SIOG Guidelines Update 2014: Oral single-agent chemotherapy

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SIOG position paper on oral single-agent chemotherapy in elderly patients

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Rob Stepney
Rationale and aims

• Compared with intravenous chemotherapy, oral administration is convenient, requires fewer healthcare resources, is generally preferred by patients
• Compliance may be an issue especially in older patients
• Evaluate the role of single agent chemotherapy (capecitabine, vinorelbine, and metronomic therapy) in breast, colorectal and NSCL cancer
• Expert recommendations (position paper)
Medication adherence: a review

Adherence connotes the degree or extent to which the patient conforms to the medication use recommendations specified by the prescriber.

**Determinants of adherence**

- 14 of patient-related factors
- 8 clusters of socio-economic-related factors
- 6 of condition-related factors
- 6 of therapy-related factors
- 6 of healthcare team- and system-related factors

Each component of clusters could have positive, negative or neutral impact

**8 clusters of socio-economic-related factors**

- Family support
- Family caregiver factors
- Social stigma of a disease
- Costs of drugs and treatments
- Prescription coverage
- Socioeconomic status
- Employment status

**6 of condition-related factors**

- Presence of symptoms
- Disease
- Clinical severity
- Psychosocial considerations
- Certain diagnosis/indication
- Duration of the disease

**6 of therapy-related factors**

- Adverse effects
- Patient fear of consequences of the treatment
- Drug self-management
- Duration of treatment
- Convenience
- We organised treatment

**14 of patient-related factors**

- **Age**
- Gender
- Education
- Ethnicity
- Marital status
- Ethical attitude
- Memory and learning difficulties
- Cognitive function
- Forgetfulness and reminders
- Knowledge
- Health beliefs
- Psychological profile
- Comorbidities & patient history
- Alcohol & substance abuse
- Patient-related barriers to compliance

Interaction patient & health system

Disease

Treatment

Patient
Factors associated with NONadherence in older patients

Review of 9 US trials evaluating barriers to medication adherence among elderly ie, age ≥ 65 years (2008-2011)

- disease-related knowledge
- health literacy
- cognitive function
- drug-related factors
- adverse effects and polypharmacy
- patient-provider relationship and various logistical barriers to obtaining medications

BREAST CANCER
N= 633 women aged ≥65 years with stage I-IIIB breast cancer
Standard chemotherapy (AC/CMF) vs capecitabine*

CALGB 49907

Table 4. Grade 3, 4, or 5 Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>CMF (N=132)</th>
<th>Doxorubicin plus Cyclophosphamide (N=183)</th>
<th>Capecitabine (N=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>2 (1)†</td>
</tr>
<tr>
<td>≥1 Event</td>
<td>92 (70)</td>
<td>109 (60)</td>
<td>101 (34)</td>
</tr>
<tr>
<td>≥1 Hematologic adverse event</td>
<td>68 (52)‡</td>
<td>99 (54)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Hematologic adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (3)</td>
<td>7 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Requirement for transfusions</td>
<td>0</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>53 (40)</td>
<td>79 (43)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (27)</td>
<td>59 (32)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (4)</td>
<td>7 (4)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>≥1 Nonhematologic adverse event</td>
<td>53 (40)‡</td>
<td>44 (24)</td>
<td>98 (33)</td>
</tr>
<tr>
<td>Nonhematologic adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (11)</td>
<td>8 (4)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (2)</td>
<td>8 (4)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (7)</td>
<td>8 (4)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (6)</td>
<td>3 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (8)</td>
<td>5 (3)</td>
<td>20 (7)</td>
</tr>
<tr>
<td>Hand–foot skin reaction</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>47 (16)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>11 (8)</td>
<td>16 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thrombus or embolism</td>
<td>5 (4)</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

*Starting dose 1000mg/m2 BID, dose escalation not feasible due to toxicity

Adjuvant setting: Polychemotherapy=standard
• Metastatic setting: Single agent chemotherapy preferred to polychemotherapy in minimally symptomatic, slowly progressive disease. Capecitabine and vinorelbine commonly used in clinical practice.

<table>
<thead>
<tr>
<th>Capecitabine in breast cancer: dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The registered dose of capecitabine monotherapy is 1250 mg/m2 twice daily, days 1–14 every 21 days.</td>
</tr>
<tr>
<td>• It appears that a capecitabine starting dose of 1000 mg/m2 twice daily enables treatment to be administered for longer periods, providing continuous exposure to cytotoxic therapy and thus prolonging the duration of disease control.</td>
</tr>
</tbody>
</table>

Review Article

The role of capecitabine in the management of breast cancer in elderly patients

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age (years)</th>
<th>Treatment line</th>
<th>Regimen, q21d</th>
<th>ORR (%) (95% CI)</th>
<th>Median TTP, months (95% CI)</th>
<th>Median OS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent capecitabine (C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Shaughnessy et al.</td>
<td>61</td>
<td>54–83</td>
<td>1st line</td>
<td>C 1255 mg/m² bid d1–14</td>
<td>30 (19–43)</td>
<td>4.1 (3.2–6.5)</td>
<td>19.6</td>
</tr>
<tr>
<td>Minea et al.</td>
<td>63</td>
<td>65–78</td>
<td>1st line</td>
<td>C 1250 mg/m² bid d1–14</td>
<td>27</td>
<td>3.5</td>
<td>NA</td>
</tr>
<tr>
<td>Bajetta et al.</td>
<td>30</td>
<td>65–89</td>
<td>1st line (93%)</td>
<td>C 1250 mg/m² bid d1–14</td>
<td>37 (20–56)</td>
<td>3.9</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td></td>
<td>or 2nd line</td>
<td>C 1000 mg/m² bid d1–14</td>
<td>35 (21–51)</td>
<td>4.1</td>
<td>16</td>
</tr>
<tr>
<td>Zamora et al.</td>
<td>23</td>
<td>68–88</td>
<td>1st line (87%)</td>
<td>C 1250 mg/m² bid d1–14</td>
<td>13 (0–29)</td>
<td>7.5 (4.5–10.5)</td>
<td>13.3 (9.6–16.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or 2nd line</td>
<td>(950 mg/m²)²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** – Grades 3 and 4 adverse events with capecitabine in elderly metastatic breast cancer patients. N = number of patients. (%) = percentage of patients experiencing grades 3 or 4 adverse events.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Regimen</th>
<th>Alopecia</th>
<th>Diarrhea</th>
<th>Fatigue/asthenia</th>
<th>Hand–foot syndrome</th>
<th>Mucositis</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Shaughnessy et al.</td>
<td>61</td>
<td>C 1255 mg/m² bid d1–14</td>
<td>0 (0)</td>
<td>8 (13)</td>
<td>5 (8)</td>
<td>15 (25)</td>
<td>8 (13)</td>
<td>7 (11)</td>
<td>5 (8)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Minea et al.</td>
<td>63</td>
<td>C 1250 mg/m² bid d1–14</td>
<td>NA</td>
<td>10 (16)</td>
<td>13 (21)</td>
<td>NA</td>
<td>3 (5)</td>
<td>NA</td>
<td>5 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Bajetta et al.</td>
<td>30</td>
<td>C 1250 mg/m² bid d1–14</td>
<td>NA</td>
<td>13 (43)</td>
<td>7 (23)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (23)</td>
<td>3 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>C 1000 mg/m² bid d1–14</td>
<td>NA</td>
<td>2 (5)</td>
<td>12 (28)</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>5 (12)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Zamora et al.</td>
<td>23</td>
<td>C 1250 mg/m² bid d1–14 (950 mg/m²)</td>
<td>0 (0)</td>
<td>9 (39)</td>
<td>13 (57)</td>
<td>13 (57)</td>
<td>9 (39)</td>
<td>4 (17)</td>
<td>4 (17)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

Bedard et al. J Ger. Oncol 2111
General considerations on capecitabine

- Elderly patients are more likely to have impaired renal function: renal function is reduced by about 1% per year beyond ages 30–40, so that by age 70 renal function may have declined by 40%46.
- Normal serum creatinine values may be misleading
- Renal impairment leads to a significant increase in systemic exposure to 5′-DFUR and sequentially to increased frequency of capecitabine-related adverse events.
- Patients with severe renal impairment (creatinine clearance <30ml/min [Cockcroft and Gault]) should not receive capecitabine, and those with mild-to-moderate dysfunction should be closely monitored

- 5′-DFUR, 5′-deoxy-5-fluorouridine

Garg et al. Kidney Int 2004
**Oral vinorelbine in older patients**

*Phase II trial of oral vinorelbine for the treatment of metastatic breast cancer in patients ≥65 years of age: an NCCTG study*

M. Baweja¹, V. J. Suman², T. R. Fitch³, J. A. Mailliard⁴, A. Bernath⁵, K. M. Rowland⁶, S. R. Alberts⁷, J. S. Kaur⁸ & E. A. Perez¹⁰

- 25 pts (median age 73); 1st-2nd (40%) line vinorelbine 60-70mg/m²/wk
- Well tolerated (G≥3 neutropenia 12.5%, G3 fatigue 12.5%, G2 neuromotor and neurosensory toxicities in 12.5% and 8.3%)
- Response rate 7%; median TTP 4.7 months

*Ann Oncol 2006*

*Low-Dose Metronomic Oral Administration of Vinorelbine in the First-line Treatment of Elderly Patients With Metastatic Breast Cancer*

Raffaele Addeo¹, Alessandro Sgambato², Gregorio Cennamo³, Liliana Montella³, Vincenzo Faiola³, Alberto Abbruzzese³, Elena Capasso³, Luigi Leo³, Gerardo Botti³, Michele Caraglia³, Salvatore Del Prete³

- 34 patients (median age 73); 1st line vinorelbine 70mg/m² fractionated on days 1, 3, and 5, for 3 weeks on and 1 week off, every 4 weeks, for a maximum of 12 cycles
- Response rate 38%; median TTP 7.7 months

*Clin Breast Cancer 2010*
Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels


MTX was administered 2.5 mg bd on days 1 and 2 each week and CTX 50 mg/day administered continuously.

Results: Sixty-four patients were enrolled, 63 were evaluable: Eastern Cooperative Oncology Group (ECOG) performance status 0–1, ≥2 sites of metastatic disease (n = 50 patients), progressive disease at study entry (n = 51), 1 regimen for metastatic disease (n = 32) and ≥2 regimens (n = 20). Among the 63 evaluable patients, there were two complete remissions (CR), 10 partial remissions (PR) for an overall response rate of 19.0% (95% CI 10.2% to 30.9%) and an overall clinical benefit (CR+ PR+ stable disease >24 weeks) of 31.7% (95% CI 20.6% to 44.7%). Grade ≥2 leukopenia was registered in only 13 patients.

Conclusions: Continuously low-dose CTX and MTX is minimally toxic and effective in heavily pretreated breast cancer patients.
COLORECTAL CANCER
• No benefit from adjuvant chemotherapy in patients aged >66 years with stage II colon cancer

J Clin Oncol 2011

• Patients aged ≥ 70 years seemed to experience reduced benefit from adding oxaliplatin to fluoropyrimidines although statistically, there was not a significant effect modification by age, whereas oral fluoropyrimidines retained their efficacy

J Clin Oncol 2013

➢ The addition of oxaliplatin to adjuvant therapy in stage III patients ≥ 70 can be discussed with the patient. Fluoropyrimidine monotherapy remains an effective standard option

➢ Within this approach, oral capecitabine is an appropriate choice (less toxic than Mayo¹, no formal comparison with infusional 5-FU)

¹ Scheithauer et al. Ann Oncol 2003
Treatment of colorectal cancer in older patients. International Society of Geriatric Oncology (SIOG) consensus recommendations 2013

- Treatment with a fluoropyrimidine (5-FU/LV or capecitabine) contributes to OS in older pts. The added value of irinotecan, oxaliplatin and targeted agents may be limited due to the lower achievable dose intensities and poorer benefit/risk ratio. These limited incremental gains are restricted to older pts with good performance status. Thus, the gains from the addition of any drugs come with increased toxicity, restricting the pts that can be treated.

Papamichael et al. Ann Oncol 2014

- AVEX trial: first-line capecitabine median OS 16.8 months

Cunningham et al. Lancet Oncol 2013

Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

of 48-h intravenous fluorouracil with levofolinate (A); oxaliplatin and 5-fluorouracil (B); capecitabine (C); or oxaliplatin and capecitabine (D); Starting dose=80% of standard

- Addition of oxaliplatin had a non-significant extension of median PFS but a better outcome in terms of OTU (overall treatment utility)
- Risk of G≥3 toxicity higher with capecitabine than with CI-5FU
- No improvement of QoL substituting 5FU with capecitabine

Seymour et al. Lancet 2011
NSCLC
Advanced/metastatic disease – chemotherapy

• Prospective trials support the use of carboplatin-based doublets in fit elderly patients.

• For less fit patients single-agent treatment (gemcitabine, vinorelbine, taxanes) represent a valid option.

• There is no data to support that any single agent offers an OS benefit compared with the other ones.

• Very limited data are available for octogenarians and, therefore, no specific recommendations can be made for this group.
A multicenter randomized phase II study of oral vs. intravenous vinorelbine in advanced non-small-cell lung cancer patients

J. Jassem,1 R. Ramlau,2 H. Karnicka-Młodkowska,3 K. Krawczyk,4 M. Krzakowski,5 P. Zatloukal,6 E. Lemarie,7 W. Hartmann,8 L. Novakova,9 M. O'Brien10 & A. Depierre11

Patients and methods: Between December 1997 and April 1999, 115 patients with stage IIB or IV NSCLC were randomized (2 to 1) to receive either oral vinorelbine at a dose of 60 mg/m²/week for the first three administrations and then increased to 80 mg/m²/week in the absence of severe neutropenia, or i.v. vinorelbine at 30 mg/m²/week.

Conclusion: The activity of oral and i.v. vinorelbine in advanced NSCLC appears to be comparable. The safety profiles of both formulations look qualitatively similar. Oral vinorelbine can therefore be considered a good alternative to i.v. administration.


PHASE II TRIAL OF METRONOMIC ORAL VINORELBINE AS FIRST-LINE TREATMENT IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (MOVE TRIAL)

A. Camerini, C. Puccetti, S. Donati, C. Valsuani, M.C. Petrella, G. Tartarelli, P. Puccinelli, D. Amoroso

Methods: 43 chemotherapy naive elderly (≥70 yrs) PS 0-2 patients with stage IIB-IV NSCLC were prospectively recruited. Median age was 80 yrs

Study treatment consisted of oral vinorelbine 50mg three times weekly (Monday-Wednesday-Friday) continuously.

Results: Patients received a median of 5 (range 1-21) cycles with a total of 272 cycles delivered. ORR was 18.6% with 7 partial and 1 complete responses; 17/43 experienced stable disease lasting more than 12 weeks leading to an overall CB of 58.1%. Median time to progression was 5 (range 2-21) and median overall survival 9 (range 3-29) months. Treatment was well tolerated with rare G3/4 toxicity. Regardless of severity main toxicities observed were anemia in 44%, fatigue in 32.4%, and diarrhoea 10.5%.

Conclusions: Metronomic oral vinorelbine is safe in elderly patients with advanced NSCLC with an interesting activity mainly consisting in long-term disease stabilization coupled with an optimal patient compliance.
Conclusions

- Single agent oral chemotherapy represents a treatment option for some elderly patients with breast, colorectal and NSCL cancer
- Metronomic chemotherapy combines good tolerability with acceptable activity
Back up
Factors associated with NONadherence in older patients

Review of 9 US trials evaluating barriers to medication adherence among elderly ie, age ≥ 65 years (2008-2011)

- disease-related knowledge
- health literacy
- cognitive function
- drug-related factors
- adverse effects and polypharmacy
- patient-provider relationship and barriers to obtaining medications

Medication adherence in older adults with cognitive impairment

Review of 594 articles published between 1965 and 2012

Unique barriers to adherence included
1. understanding new directions,
2. living alone,
3. scheduling medication into the daily routine,
4. using potentially inappropriate medications,
5. uncooperative patients

2 studies: reminder systems ⇒ NO benefit
1 study: telephone and tele-video reminders at each dosing interval ⇒ Benefit (but...)
Fundamental steps

• Task Force on **Oral, single-agent chemotherapy**
• First meeting: 20th January 2014 in Paris
  - Focus on breast, colorectal and lung cancer
  - No combination with biological therapies
• Last draft circulated to the members of the reviewing committee…… document still to be finalized