Bahrain Medical Bulletin, Vol. 28, No. 3, September 2006

Editorial

The Role of Chronotherapy in Cancer Management

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Cancer chronotherapy is one of the latest developments in the treatment and management of cancer patients. The basis behind cancer chronotherapy is to use the body's own circadian (biological) clock to help the patient maximise the efficacy of their treatment.

For centuries, the circadian clock has been observed in behavioural and physiological patterns in plants and animals. These patterns seemed to regulate themselves very strictly around the 24 hour cycles of day and night and hence led early biologists to suggest that there was an inner mechanism that regulated these changes. In humans, the circadian clock has a genetic background and many circadian genes have been identified. They serve a very important purpose as the physiological changes induced by the expression of these circadian genes allow us to organize our behaviour and physical state in response to the cyclic changes in our immediate environment. Therefore, they regulate important bodily functions such as sleeping, hormone production, digestive secretion, and immune activity in such a way that they occur at times that are most energetically favourable to us[1].

The circadian clock in humans has 3 distinct components. They are the input pathways, the central pacemaker and the output pathways. The input pathways relay sensory information to the central pacemaker concerning external cyclic cues (e.g. light and feeding times). The output pathways physically synchronise behaviour and physiology with the circadian rhythm. The central pacemaker relays the signal messages between the output and input pathways in a rhythmic fashion. The central pacemaker in mammals is in the suprachiasmatic nuclei of the anterior hypothalamus[2]. Out of all the environmental stimuli, light is the most important. However, the pathways that detect light for the purpose of circadian synchronisation are different from those that are used for visual perception. This is why certain blind human subjects still retain their circadian rhythm despite having no perception or awareness of light[3].

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The circadian clock controls cellular functioning by controlling the expression of certain circadian genes. These genes may encode key regulators of the cell cycle and this is where it shows its importance. Management of the circadian clock is important because disruption of the expression of these genes can lead to the disruption of the cell cycle which is the basis for cancer development.

A cancer is an uncontrolled proliferation of cells because of irregularities in the regulation of the cell cycle. This may be fast or slow but the cells never stop dividing. In order to achieve cancerous growths, several mutations must take place to knock out the cell cycle's natural defence against cancer. However, once sufficient damage to DNA has taken place, the development of a cancer is quite straightforward. A single mutation may express itself and give the cell a slight growth advantage over the surrounding cells. This ensures that the abnormal cells predominate in the group and gives rise to more and more mutations. Once a sufficient number of mutations have taken place and all the conditions required for the cancerous cells are there, there is nothing to stop the cells from replicating over and over.

There is very clear statistical evidence that correlates the incidence of cancer with the disruption of the circadian clock. It has also been shown that survival rates for cancer patients have very close links with the maintenance of strict daily routines[4]. These statistics show us that the circadian rhythm can be used quite effectively as a prognostic and therapeutic tool.

The circadian clock can be viewed as tumour suppressor in some respects. It affects the body at a systemic and cellular level in order to control the proliferation of cells. At the cellular level, the circadian clock controls the cell cycle progression by regulating the expression of clock-controlled genes. Several studies have shown a strong correlation between the rhythmicities of the expression of circadian genes and various cell cycle phases. Therefore, the circadian clock can indirectly control the expression of genes that regulate the 'checkpoints' between the different phases of the cell cycle. Thus, the central pacemaker can affect the expression on tumour-suppressing genes and regulatory proteins at the cellular level.

The central pacemaker also regulates the release of endocrinal hormones and has a lot of influence on the neuroendocrinal systems. The neuroendocrinal systems secrete hormones such as oestrogen and glucocorticoids to affect their endocrinal targets. We know that these hormones are under the influence of the circadian clock as we can monitor the 24 hour rhythmic changes in their levels in the body. Therefore, any disruption of the circadian clock will have an adverse affect on the secretion of these hormones and as a result disrupt cell proliferation rates.

The neuroendocrinal systems also play an important part in the immune response as many of the hormones control cytokine production and leukocyte production and distribution. This leads us to believe that the immune response is also under the influence of the circadian clock and hence is another method of tumour suppression (i.e. immunomodulation). As a result, a disrupted circadian clock can lead to a compromised

immune system which in turn leads to decreased immunosurveillance and cancer development.

The onus on cancer treatments is to maximise the cytotoxicity to cancer cells whilst trying to avoid drug-resistance. Anti-cancer drugs work by targeting actively proliferating cells. They act on a specific part of the cell cycle and focus on that phase to try and kill the cell. However, cancer cells and normal cells follow the same replication pathway so there is nothing to stop the cancer drugs from attacking normal cells. Therefore, a balance must be reached between the drug's ability to target cancer cells effectively and its negative effects on the body. This is called the 'therapeutic index'[1]. Cancer chronotherapy works to improve this index so that there are less negative effects on the body and the cancer cells are targeted faster. The main ideology behind chronotherapy is that it takes advantage of the fact that normal cells all follow the circadian rhythm when it comes to the cell cycle. As a result, it can easily be determined at which phase the cell cycle in normal cells is at a particular time of the day. However, tumour cells do not follow the 24 hour circadian rhythm and are more often than not at a different phase of the cell cycle than normal cells. In fact, it has been well documented that the DNA synthesis rhythm in healthy cells is in a phase opposite to tumour cells[5]. Therefore, the treatment is given at the time of day when there will be least damage to host tissues.

The efficiency of a cancer drug is determined by a number of key factors such as absorption, distribution, intracellular metabolism and elimination. These variables are more favourable at different times of the day because of the physiological changes due to circadian rhythm. For example, the blood supply to the tumour may vary according to circadian rhythm and therefore, by determining when there is maximal blood flow to the tumour, treatment can be given so that it maximises cytotoxicity. It has also been shown that the best time for treatment is early in the morning, because most of the target cells are very vulnerable at this time. The effectiveness of chronotherapy relies to a certain extent upon the degree of coupling between the central pacemaker and the tumour's cell cycle. In slow growing tumours, there is a greater degree of coupling and hence, chronotherapy is a lot more effective as it is possible to manipulate the patient's circadian clock to aid treatment. For example, circadian rhythm can be regulated or deregulated depending upon the desired effect through light therapy as light is the most important environmental cue for the central pacemaker. However, further controllable stimuli could include meal times, melatonin or glucocorticoid administration.

Cancer chronotherapy is currently in practice and it is being studied intensely in order to find greater ways in which to find the optimal time frame for treatment. Positive signs are emerging from clinical trials in which this treatment is being used and hopefully in the near future, the use of the circadian cycle will help to optimise cancer therapy and minimise the deleterious effects.

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