manner. That is going to be
applied should also be updated based on the experience and new
knowledge that emerges from those studies that are published related
to these new side effects. Therefore, it would be advisable to carry out
more studies related to these types of treatments.

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