Chronotherapy

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Chronotherapy aims to understand the impact that biological rhythms have on the response to a therapy to optimize its action, maximize health benefits, and minimize possible adverse effects. Chronotherapy, or clinical chronopharmacology, study the impact that circadian rhythms have on the response to a drug to optimize its action, maximize health benefits and minimize possible adverse effects on the patient.

Keywords: chronotherapy ; circadian rhythms ; cancer ; cancer therapy

1. Effect of Chronotherapy in Chemotherapy

Some drugs such as antimitotic agents, antimetabolites, alkylators, or intercalants, usually achieve the best antitumor efficacy when they are administered at the time of the day when they are best tolerated, but this property is not always used for our own benefit [1].

One of the most illustrated examples of how ignoring this property could result in the discard of a useful drug is oxaliplatin. Initially, the development of oxaliplatin was interrupted for undesirable toxicity in a phase I clinical trial [2]. Later, another company studied its safety and efficacy, taking into account chronopharmacology, and they determined that the best way to administrate oxaliplatin is using a chronomodulated delivery that peaks at 16:00 h. The clinical efficacy of oxaliplatin was validated in a large phase II clinical trial in colorectal cancer using this type of delivery and confirmed later in randomized phase III trials [3][4][5][6][7][8][9].

Cisplatin, another platinum analog, has also been studied in chronotherapy. In a study of non-small cell lung cancer by Li et al. [10], no differences were observed in the response to treatment when cisplatin was administered at different times. However, the occurrence of hematological adverse effects such as leukopenia or neutropenia (grade 3 or 4) and gastrointestinal adverse effects (grade 2) after chemotherapy was significantly lower in the group following chronotherapy. Preclinical studies in ovarian cancer patients exhibited that administration of doxorubicin in the morning (06:00) and cisplatin in the evening (16:00–20:00), when both drugs cause less toxicity and tumor response is higher, caused fewer complications and side effects. Indeed, patients treated with this schedule increased their probability of survival at 5 years to 44% [1][11][12]. Similar positive results were obtained when ovarian cancer patients were treated with pirarubicin at 06:00 and cisplatin in the evening [12]. Additionally, this schedule of doxorubicin plus cisplatin was also well tolerated and with a 60% response in patients with advanced/recurrent endometrial carcinoma. In metastatic bladder cancer, this circadian-timed combination chemotherapy also induced a clinical complete response in the majority of patients studied, with an outstanding quality of life and only modest toxicity. Indeed, this regimen also showed a good response as an adjuvant treatment for locally advanced bladder cancer [12].

Fluorodeoxyuridine (FUDR), a chemotherapeutic agent shown to have activity against a variety of malignant neoplasms, can be administered at either a variable or a constant rate. In renal cell carcinoma, continuous and circadian-modulated (68% of the daily dose administered in the evening) administration of FUDR is an effective treatment that induces a durable tumor response with little toxicity [12].

Computational and experimental analysis revealed that the schedule of administration of a given drug could cause different cytotoxicity in the different cell populations. For example, the 5-FU response depends on the oscillation in its target, the thymidylate synthase, and in the enzyme dihydropyrimidine dehydrogenase (DPD), responsible for its degradation. The peak activity of DPD is at 16:00 h, whereas its lowest activity occurs at 4:00 h, which modulates the efficacy of 5FU. On the other hand, glutathione (GSH) is an antioxidant molecule involved in drug withdrawal, and its levels peaked at 16:00 h. It has been reported that some drug toxicities were decreased when those drugs were administered during GSH time of action [11]. In clinical trials of 25 to 35 patients in phase I/II, those patients with digestive cancers who received chronomodulated treatment of 5-FU (alone or with leucovorin), oxaliplatin, or irinotecan, presented fewer adverse side effects [1].

Other clinical trials demonstrated the positive effect of oxaliplatin-5FU-leucovorin treatment through chronomodulated administration in colorectal cancer metastases. Then, to enhance efficacy, two different schedules of administration were designed: chronoFLO4, in which the three drugs were chronoadministered for 4 days with 10 days off, and FOLFOX2, a constant infusion of the drugs for 2 days. In both cases, patients were treated biweekly [8] and they achieved similar survival probabilities with reasonable toxicity. However, the chronoFLO4 scheme produced a survival advantage in males [8]. A meta-analysis corroborated that males lived longer on chronomodulated chemotherapy. Conversely, women had better survival on conventional therapy for localized colorectal cancer than men [13]. Another study showed that irinotecan tolerability was better after morning delivery in men and in the afternoon in women with metastatic colorectal cancer [14]. Therefore, sex is a determinant of better survival and response depending on the drug delivery schedule in patients with metastatic colorectal cancer [13]. This difference is probably because of unidentified differential expression of clock-related genes that control essential cellular processes such as cell cycle progression, apoptosis, mechanisms of DNA repair, and drug pharmacology, which probably makes women respond worse [8]. These findings highlight the necessity to analyze the effect of treatment separately in men and women, as different genotypic and phenotypic profiles have been reported in colorectal cancer. Indeed, women also suffer higher toxicities on 5-FU-based treatment than men, probably because of variations in drug metabolism and detoxification [8][13].

In addition, another study developed a mathematical model that allows personalization of the treatment schedule with irinotecan in colon cancer based on its pharmacokinetics and pharmacodynamics. This model also makes it possible to study the toxicity of the drug according to the levels of expression of genes related to circadian rhythms. Therefore, this model could program the patient's treatment based on their expression profile and the optimal time to administrate that drug [15].

Conversely, it appears that chemotherapy or the administration of some drugs, such as paclitaxel, also disrupts circadian rhythms, the expression of certain related genes, and suprachiasmatic nucleus behavior. All of this supports the idea that therapies based on resynchronizing biological rhythms could improve the living conditions of patients after chemotherapy [16]. In addition, many clock genes could modulate the efficacy of antitumor therapies depending on the time of the day. For example, the DNA alkylator temozolomide and the topoisomerase I inhibitor irinotecan have the maximum toxicity in glioblastoma and colorectal cancer during peak BMAL1 expression [17][18]. Indeed, high expression of *BMAL1* increased the sensitivity to oxaliplatin and paclitaxel in colorectal cancer [19][20].

Clinical trials so far have confirmed that optimal timing of treatment could decrease drug toxicity and increase efficacy, allowing a more dose-intense but successful therapy [12]. Therefore, the combination of chemotherapy with chronotherapy appears to be a promising therapeutic tool.

2. Effect of Chronotherapy in Radiotherapy

In view of the success of chronotherapy in chemotherapeutic treatments, research has started to look at radiotherapy [21]. However, the application of radiotherapy treatment at different intervals of the day has not been studied in depth. Some circadian genes are involved in the establishment of rhythmicity in the mechanisms induced by ionizing radiation, such as DNA repair or apoptosis, making cells more sensitive to radiotherapeutic treatments at certain times of the day [22]. The radiosensitivity of cells also varies in the cell cycle, being resistant in the S phase and sensitive in late G2/M [23]. Additionally, when cells are replicating they become more radiosensitive, as occurs with tumor cells [22].

A study of brain metastasis in patients with non-small cell lung cancer found a considerable increase in median survival in patients who received radiotherapy before 12:30 h (morning treatment) in comparison with those patients who were treated in the evening [24]. However, another retrospective study of high-grade gliomas showed no differences in the progression-free survival of patients who received morning radiotherapy versus patients treated in the afternoon [25].

Radiation is well known to induce many short and long-term adverse side effects, and its chronomodulated administration attempts to minimize these treatment-related symptoms. Therefore, the aim of chronoradiotherapy focus on symptoms rather than on tumor progression or overall survival [22][26].

A study by Fuzisakki et al. [27] showed that breast cancer patients who received radiotherapy in the afternoon had less skin toxicity than those who received radiotherapy in the morning. Indeed, this effect was stronger in patients homozygous for Per3 and/or for RNA deadenylase Nocturnin (NOC), another clock gene [21]. The individual genotypic profiles appear to be important for the response, as another study in rectal cancer showed increased levels of the circadian genes *CLOCK, CRY2,* and *PER2* in patients on treatment response after radiotherapy [21]. Therefore, it is important to highlight that the individual biological clock has a relevant role in the treatment outcome [21].

As in chronomodulated chemotherapy, there is also a sex dependency in radiotherapy. In a study of bone metastases, only females treated with radiotherapy between 11:00 and 14:00 exhibited a higher complete or partial response [28]. In another study, patients with rectal cancer had a better tumor response when they received radiotherapy treatment after midday, and they suggested a worse response in women [23]. The variability in circadian rhythmicity between women and men could explain this difference in response, but further research is needed in this field [28]. Another variable to take into consideration is age, as was suggested in a study performed on brain metastatic patients. The results of this study demonstrated that overall survival was considerably longer only in elderly women treated with radiotherapy in the morning [29]. However, another study in prostate cancer found that evening radiotherapy leads to worse toxicity and side effects in older patients [30].

Discordances exist in studies that evaluate the chronotherapeutic effect of radiotherapy. Therefore, the possible benefit of this approach should be confirmed in different types of tumors, and in well-designed prospective and randomized trials with proper sample selection [22].

3. Effect of Chronotherapy on the Blood–Brain Barrier

The most frequent primary brain tumor in adults is glioblastoma (GBM), which presents a very poor prognosis [31]. The standard treatment of this type of tumor consists of surgical resection followed by radiotherapy and administration of the DNA alkylator temozolomide (TMZ) [32][33]. However, the probability of patient survival at 5 years remains very low [33]. Different agonist molecules of REV-ERB (SR9009 and SR9011) and CRY (KL001) have been found to be successful therapies in mouse models of GBM [34][35]. TMZ is capable of crossing the blood barrier readily and presents a short half-life (1.5 h), two characteristics that make it an ideal chronotherapeutic drug. Because TMZ is rapidly absorbed and reaches its highest levels in plasma within 1 h after oral administration, precise dose timing is possible [36]. In a retrospective study, TMZ was shown to increase overall survival when administered in the morning in patients with methylated MGMT (O-6-methylguanine-DNA methyltransferase), the protein that repairs DNA damage induced by TMZ. Indeed, MGMT expression oscillates with the time of the day. Therefore, both MGMT methylation and silencing confer a better response to TMZ treatment [37]. In vitro studies using murine glioblastoma cells showed that administration of TMZ during peak BMAL1 expression in tumor cells can enhance its efficacy [17]. Indeed, preclinical analyzes have observed maximal TMZ efficacy when the application of the treatment coincided with the peak of BMAL1 expression. Therefore, morning TMZ administration appears to be the most effective thanks to its daily oscillations in the absorption/excretion and the sensitivity of tumor cells to DNA damage [37]. Thus, BMAL1 has an important function in the regulation of the DNA damage response, as observed in other studies on colon cancer sensitivity to irinotecan and oxaliplatin [17].

Bortezomib, an inhibitor of the proteasome, is commonly applied in clinical trials in advanced phases of GMB. In vivo studies showed that the use of bortezomib at a low dose did not induce major side effects. Besides, its administration at night was significantly more effective, inducing tumor growth inhibition near 70% in comparison with 18% inhibition of day administration. Therefore, night administration of bortezomib offers a time frame of high efficacy that coincides with when mice are metabolically active [38].

4. Effect of Chronotherapy on the Immune System

Clock components are also a potential target for immunotherapy and two strategies could be followed: drug development for circadian clock targets and chrono-immunotherapy [39].

For the first strategy, different components have been developed. Two RORγ synthetic agonists, LYC-53772 and LYC-54143, which can activate BMAL1 transcription, induce T cells differentiation, block regulatory T cell-induced immunosuppression and elevate the secretion of cytokines [40]. In addition, the treatment with RORγ agonists induced resistance to PD-L1 inhibition in T cells, which eliminate anti-tumor immunity [41]. They also increase the cytotoxic activity of T cells, enabling the regression of tumors in mice [41]. LYC-55716 is another RORγ agonist that has shown initial success in a clinical trial in phase I of locally advanced/metastatic solid tumors of different origins [42]. Besides, a similar clinical trial using this agonist in combination with the monoclonal antibody pembrolizumab in patients with non-small cell lung cancer is in progress [43]. Moreover, the RORα synthetic agonist SR1078 increased CD8+ T cell response to anticancer immunity role [44].

In the case of chrono-immunotherapy, the efficacy of the drug seems to be more relevant under certain experimental and/or clinical conditions. For example, the antitumor effect of interferon-β in mice was more evident during the day instead of at night [45]. In a clinical trial of renal cell carcinoma in phase I-II, IL-2 chronotherapy showed activity and the intravenous infusion was feasible in a standard care unit [46]. Interestingly, a study in patients with advanced melanoma

demonstrated that morning or early afternoon administration of different immune checkpoint inhibitors (such as ipilimumab, nivolumab, or pembrolizumab) extended patient overall survival in comparison with late afternoon or evening treatment. Once again, it seems that a more effective immune antitumor response is induced in the daytime in comparison with the evening [47]. A pilot study supported these data by showing that non-small cell lung cancer patients in stage IV who received nivolumab morning treatment significantly reduced their risk of progression and increased their survival [26].

On the other hand, disrupted cortisol expression is linked to tumor suppression. For example, in ovarian cancer, abnormal cortisol rhythms were associated with decreased survival and increased inflammation [48]. In this regard, studies with animal models have demonstrated that high glucocorticoid levels are associated with a reduction in the efficacy of chemotherapy and anti-PD-L1 [49]. Retrospective clinical data also propose that the use of corticosteroids has detrimental effects on anti-PD-L1 response [50][51]. Nevertheless, further studies that clarify the role of corticosteroids in the response to treatment of patients are needed.

5. Other Uses of Chronotherapy in Cancer

Other ways to take advantage of the benefits of chronotherapy and synchronize daily rhythms could be light exposure in the morning and/or taking melatonin before sleep [37]. Indeed, a link between melatonin and cancer has also been observed and Li et al. [52] discussed the possible oncostatic impact of melatonin on various types of tumors, such as breast, prostate, gastric and colorectal. This action could be due to its antioxidant activity, stimulation of apoptosis, or inhibition of angiogenesis and tumor metastasis, among others [53]. In addition, Önder et al. demonstrated that treatment with melatonin increased its repressive effect on the growth of breast cancer cells by inducing cell death in vitro [54]. Therefore, melatonin could be applied as an adjuvant treatment to chemotherapy and radiotherapy, making tumor cells more sensitive to both treatments [52][55]. Moreover, those patients that have been exposed to light during nighttime presented a reduced melatonin secretion and an increased incidence of tumor development [56].

Certain nutritional behaviors also appear to affect circadian rhythms. For example, caloric restriction, an anti-aging dietary practice, reversed the circadian and metabolic profiles of aged mice [57]. This caloric restriction is also able to reduce tumor progression and to promote tumor cells death, therefore, making antitumoral therapies more effective [58]. However, as caloric restriction also has detrimental effects, other studies have considered intermittent fasting as an alternative, suggesting that this intervention could not only prevent tumor development but also improve the antitumor response of the immune system and the sensitivity to antitumoral therapies. Therefore, a well-designed chronodietary intervention could be a promising therapeutic option against cancer [59][60].

Additionally, it would be of great interest to analyze whether the timing of exercise has an influence on cancer progression and the therapeutic response of patients [11] (**Table 1**).

Table 1. Summary of some chronotherapeutic approaches applied in cancer therapy.

Effect of Chronotherapy in Chemotherapy		
Oxaliplatin	**Chronomodulated delivery: peak at 16:00 h.**	[3][4][5][6][7][8][9]
Cisplatin	**Non-small cell lung cancer:**	
	Low hematological and gastrointestinal adverse effects in the group following chronotherapy.	[10]
Cisplatin + doxorubicin or pirarubicin	**Ovarian cancer:**	
	Cisplatin in the evening 16:00–20:00) combined with doxorubicin or pirarubicin in the morning (06:00) cause less toxicity/side effects and high tumor response.	[1][11][12]
	Cisplatin + doxorubicin had also tumor response in endometrial carcinoma and bladder cancer.	[12]
Fluorodeoxyuridine	**Renal cell carcinoma:** **Circadian-modulated (68% of the daily dose administered in the evening) administration induces a durable tumor response with little toxicity.**	[12]
5-FU	**Fewer adverse side effects in digestive cancers.** **Chronoadministration of oxaliplatin-5FU-leucovorin (ChronoFLO4) produced a survival advantage in males with colorectal cancer.**	[8]

Irinotecan	**Better tolerability after morning delivery in men and in the afternoon in women with metastatic colorectal cancer.**	[14]
	Effect of chronotherapy in radiotherapy	
	Brain metastasis in patients with non-small cell lung cancer: Better survival in patients treated in the morning (before 12:30 h).	[24]
	High-grade glioma: No differences in survival.	[25]
	Breast cancer: Radiotherapy in the afternoon induced less skin toxicity.	[27]
	Bone metastases: Females treated with radiotherapy in the morning exhibited a higher complete or partial response.	[28]
	Effect of chronotherapy on the blood–brain barrier	
Temozolomide (TMZ)	**Morning administration increases overall survival in patients with methylated MGMT, coinciding with the peak of BMAL1 expression.**	[37]
Bortezomib	**Night administration induces 70% tumor growth inhibition.**	[38]
	Effect of chronotherapy on the immune system	
LYC-53772 and LYC-54143	**RORγ synthetic agonists: Activate BMAL1 transcription, induce T cells differentiation, block regulatory T cell-induced immunosuppression, elevate the secretion of cytokines, induced resistance to PD-L1 inhibition in T cells, and increase the cytotoxic activity of T cells.**	[40][41]
SR1078	**RORα synthetic agonist: Increases CD8+ T cell response.**	[44]
Interferon-β	**Better antitumor effect during the day in mice.**	[45]
Ipilimumab, Nivolumab, or Pembrolizumab	**Melanoma: Morning or early afternoon administration extended overall survival.**	[47]

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