Telomere and aging

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Conflict of interests

• None to declare
The telomere connection

- 1938–9: Muller -McClintock: telomere « telos » « meros »
- 1961: Hayflick Hypothesis (Mitotic clock)
- 1973: Olovnikov - A theory of marginotomy - the end-replication problem
- 1997: Telomerase gene discovery
- 1999: Terc null mice display a premature aging phenotype
- 2009: Nobel prize pour E. Blackburn, C. Greider et J. Scoztack
- 2011: « telomere »: 13182 PubMed references
Telomerase activation
ALT telomere lengthening
Chromosomal recombinations – telomere healing
Senescence
Tissue renewal loss
Pro-inflammatory secretory phenotype
Pro-tumorogenic potential

Diagram shows the relationship between telomere length and age, with different lines representing various aspects such as germ line, somatic cells, premature aging syndromes, and cancer. The diagram illustrates how telomere length decreases with age, leading to health and disease conditions.
Measuring telomere health?

- loss of telomerase activity?
- Higher turn over?
- Inflammaging?
- Oxidative stress?
• **Mortality**: controversial data:
  - Cawthon RM & al: *Association between telomere length in blood and mortality in people aged 60 years or older*. Lancet 2003;361:393-5

• **Degenerative diseases**:
  - van der Harst P & al: *Telomere length of circulating leukocytes is decreased in patients with chronic heart failure*. J Am Coll Cardiol 2007;49:1459-1464
  - van der Harst P & al: *Possible association between telomere length and renal dysfunction in patients with chronic heart failure*. Am J Cardiol 2008;102:207-210
Telomerase activity

Telomere-dysfunction Induced foci (TIFs)

- Measuring directly DNA damage response


Augereau et al, Blood 2011
DNA-damage biomarkers

- Proteins induced by telomere dysfunction and DNA damage represent biomarkers of human aging and disease

Jiang et al, PNAs 2008
Any clinical relevance of telomere analysis in oncogeriatrics?

- Treatment decision
  - Metastatic
    - Feasibility
    - Toxicities
    - Benefit/risk ratio
  - Adjuvant
    - Expected survival out of cancer
    - Short term Toxicities
    - Long term Toxicities
GINECO’s experience

- 1999-2003 (FAG1): CC treatment feasibility
  - 73 patients - Feasibility 72%
- 2004-2006 (FAG2): CP treatment feasibility
  - 82 Patients - Feasibility 68%
- Multivariate analysis: negative impact of:
  - Age
  - Depression and emotional disorders
  - Paclitaxel-based treatment
  - Stage (IV vs III)
- 2007-2010 (FAG3): C - Impact of emotional disorders
  - Feasibility 74%
Working hypothesis

Other vulnerability factors?

Depression
Emotional disorders

Old age

↓ telomere length
(= telomere attrition)

FAG 1 et
FAG 2

↓ Survival
↑ Toxicities

Lymphocyte dysfunction

↓ telomerase activity

Lymphopenia
Preliminary data of FAG3 study: telomere length

- 111 patients, 111 blood samplings

\[ y = -26.934x + 8082.3 \]

\[ R^2 = 0.0326 \]
Short telomere are associated with a decreased feasibility of treatment.

### Pts characteristics

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Total (%)</strong></td>
<td>111 (100)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>78</td>
</tr>
<tr>
<td>≥ 80</td>
<td>45 (41)</td>
</tr>
<tr>
<td>Extremes</td>
<td>70-93</td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
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<tr>
<td>0-1</td>
<td>63 (57)</td>
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<tr>
<td>2-3</td>
<td>48 (43)</td>
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<tr>
<td>≥ 1 dependance ADL</td>
<td>61 (55)</td>
</tr>
<tr>
<td>≥ 1 dependance on IADL</td>
<td>93 (75)</td>
</tr>
<tr>
<td><strong>Emotional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td>20 (18)</td>
</tr>
<tr>
<td>HADS ≥ 15</td>
<td>41 (37)</td>
</tr>
<tr>
<td>≥ 4 co-medications</td>
<td>76 (69)</td>
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### Feasibility of 6 Carboplatin courses

**p=0.0419**

### Non hematological toxicities

**p=0.0713**
And have a nearly significant impact on survival

1.0
ST5800=0
ST5800=1
Long telomeres
Short telomeres

Median OS 13.5 vs 19.2 mths
p=0.15

• Multivariate analysis:
  - Stage (IV vs III) HR=2.53 (p=0.0004)
  - Short telomeres HR=1.53 (p=0.09)
Towards a future challenge

Observational study of every elderly patient with AOC assesses the pre-inclusion criteria

at least one “factor of vulnerability"
- Lymphopenia
- Albuminemia < 35g/l
- ≥ 1 ADL
- IADL ≤ 27
- emotional disorders

YES VULNERABLE pts

N = 240

Biomarkers of aging

NO FIT patient: on-going trials

Standard Carboplatin AUC5 + Paclitaxel 175mg/m² J1=J21, 6 cycles

Single agent Carboplatin AUC5 J1=J21, 6 cycles

Weekly Carboplatin AUC2 + Paclitaxel 60mg/m² d1, d8, d15, J1=J28, 6 cycles