

Considering temporal dimension for NSCLC medical management?

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Life is structured in space but also in time. Biological rhythms, ie circadian ones, have been documented in all processes involved in the malignant transformation of cells as well as in the cellular proliferation of both healthy and tumor tissues [1].

Recent advances identify critical molecular events that rhythmically control drug metabolism and detoxification, cell cycle, molecular targets, DNA (deoxyribonucleic acid) repair, apoptosis, and angiogenesis [2-5]. The coordination of these processes along the 24-h period is ensured by the circadian timing system (CTS) [1-3]. The CTS coordinates physiology and cellular functions over a 24 h period. This circadian physiology is generated and controlled by a central pacemaker, the suprachiasmatic nuclei (SCN) in the hypothalamus, through diffusible signals, including transforming growth factor alpha (TGF- α), epidermal growth factor (EGF), prokineticin-2, cardiotrophin-like cytokine and neuroanatomic sympathetic and parasympathetic pathways (4). A dozen specific clock genes constitute the core of the molecular clock in mammals. In particular, the CLOCK-BMAL1 (circadian locomotor output cycles kaput-brain and muscle ARNT like protein-1) or NPAS2-BMAL1 protein dimers play a key role in the molecular clock through the activation of transcriptional clock genes Period's (Per's), Cryptochrome (Cry's), and Revb's. In mammals, the core clock genes, Per1 and Per2, are key regulators of circadian rhythms both in central clock, in hypothalamus and in peripheral tissues [1-4]. Recent findings revealed molecular links between Per genes and cellular components that control fundamental cellular processes such as cell division and DNA damage.

Disregulation of circadian rhythms might influence the susceptibility to cancer development (breast, colorectal, lung, prostate...) and provide further support for the emerging role of circadian genes in tumor suppression [5]. Precisely, silencing of tumor suppressor genes, such as the Per's – clock core gene, resulting from epigenetic alterations may occur early in lung cancer tumorigenesis. Alterations of sleep quality and disruption of melatonin circadian rhythms (peak at night after dim-lighting) may enhance the risk of various cancers including lung ones [6].

Various mechanisms responsible for the deregulation of cell cycle and enhanced susceptibility to oncogenesis through activation of cell proliferation and cancer promotion have been identified. For example, in NSCLC, over-expression of cyclin D1 and mutation of p16 leading to a shortened and accelerated G1-phase and permanent phosphorylation and inactivation of pRb have been observed. Per1 and Per2 exert their tumor suppressor functions in a circadian time-dependent manner [7]. Their overexpression inhibits neoplastic growth both in vitro and in vivo and increases apoptosis while their down regulation enhanced

tumor development and growth. Monitoring of circadian rhythm in VEGF production may be useful for choosing the most appropriate time of day (i.e. when VEGF production is increased) for administering antiangiogenic agents. WNT10A (wingless gene 10A) could stimulate growth of both microvascular endothelial cells and fibroblasts in tumors along with marked increases in angiogenesis [7]. Circadian disruption may induce progression of malignant tumors via a WNT 10A signaling pathway allowing microvascular endothelial cells and fibroblasts in models involving tumor cells similar to that encountered in human NSCLC [8].

Parameters and dissociation constant of EGF-R (epithelial growth factor receptor) exhibit circadian variations [9]. EGF-R by itself was found to phase shift the prominent circadian rhythm of DNA synthesis, i.e. in the esophagus. Also gene expression response to EGF-R is circadian-time dependent. EGF-R and its ligand transforming growth factor-alpha (TGF- α) are highly expressed in suprachiasmatic nucleus where they exert a circadian-time-dependent neuromodulatory function [4]. The core clock proteins BMAL1, CLOCK, and REV-ERB α , controls fundamental aspects of the immune response [10,11]. As a matter of fact, Bmal1 deficiency in macrophages increases PKM2 (pyruvate kinase M2) expression and lactate production, which is required for expression of the immune checkpoint protein PD-L1 (programmed cell death-ligand1) [10,11]. Also Clock as a member of histone acetyltransferases, controls acetylation of histone 4 required for repair of DNA double strand breaks thanks to several repair genes such as ERCC1 (excision repair cross-complementing group 1) or API (activator protein 1) [12]; its expression is associated with cisplatin resistance [12,13].

Circadian variation in pharmaco-kinetics (PK) has been evidenced in rodents and later in humans for all drugs routinely used in LC patients, i.e. pyrimidine derivatives, anthracyclines, vinca-alkaloids (vinorelbine), topo-isomerase inhibitors, taxanes, platinum derivatives, gemcitabine and other antimetabolites [2,3,14,15]. Also chronotolerance and even chronoefficacy have been observed in rodent studies long time ago for any chemotherapy agents active in NSCLC [2,3,14,15]. Diurnal varying pharmacokinetics of erlotinib (a largely used TKI - tyrosine kinase inhibitor for treating human NSCLC)

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have also been reported in Lewis Lung and in NSCLC-xenografts tumor-bearing mice [16,17]. Chronotolerance was also reported in 3 different randomized studies in chemotherapy naive advanced NSCLC patients (18,19). An overall excellent therapeutic index was observed with an infusional chemotherapy for 5 days, with sinusoidal varying administration of 5-fluorouracil and carboplatin with the best schedule (peak of 5FU at 4 am; peak of carboplatin at 4pm) [18,19].

Altered circadian rhythmicity of cortisol, TRH, TSH and GH serum level and all lymphocyte subsets (except CD4) related to the advancing stage of disease as well as a melatonin/cortisol ratio was evidenced in LC patients [20,21]. Circadian time structure like that of control normal subjects seems to be an independent prognostic factor, in advanced breast or colon and also in lung cancer patients [22,23]. Circadian rest-activity rhythms as gauged by actometry have shown that circadian destructors measurements were correlated with Quality of Life (QOL), fatigue, altered moods and severe disturbances of daily sleep-activity cycles [24,25]. As a matter of fact, in NSCLC, only a few studies dealt with considerations on temporal dimension for drug-delivery: only one limited study has observed better outcome of patients with a circadian sequential schedule; 3 others showed differences in drug dose intensities and /or toxicity but with no evident clinical benefit [18,19]. Lissoni and al observed improvement of tumor outcome (response rate; one year survival,...) and QOL by associating to standard cisplatin-based chemotherapy, melatonin and sometimes interleukin-2 [26]. The same observation was provided by Hrushesky's group in a randomized blinded trial on advanced NSCLC patients receiving chemotherapy with etoposide and cisplatin together with melatonin or placebo: those patients receiving melatonin during the evening enjoyed higher response rates (29 vs 8-11%) and longer survival in multivariate analysis (personal communication). According to 2 recent meta-analyses, the administration of melatonin reduces the relative risk of death at one year by an average of 37%, doubles the frequency of complete response and reduces the prevalence and/or severity of chemotherapy induced nausea/vomiting, hypotension and hematological toxicity [27,28]. Thus some authors consider melatonin as a probable effective treatment for human NSCLC [27,28]. In fact, outside its circadian rhythms re-synchronizing properties, melatonin may prevent tumor metastasis via inducing apoptosis processes and restraining the autonomous cell proliferation. Moreover, it inhibits the progression of tumors due to its oncostatic, pro-oxidant and anti-inflammatory effects [27,28].

During the last decade, the management of NSCLC has evolved [29,30]. Platinum-based chemotherapy remains the standard front-line in treatment of advanced unresectable NSCLC in which cisplatin or carboplatin are combined with another chemotherapeutic agent such as taxanes, pemetrexed or gemcitabine. However results in terms of tumour outcome remained stable over time! [31]. Thus, progresses confirmed by positive phase III trials, came from targeted and immunotherapeutic biological approaches [29,30]. Targeted therapies against EGFR mutations and anaplastic lymphoma kinase (ALK) gene re-arrangement have improved the survival in the small proportion of patients whose tumors were expressing these molecular abnormalities [29]. Also recent development and success of immune check-point inhibition programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have opened new pavements for fruitful research [30,31]. Unfortunately to the best of our knowledge, despite precise theoretical observations depicted above related to circadian expression, both on targets of TKI-inhibitors, EGF-R blockers, anti-angiogenic agents or

/ on immune active-agents (lymphoid system; PD1; PDL1), by now no study has been launched taking into account any chronobiological considerations!! However these knowledges would bring hope to still improve overall tumor outcome by optimizing 'classical' therapeutic index of medical therapies but also circadian host rhythmicity by acting on the central clock (ie by TKI administration) and/or molecular machinery (receptors; various enzymatic pathways; DNA metabolism and repairing; immunology pathways.....).

The potential role of melatonin as resynchronizing agent and as a potentially active antitumour agent warrants also further evaluations.

Source

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