Toward Systems Cancer Chronotherapeutics and its integration into home care.

Francis Lévi, MD, PhD
Toward Systems Cancer Chronotherapeutics and its integration into home care.

Francis Lévi, MD, PhD
Cancer treatments finding the right balance between safety and efficacy

ACTIVITY

Different mechanisms of action and resistance

SAFETY

Acceptable side-effects

• Dose
• Schedule
• Combinations
• Route

• Systems Cancer Chronotherapeutics

Acceptable side-effects
Cancer treatments
finding the right balance between safety and efficacy

- Dose
- Schedule
- Combinations
- Route

Relevance of biological timing systems?

Different mechanisms of action and resistance
Acceptable side-effects
Cancer treatments
finding the right balance between safety and efficacy

ACTIVITY
Different mechanisms of action and resistance

SAFETY
Acceptable side-effects

Relevance of biological timing systems?
Usual timing of cancer treatments

Diagnostic & treatment procedures

Medical consultations
Medical or surgical procedures
New drug development
Adverse events & efficacy
Usual timing of cancer treatments

- Diagnostic & treatment procedures
- Medical consultations
- Medical or surgical procedures
- New drug development
- Adverse events & efficacy
Usual timing of cancer treatments

Medical consultations
Medical or surgical procedures
New drug development
Adverse events & efficacy

Hypothesis:
Biological functions operate at constant or random pace
Serum cortisol (0-16 µg/ml)

Clock time (h)
Serum cortisol (0-16 µg/ml)
Serum melatonin (0-70 pg/ml)
Core body temperature (35.7–37.5 °C)

Serum cortisol (0-16 µg/ml)

Serum melatonin (0-70 pg/ml)

Clock time (h)
Clock on symptoms

Awaiting 6:30 for resting...
The Circadian Timing System

Environment
- Day/night
- Social
- Familial
- Meal timing

Clock genes

Suprachiasmatic nuclei

Cortisol, melatonin

Temperature

Heart rate

Sleep/wakfulness

Rest-activity

Feeding pattern

Circadian biomarkers

Systems Cancer Chronotherapeutics
The Circadian Timing System

- Clock genes
- Suprachiasmatic nuclei
- Sleep/wakefulness
- Rest/activity

Environment
- Day/night
- Social
- Familial
- Meal timing

Biomarkers
- Cortisol
- Melatonin
- Temperature
- Feeding pattern
- Heart rate

Circadian biomarkers
The Circadian Timing System

- **Environment**
  - Day/night
  - Social
  - Familial
  - Meal timing

- **Circadian biomarkers**

- **Suprachiasmatic nuclei**
  - Sleep/wakfulness
  - Rest-activity
  - Cortisol, melatonin
  - Temperature
  - Feeding pattern

- **Circadian clocks in peripheral organs**

- **Heart rate**

- **Cell cycle, apoptosis, and DNA repair**
- **Drug metabolism and detoxification**
- **Angiogenesis**

- **Clock genes**
The Circadian Timing System

- Clock genes
- Suprachiasmatic nuclei
- Cortisol, melatonin
- Temperature
- Feeding pattern
- Rest-activity
- Sleep/wakefulness
- Environment
  - Day/night
  - Social
  - Familial
  - Meal timing

Circadian clocks in peripheral organs:
- PER
- CRY
- REV-ERB
- α/β

Circadian biomarkers:
- Cell cycle, apoptosis, and DNA repair
- Drug metabolism and detoxification
- Angiogenesis

Heart rate
The Circadian Timing System

- Clock genes
- Suprachiasmatic nuclei
- Rest/activity
- Sleep/wakefulness
- Cortisol, melatonin
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- Heart rate
- Circadian clocks in peripheral organs

Environment:
- Day/night
- Social
- Familial
- Meal timing

Circadian biomarkers

Rhythm monitoring in cancer patients

Chronotherapeutics:
- Cell cycle, apoptosis, and DNA repair
- Drug metabolism and detoxification
- Angiogenesis
The Circadian Timing System

- Clock genes
- Suprachiasmatic nuclei
- Sleep/wakefulness
- Rest-activity
- Circadian biomarkers
- Rhythm monitoring in cancer patients
- Chronotherapeutics

Environment:
- Day/night
- Social
- Familial
- Meal timing

Circadian clocks in peripheral organs:
- Cell cycle, apoptosis, and DNA repair
- Drug metabolism and detoxification
- Angiogenesis
Clock- Cell cycle coupling at single cell level

- Clock- Chronopharmacology at cell population level
- Cancer Chronopharmacology in mice
- Cancer Chronotherapy in patients
- Integration into home care
• Clock- Cell cycle coupling at single cell level

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• Cancer ChronoTherapy in patients

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Systems Cancer Chronotherapeutics

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Systems Cancer Chronotherapeutics

Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010
Systems Cancer Chronotherapeutics

Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010
Systems Cancer Chronotherapeutics

Chronotolerance
40 anticancer drugs

Chronoeficacy
28 anticancer drugs

Lévi & Schibler, Annu Rev Pharm Toxicol 2007
Lévi et al. Annu Rev Pharm Toxicol 2010
Sex and genetic differences in irinotecan chronotolerance in mice: 3 classes
Sex and genetic differences in irinotecan chronotolerance in mice: 3 classes

A, B, C, D, E: Graphs showing body weight loss (%) over different Zeitgeber times (h) for B6D2F1 and B6CBAF1 strains, with bars indicating the range and error bars showing variability. The x-axis represents Zeitgeber time (h) from 3 to 23, and the y-axis represents body weight loss (%) from -15 to 0.

Li et al. Cancer Res 2013
Sex and genetic differences in irinotecan chronotolerance in mice: 3 classes

Li et al. Cancer Res 2013
Best for

- **Per2<sup>m/m</sup>**
- **C57Bl/6**
- **B6D2F1**
- **B6CBAF1**

- **Per2<sup>m/m</sup>**
- **C57Bl/6**
- **B6D2F1**
- **B6CBAF1**
Worst for

♂ B6CBAF1
♀ B6CBAF1
♀ Per2m/m

Best for

♂ C57Bl/6
♂ B6D2F1
♂ Per2m/m

♀ C57Bl/6
♀ B6D2F1
♀ B6CBAF1
♀ B6CBAF1
♀ Per2m/m

ZT0

ZT12

ZT24/0
Worst for

♂ B6CBAF1
♀ B6CBAF1
♀ Per2\(^{m/m}\)

ZT0

♀ C57Bl/6
♂ B6D2F1
♀ Per2\(^{m/m}\)

ZT12

♀ C57Bl/6
♀ B6D2F1
♂ B6CBAF1
♀ B6CBAF1

ZT24/0

8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Best for

♀ Per2\(^{m/m}\)
♂ Per2\(^{m/m}\)
Sex and genetic differences in circadian clock & clock-controlled gene transcription in mouse liver

Li et al. Cancer Res 2013
8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Which of 27 liver or colon circadian gene transcription patterns predict for optimal timing if any?
8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Which of 27 liver or colon circadian gene transcription patterns predict for optimal timing if any?
8 h-range for optimal irinotecan timing (tolerability) according to sex & genotype in mice

Which of 27 liver or colon circadian gene transcription patterns predict for optimal timing if any?

Li et al. Cancer Res 2013
A circadian clock transcription model for the personalization of cancer chronotherapy timing

Li et al. Cancer Res 2013
A circadian clock transcription model for the personalization of cancer chronotherapy

Li et al. Cancer Res 2013
Circadian Time (hours, referred to light onset)

Liver

Tumor

mRNA transcription
- Rev-erbα
- Per2
- BMal1
- Systematic exploration of role of clock genes in liver and cancers for cell cycle, drug metabolism and chronotherapeutic effects
- Continuous physiology monitoring & dynamic molecular imaging

Per2::luc/Bmal1::luc ± si/shRNA Rev-Erbα-FUCCI

Clock mutant Cancer prone

Lumicycle
RT-Bio
IVIS Spectrum
Systems Cancer Chronotherapeutics

- Clock- Cell cycle coupling at single cell level
- Clock- Chronopharmacology at cell population level
- Cancer Chronopharmacology in mice
- Cancer Chronotherapy in patients
- Integration into home care
Curative intent onco-surgery strategy in patients with metastatic colorectal cancer

Liver resection & transplantation

Oxaliplatin

Chronotherapy

Systems Cancer Chronotherapeutics

Research & Development

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~3 000 patients
Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~3,000 patients
Systems Cancer Chronotherapeutics

Research & Development

Oncologist Consultation Patient

Personnalized medical care plan Prescription, verification

Coordination

Programmation Pharmacy Care Unit

Home Care

Home

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients
Systems Cancer Chronotherapeutics

Research & Development

Education
- health care personals
- patients

Oncologist Consultation Patient

Personalized medical care plan
Prescription, verification

Coordination
- Programming
- Pharmacy
- Care Unit

Home Care

Home

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients
Systems Cancer Chronotherapeutics

Research & Development

Education
- health care personnels
- patients

Oncologist Consultation Patient

Personnalized medical care plan
Prescription, verification

Coordination
Programmation Pharmacy Care Unit

Home Care

Home

Family doctor

Chronotherapy Unit, Hôpital Paul Brousse, Villejuif
1990-2014: ~ 3 000 patients
## Chronotherapeutic trials with 5-FU-LV-oxaliplatin (1988-2006)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Schedule</th>
<th>Gr 3-4 toxicity (% pts)</th>
<th>Objective responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>278 pts, 1st line</td>
<td>Chrono-std</td>
<td>14%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Constant</td>
<td><em>P</em> &lt; 0.001</td>
<td><em>P</em> = 0.003</td>
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<tr>
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<td></td>
<td>76%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Phase I-II staggered</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>114 pts 2-3rd line</td>
<td>Chrono-std</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Chrono-std ±12h</td>
<td>80%</td>
<td>12%</td>
</tr>
</tbody>
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## Chronotherapeutic trials with 5-FU-LV-oxaliplatin (1988-2006)

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Survival improvement in men on chronoFLO for metastatic colo-rectal cancer (meta-analysis of 3 randomized international trials in 842 patients)

<table>
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<tr>
<th>Sex (N patients)</th>
<th>Drug delivery schedule</th>
<th>Median survival, months [95% CL]</th>
<th>% alive at 5 years</th>
<th>P (Logrank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (N = 345)</td>
<td>Chrono</td>
<td>16.6 [13.9-19.0]</td>
<td>8</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Conventional</td>
<td>18.4 [16.6-20.2]</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Men (N=497)</td>
<td>Conventional</td>
<td>17.5 [16.1-18.8]</td>
<td>18</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Chrono</td>
<td>20.8 [18.7-22.9]</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

564 patients first line treatment for metastatic colorectal cancer
36 centers, 10 countries

Giacchetti et al. J Clin Oncol 2006;
Ann Oncol 2012
Innominato et al. Chronobiology Int 2011
Int J Cancer 2012; Cancer 2013
Improved tolerability associated with improved survival on chronotherapy not on conventional FOLFOX

Innominato et al. Chronobiology Int 2011
Int J Cancer 2012; Cancer 2013; Ann Med 2014, in press
Clinical relevance of rest-activity rhythm
436 patients with metastatic colorectal cancer

Rest-activity monitoring
Computation of I<O

Patient #1
I<O = 100%

Patient #2
I<O = 77.6%

Circadian disruption: I<O less than 97.5%
Clinical relevance of rest-activity rhythm
436 patients with metastatic colorectal cancer

Rest-activity monitoring
Computation of I<0

I<0 prediction of overall survival
in 436 patients

Circadian disruption: I<0 less than 97.5%

Lévi et al. Chronobiology Int 2014
Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice
Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

Motionlogger® Watch
Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

Before irinotecan

R24 = 0.48

PS = 0

Motionlogger® Watch
Circadian disruption on chemotherapy

Circadian disruption induced by 12 anticancer drugs according to dose & timing in mice

Before irinotecan

After irinotecan

Motionlogger® Watch

R24 = 0.48
PS = 0

R24 = -0.04
PS = 4
Asthenia grade 3
Anorexia, grade 3
Circadian disruption of rest-activity in patients on chemotherapy a significant predictor of poor survival

77 patients with metastatic colorectal cancer

Innominato et al. Int J Cancer 2012
Circadian disruption of rest-activity in patients on chemotherapy a significant predictor of poor survival

77 patients with metastatic colorectal cancer

Innominato et al. Int J Cancer 2012
Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms
10 individual patients before, during and after a 4-day course of chronotherapy
Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms
10 individual patients before, during and after a 4-day course of chronotherapy

Before

During

Time (clock hours)

Rest-activity

Temperature patch

#1 #2 #3 #4
Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms
10 individual patients before, during and after a 4-day course of chronotherapy

Before

During

After

Time (clock hours)

Rest-activity

Temperature patch  ◆ #1  ▲ #2  ◇ #3  ☆ #4
Timing of circadian maximum (acrophase) in rest-activity and skin surface temperature rhythms
10 individual patients before, during and after a 4-day course of chronotherapy
Circadian physiology
- Rest-activity
- Body temperature
- Hormones & cytokines
- Feeding pattern

Tolerability

Anticancer drug

Drug detoxification

Predictable optimal timing

Tumor inhibition

Coordinated peripheral clocks

Lévi et al. Annu Rev Pharm Toxicol 2010
Systems Cancer Chronotherapeutics

Circadian physiology
- Rest-activity
- Body temperature
- Hormones & cytokines
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Predictable optimal timing

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Toxicity

Lévi et al. Annu Rev Pharm Toxicol 2010
Systems Cancer Chronotherapeutics

Circadian physiology
- Rest-activity
- Body temperature
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Disruption

Toxicity

Anticancer drug
- Drug detoxification
- Predictable optimal timing

Tumor inhibition

Coordinated peripheral clocks

Lévi et al. Annu Rev Pharm Toxicol 2010
Systems Cancer Chronotherapeutics

Circadian physiology
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Predictable optimal timing

Poor coordination

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Lévi et al. Annu Rev Pharm Toxicol 2010
Circadian physiology

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Lévi et al. Annu Rev Pharm Toxicol 2010
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Lévi et al. Annu Rev Pharm Toxicol 2010
Circadian physiology

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- Hormones & cytokines
- Feeding pattern

Disruption

Toxicity

Anticancer drug

- Poor detoxification
- Unpredictable optimal timing

Poor coordination

Tumor progression

Lévi et al. Annu Rev Pharm Toxicol 2010
A shift in paradigm of cancer treatments?

Conventional chemotherapy principle:
The more the toxicity, the better the efficacy

Chronotherapeutics principle:
The better the tolerability, the better the efficacy!
Circadian clocks in healthy liver cells
Disrupted clocks in cancer cells
Circadian clocks in healthy liver cells
Disrupted clocks in cancer cells

Liver metastases from colorectal cancer
Healthy liver

Rev-erbα

Huisman et al. Cancer Res 2011
71 (8, Suppl 1), abstr 1515
Circadian clocks in healthy liver cells
Disrupted clocks in cancer cells

Liver metastases from colorectal cancer

Healthy liver

**Rev-erba**

*Huisman et al. Cancer Res 2011*  
71 (8, Suppl 1), abstr 1515

**Time (ZT, hours)**

Irinotecan 160 mg/m² day1  
Oxaliplatin 80 mg/m² days 2-5  
5-FU 2.4 g/m² days 2-5

**Every 3 weeks**

Bouchahda et al. Cancer 2009
Systems Cancer Chronotherapeutics

- Clock- Cell cycle coupling at single cell level
- Clock- Chronopharmacology at cell population level
- Cancer Chronopharmacology in mice
- Cancer Chronotherapy in patients

Integration into home care
Systems Cancer Chronotherapeutics

- Actimetry
- Home Gateway
- Tele-health System (SARA)
- GPRS or IP Network
- Remote Service Provider
- Tele-health Service (SARA)
- Hydra Middleware
- Medical Web App
- Contact Centre
- Social Response
- Medical Response
- Technical Provider

Body weight
Self-rated symptoms (MDASI)
Rest activity rhythm
Systems Cancer Chronotherapeutics

**Tele-health System (SARA)**

- **Home Gateway**
- **GPRS or IP Network**
- **Actimetry**
- **Tele-health**

**Remote Service Provider**
- **Hydra Middleware**
- **Tele-health Service (SARA)**

**Medical Response**
- **Medical Web App**
- **Social Response**
- **Contact Centre**
- **Technical Provider**

- **Body weight**
- **Self-rated symptoms (MDASI)**
- **Rest, activity, rhythm**
Daily teletransmission of rest-activity pattern throughout chronotherapy (chronoIFLO4) at home

Two patients with mCRC or pancreatic ca on Irinotecan, Oxaliplatine, 5-Fluorouracile, Leucovorin (chronoIFLO4)
Objectives

Patient-centered health system integrating biological rhythms, information & communication technologies, services, and patient chart

For improving patient autonomy, QoL, & survival through medical progress stimulation

• Early non invasive detection of predictors of health alteration in chronic disease patients (cancer)

• Proactive interventions for preventing patient deterioration and emergency hospitalization

• Adjustment of treatment delivery to the individual patient and to his (her) own clocks
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Altran, Voluntis, FSI, Axon Cable, Blue Linea, UTT, Univ Reims, INSERM
Objectives

Patient-centered health system integrating biological rhythms, information & communication technologies, services, and patient chart
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- Adjustment of treatment delivery to the individual patient and to his (her) own clocks
Conclusions

• Circadian clocks control cancer processes and treatment effects
• Targeting host and/or tumor clocks could improve patient outcomes
• Joint optimization of tolerability & efficacy in each patient through personalized chronotherapy delivery according to CTS monitoring at home
• Mathematical models and dedicated technologies for designing optimal treatment strategy & delivering optimal chronotherapy schedule
Rythmes Biologiques et Cancers

Virginie Hossard  Alexandre Arbaud  Pasquale Innominato

René Adam  Sylvie Giacchetti  Monique Lévi  Sandrine Dulong  Jacques Beau  Jean Clairambault  Ali Mteyrek  Elisabeth Filipski  Xiao-Mei Li  Elisabeth Ortiz-Tudela

Cancersensor  OPTILIV

ANR-TECSAN  EUDRACT  2007-00463224