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CANCER CHRONOMICS II

Origins of timing cancer treatment

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This paper is a memorial to Mikhail Victorovich Berezkin (MVB) (10 April 1940 – 16 January 2005), an enthusiastic advocate of chrono-oncology. It illustrates his early dose- and circadian time-response curves, limited as yet by a 4-timepoint approach, provides a list of his publications, and offers a succinct overview of individualized marker rhythm-guided oncotherapy.

Key words: chronotherapy, circadian, cosinor, cyclophosphamide, dose response curve, vincristine

Mikhail Victorovich Berezkin, in the laboratory of Dr. Elena Vasilievna Syutkina.

INTRODUCTION

Mikhail Victorovich Berezkin (MVB) is no longer with us, but his legacy, the timed treatment of cancer, remains a challenge for generations to come. He will be remembered in particular by those who behind the iron curtain participated in symposia on chronobiology and chronomedicine, held in Halle an der Saale by investigators from East Germany with their colleagues

†*Before his untimely death, Mikhail Victorovich Berezkin sent his data to Minnesota where they were analyzed by the senior author. This paper also contains references to his various original publications and to a few of his Russian colleagues' contributions.*

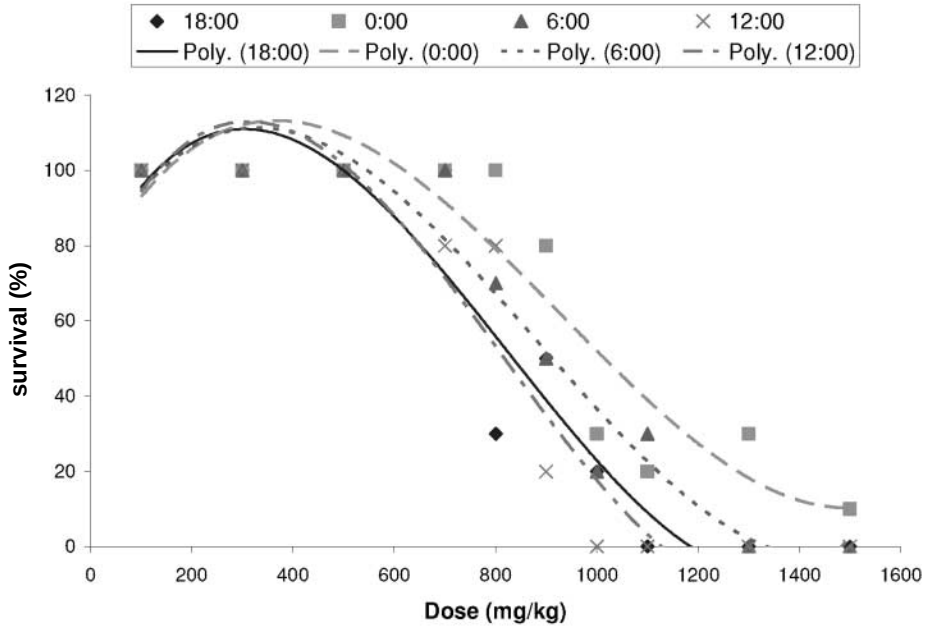


Figure 1. Percentage of survivors among 10 mice/group/day after the injection of graded doses of cyclophosphamide. Original data of M.V. Berezkin. © Halberg.

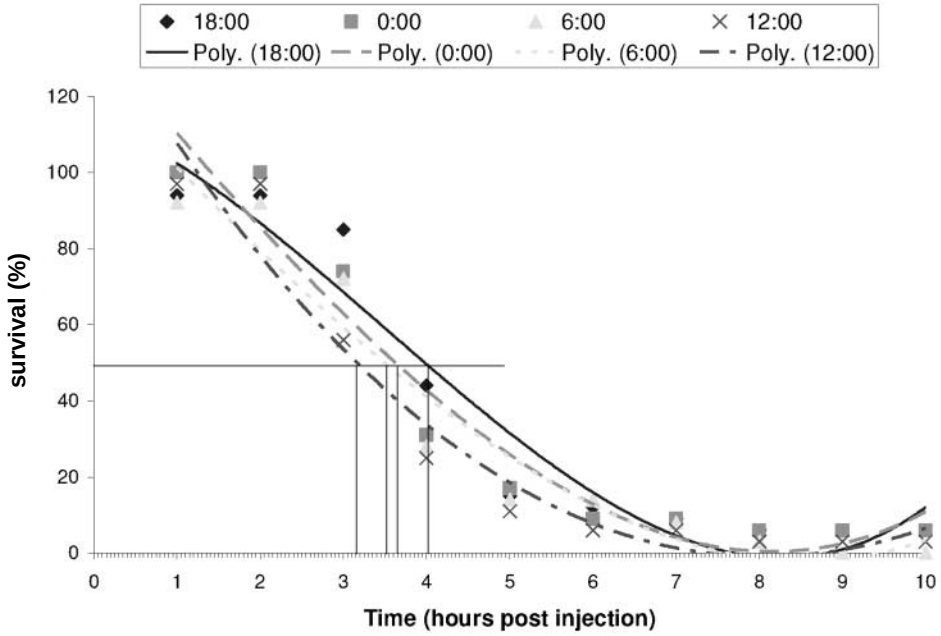
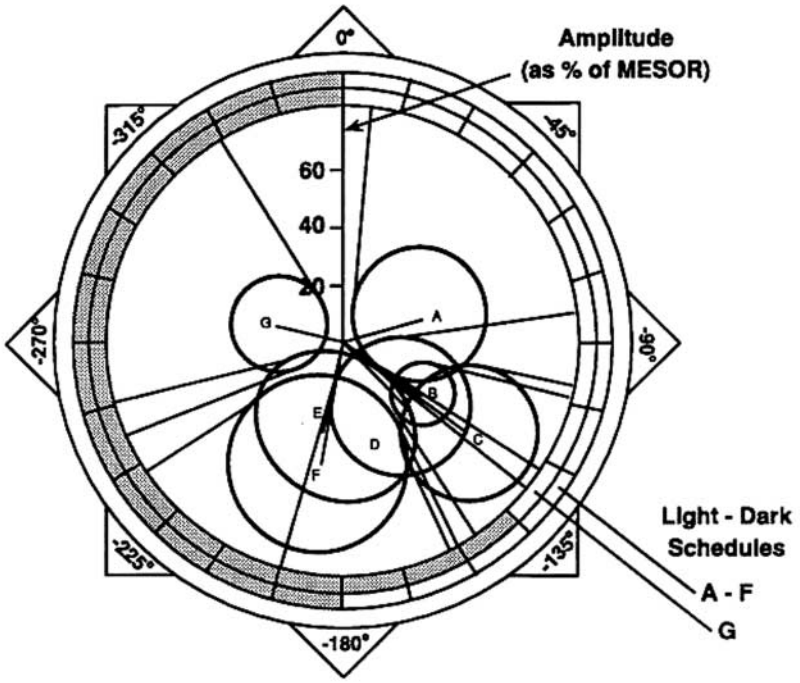


Figure 2. Percentage of survivors of 36 mice receiving 900 mg/kg cyclophosphamide at one of 4 clock-hours 6 hours apart. Original data of M.V. Berezkin. © Halberg.

from the Soviet Union. There, Mikhail Victorovich was Mr. Cancer Chronotherapy, based on his work with cyclophosphamide and vincristine (references 33 and 36 in his bibliography in Appendix), studies which he continued subsequently at a stomatological institute in Moscow, where he mobilized the press to help disseminate information about chronobiology. Contributions by other Russian chrono-oncologists are noted. Tatiana P. Ryabykh discovered circaseptans in oncology and explored the role of the cosmos (1, 2).

CIRCADIAN RHYTHMICITY IN MURINE TOLERANCE OF ANTICANCER DRUGS, EVALUATED FROM DATA ON PERCENT SURVIVAL AS A FUNCTION OF TREATMENT TIMING



For ø in Degrees: 360° ≡ 24 Hours
0° = Onset of Daily Light Span

Single Cosinor [1]

Key to Ellipses	Drug Tested [2]	N Studies	Total N Animals	P [3]	% Rhythm [4]	Amplitude [5] (95% C.L.)	Acrophase, ø
A	Daunomycin	4	690	.021	31	29 (4, 54)	-67° (-8, -127)
B	Adriamycin	6	1,072	< .001	60	33 (21, 45)	-124° (-103, -146)
C	ARA-C	2	480	< .001	76	56 (32, 80)	-126° (-100, -151)
D	Melphalan	4	456	.015	33	31 (18, 57)	-138° (-83, -193)
E	Cyclophosphamide	6	826	.027	18	32 (3, 60)	-185° (-123, -255)
F	Vincristine	2	239	.007	67	46 (15, 76)	-193° (-150, -235)
G	DDPt	11	1,503	.002	18	24 (8, 39)	-289° (-246, -331)

1 - Results from least-squares fitting of 24-h cosine curve; 2 - i.p., all drugs, except DDPt, tested in mice kept in LD 12:12, DDPt tested in rats kept in LD 8:16; 3 - P from test of zero-amplitude hypothesis; 4 - % rhythm = % of total variability attributable to fitted cosine; 5 - Expressed as % of MESOR

Figure 3. Different times of optimal resistance to the toxicity of a few anticancer drugs. Polar display of cosinor results. Original data of the Minnesotan authors. © Halberg.

Mikhail Arkadyevich Blank, both a basic and clinical leader in oncology, has also turned to the study of physical environmental effects (3, 4), in the tradition of Chizhevsky (5) and others (6, 7). Furthermore, Blank was first to document, by inferential statistics, the effects of the cosmos upon clinical cancer therapy by radiation or by drugs (3, 4). Like Ryabykh, he extended the circadian perspective to circaseptans and broader chronomes (time structures, from chronos = time and nomos = rule) (1, 7; cf. 8).

DOSE RESPONSES AND TIME RESPONSES AT DIFFERENT CLOCK-HOURS

We show response curves in relation to the administration of cyclophosphamide or vincristine, based on data from mice presumably kept under natural and artificial lighting, except where continuous artificial light was specified. Treatment was administered at one of four test times, 6 hours apart, at

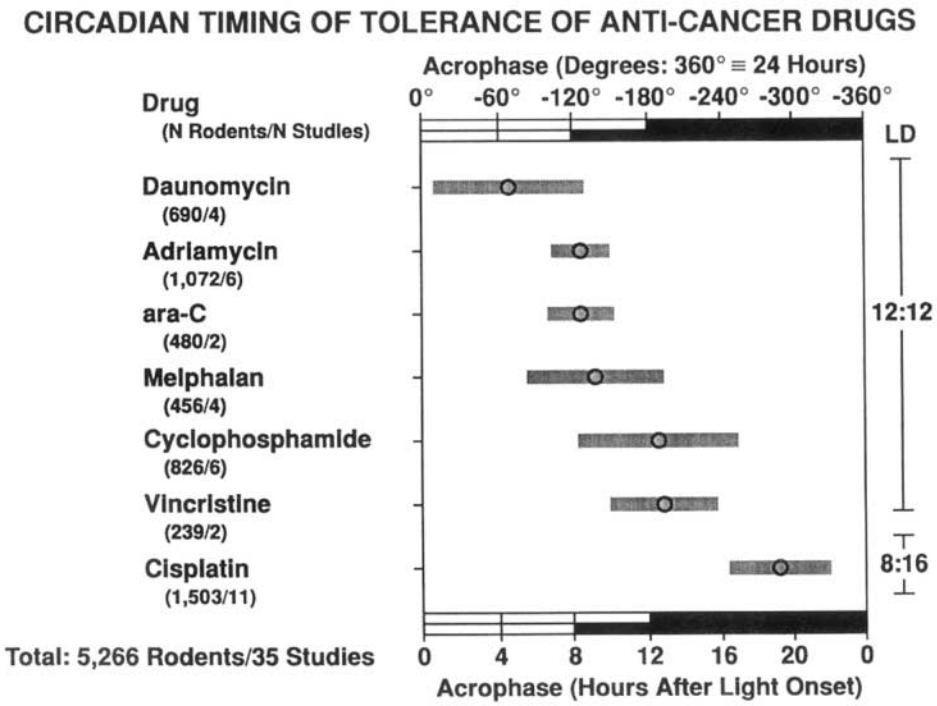


Figure 4. Different times of optimal resistance to the toxicity of a few anticancer drugs. Acrophase chart of cosinor results. Original data of the Minnesotan authors. © Halberg.

18:00, 24:00, 06:00 and 12:00, rather than at the more desirable schedule of 6 test times, 4 hours apart, empirically found to be acceptable (e.g., 9).

In experiment 1, the percentage survival of mice was noted one day after the administration of cyclophosphamide in varying doses, ranging from 100 to 1500 mg/kg, to groups of 10 mice at each dose. In experiments 2, 3 and 4, the percentage survival of a total of 100, 90 or 100 mice was noted at different times after cyclophosphamide injection, ranging from 4 to 48, 24, or 8 hours after injection of a 900 mg/kg dose, respectively. In experiments 1-4, mice were kept in the natural light/dark regimen. In experiment 5, the percentage survival of 36 mice receiving 900 mg/kg cyclophosphamide was recorded at different times after drug administration ranging from 1 to 10 hours, animals being kept in continuous light. In experiment 6, the percentage survival of 10 mice per group was studied three days after the administration of varying doses of vincristine ranging from 2 to 15 mg/kg. In experiments 6-9, the percentage survival of 100, 30, or 38 mice was studied after administration of 2 mg/kg of vincristine at different times after treatment of 1 to 4, 6, or 7 hours, respectively. Mice were kept in natural lighting conditions in experiments 5-8 and in continuous light in experiment 9.

RESULTS

In order to assess any circadian stage-dependence of the administration of cyclophosphamide or vincristine, a third-order polynomial was fitted to the data from each administration time, as illustrated in Figure 1 for experiment 1. From this model, the dose or time corresponding to the inflection point was determined, as well as the dose or time corresponding to 50% mortality (or another fixed percentage mortality in mid-range of the response curves), as illustrated in Figure 2 for the case of experiment 5. For each experiment, these two endpoints together with the four coefficients of the third-order model were fitted with a 24-hour cosine curve by cosinor. Results from similar experiments were further summarized by population-mean cosinor.

In view of the limited 4 timepoints, leaving only a single degree of freedom for the single cosinor fit, statistical significance at the 5% probability level is reached in only 3 cases, namely for the coefficient of the cubic term in experiment 2, and for the inflection point in experiments 2 and 3. In all three cases, the acrophase occurs slightly before midnight. Of interest is the observation that the acrophase tends to cluster around midnight for both the inflection point and the response at a fixed percentage mortality for experi-

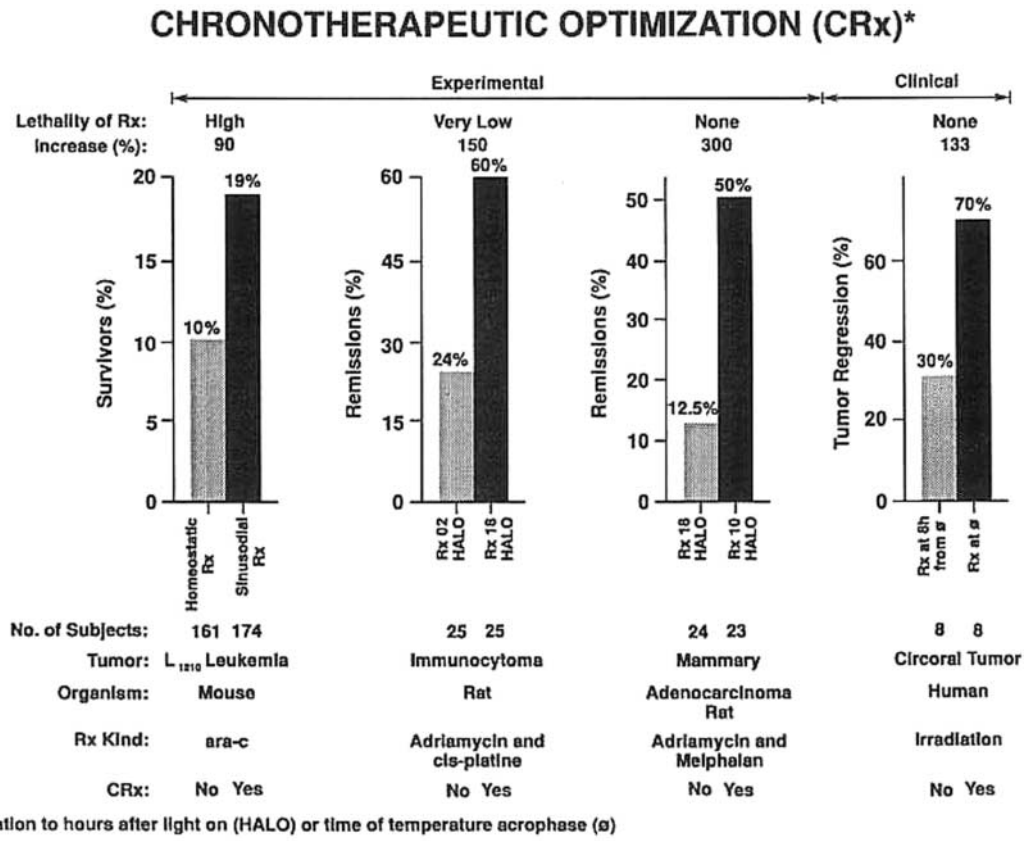


Figure 5. Nearly 100% or larger gain from timing anticancer treatment in Minnesota on rodents and in the clinic, the latter in studies designed with Dr. B.D. Gupta of the Postgraduate Institute for Medical Research in Chandigarh, India. Cancer treatment is chronotherapeutically optimized in experimental animals (in the first 6 columns) and in clinical radiotherapy research in the last 2 columns (cf. also Figure 6). In each pair, the column on the right shows the gain from timing, with the column on the left serving as a reference standard. The last two columns describe clinical outcomes. Original laboratory animal data of Minnesotan authors. © Halberg.

ments 1-4, but deviates from this time in experiment 5, wherein mice were studied in continuous light. Results from a summary by population-mean cosinor of experiments 1-4, with amplitudes equated to one to accommodate different scales, indicate the circadian stage-dependence of susceptibility to cyclophosphamide. For the inflection point, the acrophase occurs about one hour before midnight (P=0.006) and for the response at a fixed percentage mortality, the acrophase occurs about 1.5 hours after midnight (P=0.003). In the case of vincristine, a summary of experiments 6-9 finds that the response at a fixed percentage mortality is circadian stage-dependent (P=0.032), with an acrophase around 08:30. Results are not statistically significant for the inflection point when experiments 6-9 are considered, but after exclusion of experiment 7 including only 4 values to assess the response curve, circadian stage-dependence is statistically significant (P=0.006), with an acrophase around 18:00. Whereas there is a relatively good agreement between the two endpoints for cyclophosphamide, this is not the case for vincristine.

Further experiments would have benefited from including more than 4 timepoints, 6 hours apart. Actually, with 6 timepoints 4 hours apart, a susceptibility rhythm to both cyclophosphamide and vincristine could be established (9-16) and was found to differ among some drugs investigated, as shown in Figures 3 and 4.

CHALLENGE

In all species examined by us, the use of a properly timed (e.g., sinusoidal) drug administration pattern had clear benefits, Figure 5, not only in terms of reduced toxicity, Figures 3 and 4, but overall, as seen by a circadian rhythm in therapeutic results (17), Figure 5. Progress in individualized chronochemotherapy followed (18, 19). In the opinion of a leading clinician who founded the specialty of oncology in the USA

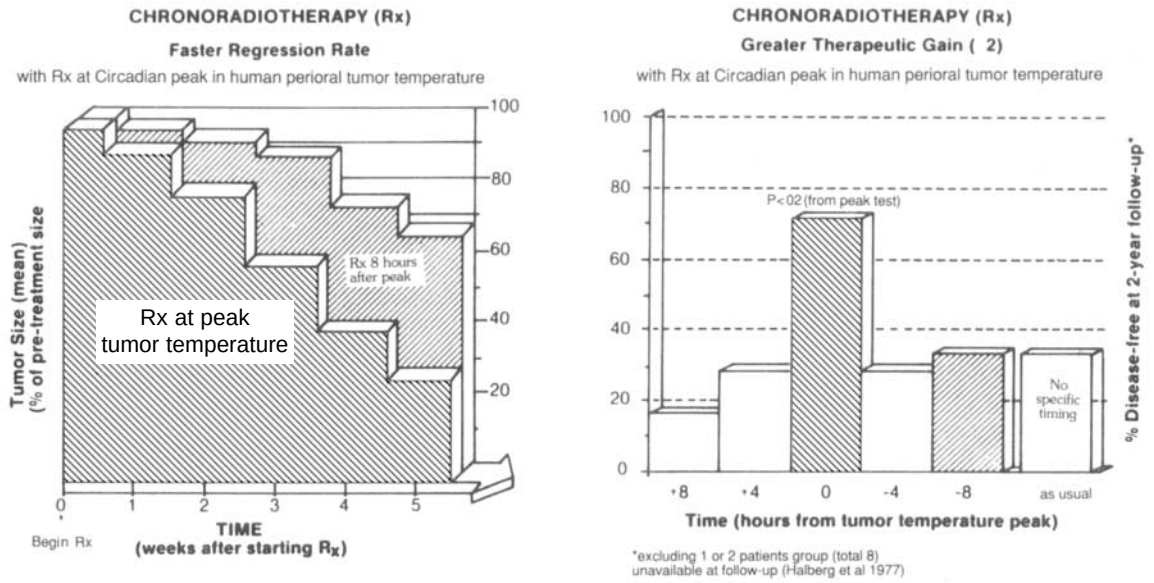


Figure 6. Treatment timing at peak tumor temperature leads to faster tumor regression (left) and to more than doubling of the 24-month survival rate (0 on abscissa, right), as compared to reference groups treated 4 or 8 hours before or after the tumor temperature peak (+8, +4, -4, -8 on abscissa, right) or "as usual" (last column, right) (23). (c) Halberg.

(20), the individualized cancer marker-guided treatment with drugs (18, 19) added a few years to the life of a patient serving as a test pilot for the optimization of cancer chronotherapy by the use of circadian and circaseptan rhythms in cancer markers.

In the absence of marker rhythmometry, the shortcut of chemotherapy by time of day has been a success (21), but not invariably (22; cf. 23). In the long term, there must be no compromise with cancer marker-rhythm-guided individualized timed chemotherapy or, as a second choice, with an attempt to “chronize” the individual patient by setting the desired timing by a drug or non-drug pretreatment, as in the case of synchronization in the experimental animal laboratory by the lighting regimen or by an ACTH-analog. The latter procedure (24) is not validated in the clinic as yet.

In the case of very advanced perioral cancers, marker rhythmometry using the circadian peak of tumor temperature for radiation treatment has doubled the 2-year disease-free survival rate, Figure 6 (25-29). Cancer markers undergo circadian and circaseptan rhythms (bottom of Figure 4 in 29; cf. 30-45). Once the demand for these markers is realized, their prices will be much lower, just as we have seen fountain pens and computers become affordable. Enthusiasts such as Mikhail Victorovich Berezkin are indispensable to take into a clinical routine the lessons from laboratory studies and the self-investigations by equally important “test pilot” patients. MVB’s demonstration of the complementary time- and dose-dependence of anti-cancer drugs was a milestone that must not be forgotten, as were the introduction of sinusoidal drug administration patterns (17) and the documentation of benefit from them in terms of not only prolonged survival but added cures in rodents (46, 47) and the doubling of 2-year disease-free survival rate in humans (25, 26; cf. 28).

SUPPORT

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APPENDIX

Publications by Mikhail Victorovich Berezkin

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