Published in final edited form as:

Future Oncol. 2012 November ; 8(11): 1401–1406. doi:10.2217/fon.12.126.

Personalized therapy for metastatic melanoma: could timing be everything?

Roxana S Dronca^{1,*}, Alexey A Leontovich², Wendy K Nevala³, and Svetomir N Markovic^{1,3,4}

¹Department of Medical Oncology, Mayo Clinic, Rochester, MN, USA

²Department of Health Science Research and Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

³Department of Immunology, Mayo Clinic, Rochester, MN, USA

⁴Department of Hematology, Mayo Clinic, Rochester, MN, USA

Abstract

There is ample evidence that immune-related processes in humans are under temporal regulation. The circadian variation of humoral and cellular immunity is well documented and appears to be hormonally modulated via the hypothalamic–pituitary–adrenal axis. In advanced melanoma, it has recently been demonstrated that systemic immunity is repolarized toward a global state of chronic inflammation (Th2 dominance) and appears to be governed by infradian biorhythms of cytokines and immune cell subsets, which extend beyond the 24-h circadian variability reported in healthy volunteers. It is suggested that synchronizing administration of lymphodepleting chemotherapy (temozolomide) with these endogenous (individualized) immune dynamics (biorhythms) in patients with advanced/metastatic melanoma improves clinical outcomes compared with temozolomide used in a conventional ‘random delivery’ fashion.

Keywords

biorhythms; cancer; chemotherapy; cytokine; immunity; infradian; melanoma

The dramatic rise in cancer-care cost in the USA in the last decade has been attributed to increases in both the cost of care [1] and the cost of therapy [2]. It is currently estimated that newly developed drugs account for more than 70% of anticancer drug sales with most such drugs priced at US\$5000 per month or more [3]. Therefore, identification of more efficient

© 2012 Future Medicine Ltd

*Author for correspondence: dronca.roxana@mayo.edu.

For reprint orders, please contact: reprints@futuremedicine.com

Disclaimer

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Financial & competing interests disclosure

This publication was made possible by CTSA Grant Number KL2TR000136-07 from the National Center for Advancing Translational Sciences (NCATS), a component of the NIH. This research has also been supported in part by the Mayo Clinic Foundation and by Merck Oncology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

means of utilizing existing or old agents will likely have a positive impact not only on patient outcomes, but also on the current economic climate of healthcare. One such approach involves stimulation of endogenous anticancer immunity as a means of enhancing the effectiveness of conventional anticancer therapies. Many cytotoxic drugs and targeted agents have been shown to have additional effects on the immune system [4], which are often unrecognized, in addition to their direct effects on cancer cells. For instance, the chemotherapeutic agent paclitaxel has been found to have additional immune modulatory properties when administered to patients with non-small-cell lung cancer, through differential destruction of Treg and suppression of Treg inhibitory function, while preserving effector T cells [5]. Similarly, metronomic administration of low-dose temozolomide (TMZ) was associated with a reduction in the number and the inhibitory function of circulatory Tregs in a rat glioma model [6]. These effects are relevant, as strategies that selectively ablate Tregs have been advocated in the clinic in order to improve the antitumor activity of endogenously arising tumor-reactive T cells and enhance the response to cancer therapy. Recently, adoptive transfer studies have definitively demonstrated that ‘resetting’ (lymphodepleting) endogenous immune homeostasis may be a prerequisite for the therapeutic success of infused, *in vitro*-activated, tumor-specific cytotoxic T cells [7,8]. These strategies imply that the immune dysfunction in patients with cancer is established and static, requiring depletion. On the contrary, animal studies suggest that this process is dynamic, and that Tregs (and possibly other immunosuppressive elements) undergo synchronous clonal expansions at particular times post-viral or -tumor inoculation [9]; they then act to suppress the activity of effector T cells undergoing clonal expansion some days prior [10,11]. Indeed, in animal models cytotoxic chemotherapy administration at defined times post-antigen challenge has resulted in ‘unblocked’ immune responses leading to prevention of murine AIDS progression [9] or immunologically mediated regression of advanced lymphomas [12].

Antitumor immunity in metastatic melanoma is a dynamic process

Accumulating evidence suggests that similar dynamics operate the antitumor immune response in humans. Moreover, these dynamics could be therapeutically relevant in cancer, similarly to the way in which the discovery of the episodic/dynamic nature of hormonal secretion brought forth critical insights into the development of effective endocrine therapy (i.e., pulsatile/rhythmic secretion and replacement of hormones). In metastatic melanoma the authors have recently shown that, while systemic immunity is globally repolarized towards a state of chronic inflammation (Th2 dominance) [13], this tolerant state is not a static phenomenon but fluctuates over time between phases of immune up- and downregulation [14]. This complex and dynamic equilibrium between the tumor and the host immune system seems to result in alternating phases of tumor rejection followed by inhibition of the immune advances by the tumor. At first glance, this is no different than the biphasic immunological events of normal pregnancy, where blastocyst implantation creates endometrial inflammation, followed by the establishment of angiogenesis and maternal tolerance required for adequate placentation and fetal growth, and then restoration of a Th1 state at parturition [15]. Analogous to the transient immunological tolerance of placentation, the abnormalities of immune competence in advanced cancer seem to manifest as long as

there is an active or clinically detectable (advanced) malignancy, as a similar Th2 bias has not been identified in patients with completely surgically removed early stage melanoma or in healthy volunteers [13].

As one considers these complex immune responses within a person with cancer, it becomes clear that understanding the dynamics of anti-tumor immunomodulation at a systemic level is a crucial step if new therapies, especially immunotherapies, are to be successful in the clinic. Therefore, merely attempting to boost unknown pre-existing endogenous immunity may fail due to our limited understanding of the mechanisms that govern the Th1/Th2 equilibrium and the kinetics of the immune response in cancer. Such therapies may only augment the pre-existing state of Th2-biased ‘abnormal’ immune homeostasis if applied in the ‘down’ phase of the antitumor immune response. This may explain the varied levels of ‘responsiveness’ to immune modulating drugs (e.g., ipilimumab therapy in metastatic melanoma), with only a minority of patients achieving durable responses [16]. While numerous studies have previously focused on immune responses that develop over weeks to months, the authors have recently shown that systemic immunity in patients with metastatic melanoma is a dynamic process that fluctuates over a much shorter time period, governed by infradian immune biorhythms of both immune cell subpopulations and cytokines (Figure 1A & B). Other groups have noted similar infradian immune patterns, such as cyclical variations in CRP levels, a biomarker of inflammation in patients with melanoma and other advanced cancers, with a reproducible periodicity of 6–7 days [17].

Evidence exists that many other immune-related processes in humans are under temporal regulation. For instance, the circadian variation of humoral and cellular immunity is well documented and appears to be hormonally modulated [18–20]. Daily rhythms exist in the immune system similarly to biological 24-h clock (circadian) rhythms identified in most physiological and behavioral variables, such as body temperature, sleep or hormonal secretion. As early as the 1960s, Halberg *et al.* showed that there is a pronounced circadian variation in the susceptibility to lethal doses of bacterial lipopolysaccharide endotoxin and TNF in rodents, with higher mortality occurring during the day [21]. Later studies in humans suggested a diurnal rhythmicity in cytokine production [22], as well as pronounced circadian rhythms of immune cell subpopulations, which are hormonally modulated via the hypothalamic–pituitary–adrenal axis [20]. Several of the observed variations were so large [20], that some researchers questioned whether the normal range for these variables should specify a time for collection (similar to hormone measurements in endocrinology), if the normal range is to be at all meaningful [23]. Previously mentioned studies suggest that the circadian rhythms of various cytokines and immune cell subpopulations differ considerably with respect to peak times and amplitudes, with some immunological variables showing acrophases during the night, while others peak during the day. Therefore, in order to study the global infradian pattern of fluctuation of various immunological variables and to minimize the contribution of circadian variation, in the authors’ studies, blood samples were consistently collected at approximately the same time of day (between 0800 h and 1000 h).

Synchronization of cancer therapy with infradian immune dynamics in metastatic melanoma

Biorhythm-based delivery of anticancer therapy (chronotherapy) has been an area of great interest in oncology for many years [24,25]. The hypothesis was that administration of chemotherapy at the ‘right time of day’ could take advantage of asynchronies in cell proliferation between normal and malignant cells, thereby minimizing chemotherapy toxicity and increasing treatment efficacy. Indeed, most such trials showed a difference in tolerability in favor of chronotherapy; however, the two largest randomized studies [26,27] did not show a benefit in treatment efficacy. Therefore, chronotherapy has remained an experimental approach with limited influence on current treatment guidelines. As previously reviewed [14], a potential explanation for the unrealized potential of cancer chronotherapy, as employed in the past, may lie in the complexity of biological systems and the time-dependent variation of the immune system’s response to malignancy, which seems to extend beyond circadian rhythms.

In the authors’ previously published pilot study in advanced melanoma (M057f) [14], it was noted that these infradian immune dynamics are highly individualized across patients and also seemed to be therapeutically relevant with respect to timing of therapy administration and clinical outcomes. It was shown that administration of lymphodepleting cytotoxic chemotherapy (TMZ) in a unique phase of the antitumor immune response cycle favors active immunity over tolerance, probably contributing to the observed clinical benefit beyond that of historical controls randomly treated with TMZ [14,28]. The initial studies utilized timed delivery of chemotherapy based on a single empirically selected biomarker of immune activation (CRP). Although relevant, CRP (or any single longitudinally assessed biomarker, for that reason) is probably inadequate for the global analysis of systemic immune changes over time in response to cancer. Indeed, our improved understanding of immune dynamics in advanced melanoma has since led to an increased appreciation of the complexity of this biological phenomenon resulting from the dynamic interaction of multiple fluctuating immunological factors. Moreover, a retrospective analysis of time-dependent profiles of 51 longitudinally measured immune biomarkers (in addition to CRP) in patients treated in the M057f trial suggested that application of therapy when the sum of the relative concentration/cell frequency and the first derivative of a given variable has a maximum value is associated with an improved clinical outcome [14]. Albeit intriguing and suggestive, these pilot data can only be interpreted as hypothesis generating due primarily to the small number of patients and specimens studied. A larger Phase II validation trial utilizing identification of periodical patterns in patients with metastatic melanoma scheduled to undergo TMZ chemotherapy is currently underway (NCT01328535) [101]. In this trial, patients with metastatic melanoma eligible for TMZ chemotherapy are scheduled to undergo immunological monitoring consisting of ten daily peripheral blood collections (10 ml) prior to initiation of treatment, for measurement of dynamic changes in immune cell subsets and plasma cytokines. Since the authors’ initial trial, improved understanding of immune dynamics in metastatic melanoma led to the exploration of more stable biorhythms of a larger number of immune parameters (such as IL-12p70, IL-1RA, IL-9, IL-10, IL-13, IL-15, IL-17, G-CSF, VEGF, Th1 cells [CD4⁺TIM3⁺], Th2 cells [CD4⁺294⁺], Tregs

[CD4⁺25⁺FoxP3⁺], type 1 dendritic cells [CD11c⁺HLA-DR⁺], type 2 dendritic cells [CD123⁺HLA-DR⁺], type 1 macrophages [CD14⁺197⁺] and type 2 macrophages [CD14⁺206⁺]) deemed critical for the construction of the personalized immune biorhythms. Time-dependent profiles for each immune variable are computed utilizing the previously described method for temporal pattern analysis [14], as well as coherence function analysis [29]. The global assessment of the immune system at a specific time point in the immune response cycle relies on modified K-means clustering algorithm, which computes time points when the sum has the maximum value for each variable, performs clustering for all possible combinations, and computes the date when the sum of indices for all clustered profiles is maximal. Therefore, internal relationships between different immune biomarkers (cell subsets and cytokines) across different phases of the immune system are analyzed against each other and the optimal time (day) for initiation of treatment is prospectively predicted by the summary biorhythm of these measured immune parameters in each individual patient (Figure 2).

Biorhythms & cancer

Temporal variations in the immune response to cancer have not been extensively studied. However, they likely have significant implications in the immune monitoring, pathogenesis, and treatment of malignant diseases. Epidemiologic studies have shown that individuals whose circadian rhythms are chronically disrupted (e.g., night shift workers) are more prone to developing cancer [30]. Likewise, cancer growth may affect biorhythms in the host [31–33]. In metastatic melanoma, the authors have found that patients with a disorganized (nonperiodical) immune response experienced a decreased disease-free survival relative to those in whom the measured immune parameters followed a predictable biorhythm [14]. It is possible that timed delivery of chemotherapy in that context may have allowed for a more precise therapeutic intervention leading to putative depletion of immune downregulatory elements in favor of effective antitumor immunity.

The mechanisms governing these immune biorhythms in patients with advanced melanoma are unknown. These rhythmic oscillations of systemic immunity between states of up- and downregulation could be a simple product of tumor antigen exposure, or other regulatory influences such as neuroendocrine modulation may play a role. Natural fluctuations are intrinsic characteristics of hormonal secretion and action, and hormonal modulation of circadian humoral and cellular immune variation is well documented [20]. In addition, evidence for hormonal involvement in cancers other than breast and prostate (including melanoma) is accumulating [34–36]. While most studies have focused on sex-steroid receptor expression in nonclassical hormone-sensitive tumors, relatively little is known on the immunomodulatory effects of hormones in cancer, despite mounting evidence that a variety of (neuro)hormones influence immune functions [19,20,37,38]. Without a doubt, elucidation of the dynamic system integration between the immune endocrine and nervous systems in response to cancer will advance our ability to administer personalized and cost-effective treatment, namely administering the right combination of drugs at the right time for each individual patient.

Future perspective

Anticancer agents with different mechanisms of action have been noted to cause significant or even complete responses in a minority of patients with advanced malignancies in a ‘random’ and unpredictable fashion [39]. The individual dynamics of host antitumor immune modulation are increasingly recognized as being intricately associated with the response to immunotherapy, and also conventional chemotherapeutic agents. Therefore, the development of a reproducible and clinically feasible method of predicting optimal times for therapy delivery based on personalized antitumor immune dynamics may enhance the effectiveness of such therapies by stimulation of endogenous anticancer immunity in addition to cytotoxic cancer cell damage, and increase the success from already available therapeutics at diminished cost. Additionally, expanding our understanding of the ‘actuators’ and ‘modulators’ of infradian immune responses will likely be relevant to a broad range of clinical conditions, including other cancer therapies, antimicrobial immunization in adults, fertility and autoimmune diseases, among others.

References

Papers of special note have been highlighted as:

■ of interest

1. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst.* 2008; 100(9):630–641. [PubMed: 18445825]
- 2■. Elkin EB, Bach PB. Cancer’s next frontier: addressing high and increasing costs. *JAMA.* 2010; 303(11):1086–1087. Reviews the trends and reasons for the overall increase in spending for cancer care in the last two decades in the USA. [PubMed: 20233828]
3. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med.* 2011; 364(21):2060–2065. [PubMed: 21612477]
4. Zitvogel L, Apetoh L, Ghiringhelli F, Andre F, Tesniere A, Kroemer G. The anticancer immune response: indispensable for therapeutic success? *J Clin Invest.* 2008; 118(6):1991–2001. [PubMed: 18523649]
- 5■. Zhang L, Dermawan K, Jin M, et al. Differential impairment of regulatory T cells rather than effector T cells by paclitaxel-based chemotherapy. *Clin Immunol.* 2008; 129(2):219–229. *In vitro* study highlighting the immunomodulatory properties of the chemotherapeutic agent paclitaxel. [PubMed: 18771959]
6. Banissi C, Ghiringhelli F, Chen L, Carpentier AF. Treg depletion with a low-dose metronomic temozolomide regimen in a rat glioma model. *Cancer Immunol Immunother.* 2009; 58(10):1627–1634. [PubMed: 19221744]
7. Dudley ME, Yang JC, Sherry R, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol.* 2008; 26(32):5233–5239. [PubMed: 18809613]
8. Hong JJ, Rosenberg SA, Dudley ME, et al. Successful treatment of melanoma brain metastases with adoptive cell therapy. *Clin Cancer Res.* 2010; 16(19):4892–4898. [PubMed: 20719934]
- 9■. Beilharz MW, Sammels LM, Paun A, et al. Timed ablation of regulatory CD4⁺ T cells can prevent murine AIDS progression. *J Immunol.* 2004; 172(8):4917–4925. Seminal paper describing the immunomodulatory and therapeutic effects of timed chemotherapy administration in murine AIDS. [PubMed: 15067071]
10. North RJ, Bursucker I. Generation and decay of the immune response to a progressive fibrosarcoma. I Ly-1+2- suppressor T cells down-regulate the generation of Ly-1-2+ effector T cells. *J Exp Med.* 1984; 159(5):1295–1311. [PubMed: 6232335]

11. Heimberger AB, Sun W, Hussain SF, et al. Immunological responses in a patient with glioblastoma multiforme treated with sequential courses of temozolomide and immunotherapy: case study. *Neuro Oncol.* 2008; 10(1):98–103. [PubMed: 18079360]
12. North RJ, Awwad M. Elimination of cycling CD4⁺ suppressor T cells with an anti-mitotic drug releases non-cycling CD8⁺ T cells to cause regression of an advanced lymphoma. *Immunology.* 1990; 71(1):90–95. [PubMed: 2145216]
13. Nevala WK, Vachon CM, Leontovich AA, Scott CG, Thompson MA, Markovic SN. Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma. *Clin Cancer Res.* 2009; 15(6):1931–1939. Seminal paper describing tumor-associated immune suppression in patients with advanced melanoma driven, at least in part, by VEGF overproduction by malignant tumors. [PubMed: 19240164]
14. Leontovich AA, Dronca RS, Suman VJ, et al. Fluctuation of systemic immunity in melanoma and implications for timing of therapy. *Front Biosci (Elite Ed).* 2012; 4:958–975. The authors' original manuscript describing potential therapeutic implications of temporal variations in the immune response to advanced melanoma. [PubMed: 22201928]
15. Holtan SG, Creedon DJ. Mother knows best: lessons from fetomaternal tolerance applied to cancer immunity. *Front Biosci (Schol Ed).* 2011; 3:1533–1540. Manuscript highlighting similarities between the mechanisms of fetomaternal tolerance in normal human pregnancy and those of advanced melanoma. [PubMed: 21622288]
16. Hodi FS, O'day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010; 363(8):711–723. [PubMed: 20525992]
17. Coventry BJ, Ashdown ML, Quinn MA, Markovic SN, Yatomi-Clarke SL, Robinson AP. CRP identifies homeostatic immune oscillations in cancer patients: a potential treatment targeting tool? *J Transl Med.* 2009; 7:102. [PubMed: 19948067]
18. Mazzocchi G, Sothorn RB, De Cata A, et al. A timetable of 24-hour patterns for human lymphocyte subpopulations. *J Biol Regul Homeost Agents.* 2011; 25(3):387–395. [PubMed: 22023763]
19. Mazzocchi G, De Cata A, Greco A, Carughi S, Giuliani F, Tarquini R. Circadian rhythmicity of lymphocyte subpopulations and relationship with neuro-endocrine system. *J Biol Regul Homeost Agents.* 2010; 24(3):341–350. Manuscript describing the circadian variation of human lymphocyte subpopulations and their timed relationships with neuroendocrine hormones. [PubMed: 20846482]
20. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. *Blood.* 2009; 113(21):5134–5143. [PubMed: 19293427]
21. Halberg F, Johnson EA, Brown BW, Bittner JJ. Susceptibility rhythm to *E coli* endotoxin and bioassay. *Proc Soc Exp Biol Med.* 1960; 103:142–144. [PubMed: 14398944]
22. Petrovsky N, Harrison LC. Diurnal rhythmicity of human cytokine production: a dynamic disequilibrium in T helper cell type 1/T helper cell type 2 balance? *J Immunol.* 1997; 158(11): 5163–5168. Study describing circadian variation of humoral immunity. [PubMed: 9164932]
23. Knapp MS, Pownall R. Lymphocytes are rhythmic: is this important? *Br Med J (Clin Res Ed).* 1984; 289(6455):1328–1330.
24. Hrushesky WJ. Circadian timing of cancer chemotherapy. *Science.* 1985; 228(4695):73–75. [PubMed: 3883493]
25. Hrushesky WJ, Bjarnason GA. Circadian cancer therapy. *J Clin Oncol.* 1993; 11(7):1403–1417. [PubMed: 8315438]
26. Price TJ, Ross PJ, Hickish T, et al. Phase III study of mitomycin-C with protracted venous infusion or circadian-timed infusion of 5-fluorouracil in advanced colorectal carcinoma. *Clin Colorectal Cancer.* 2004; 3(4):235–242. [PubMed: 15025796]
27. Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2000; 18(1):136–147. [PubMed: 10623704]

28. Middleton MR, Grob JJ, Aaronson N, et al. Randomized Phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000; 18(1):158–166. [PubMed: 10623706]
29. Lingstrom J, Kokko H, Ranta E. Detecting periodicity in short and noisy time series data. *Oikos*. 1997; 78:406–410.
30. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*. 2001; 93(20):1563–1568. [PubMed: 11604480]
31. Mormont MC, Langouet AM, Claustrat B, et al. Marker rhythms of circadian system function: a study of patients with metastatic colorectal cancer and good performance status. *Chronobiol Int*. 2002; 19(1):141–155. [PubMed: 11962672]
32. Mazzocchi G, Tarquini R, Durfort T, Francois JC. Chronodisruption in lung cancer and possible therapeutic approaches. *Biomed Pharmacother*. 2011; 65(7):500–508. [PubMed: 21993005]
33. Mazzocchi G, Vendemiale G, De Cata A, Carughi S, Tarquini R. Altered time structure of neuro-endocrine-immune system function in lung cancer patients. *BMC Cancer*. 2010; 10:314. [PubMed: 20565977]
34. Folkard EJ, Dowsett M. Influence of sex hormones on cancer progression. *J Clin Oncol*. 2010; 28(26):4038–4044. [PubMed: 20644089]
35. De Giorgi V, Mavilia C, Massi D, et al. Estrogen receptor expression in cutaneous melanoma: a real-time reverse transcriptase-polymerase chain reaction and immunohistochemical study. *Arch Dermatol*. 2009; 145(1):30–36. [PubMed: 19153340]
36. Mervic L, Leiter U, Meier F, et al. Sex differences in survival of cutaneous melanoma are age dependent: an analysis of 7338 patients. *Melanoma Res*. 2011; 21(3):244–252. [PubMed: 21540649]
37. Lee S, Kim J, Jang B, et al. Fluctuation of peripheral blood T, B, and NK cells during a menstrual cycle of normal healthy women. *J Immunol*. 2010; 185(1):756–762. [PubMed: 20530263]
38. Maret A, Coudert JD, Garidou L, et al. Estradiol enhances primary antigen-specific CD4 T cell responses and Th1 development *in vivo* Essential role of estrogen receptor α expression in hematopoietic cells. *Eur J Immunol*. 2003; 33(2):512–521. [PubMed: 12645950]
39. Coventry BJ, Ashdown ML. Complete clinical responses to cancer therapy caused by multiple divergent approaches: a repeating theme lost in translation. *Cancer Manag Res*. 2012; 4:137–149. Critically reviews issues and caveats in responsiveness of malignant diseases to therapeutic agents with various mechanisms of action. [PubMed: 22740774]

Website

101. Individualized Temozolomide in Treating Patients With Stage IV Melanoma That Cannot Be Removed By Surgery. <http://clinicaltrials.gov/ct2/show/NCT01328535?term=melanoma+and+temozolomide+and+mayo&rank=1>

Executive summary

Antitumor immunity in metastatic melanoma is a dynamic process

- Systemic immunity in metastatic melanoma is globally repolarized towards a state of chronic inflammation (Th2 dominance).
- In patients with active or clinically detectable (advanced) melanoma, antitumor immune dynamics follow predictable infradian rhythms of both immune cells and cytokines.

Synchronization of cancer therapy with infradian immune dynamics in metastatic melanoma

- Timed therapy administration in patients with advanced melanoma depends upon a complex dynamic interaction between multiple fluctuating immunological factors.
- Single time-point studies are likely to be inadequate and insufficient for assessing the state of immune homeostasis in patients with cancer and for guiding therapy.

Biorhythms & cancer

- The mechanisms governing the immune biorhythms in patients with advanced melanoma are unknown but neuroendocrine modulation of immunity may play a role in addition to tumor antigen exposure.

Figure 1.

Example of infradian biorhythms of selected cytokines (A) and immune cells (B) in a patient with metastatic melanoma.

Figure 2. Clustering of immunological profiles for prediction of optimal time of chemotherapy delivery in a patient with metastatic melanoma

Bottom panel shows extrapolated relative concentration of selected cytokines; red line shows the summary biorhythm resulting from clustering of immune variables.