Impact of cachexia and malnutrition on cancer treatment decisions:
- Adapt dosing of anticancer treatment
- Anticancer treatment to improve cachexia

Muscle mass (Sarcopenia) is associated with more toxicity, poorer OAS & poor QoL
Oncologist «promise» anticancer treatment improves cancer-related symptoms

1 Case challenge of anticancer treatment and palliative interventions patient value based

7 Facts
- Sarcopenia → OAS → Tox
- Anticancer Tx → Muscle → S-NIS
- Goals → RR & QoL → Cachexia

3 Questions and state-of-the-art answers
- Dose reduction in SP because of worse OAS?
- Dose reduction in SP preventing toxicity?
- How give anticancer treatment in cachexia?
DISCLOSURE SLIDE

Unrestricted Grant to Institution for Cachexia research from Helsinn Advisory Boards, Expert Opinion reimbursed to Institution last two years from Danone-Nutricia, Grünenthal, Helsinn, Mundipharma, Novartis, Ono, PrIIME, Vifor MASCC Working Group Nutrition & Cachexia Co-Chair ESMO Designated Centers WG Chair
Ms V, Italian, mid fifties; no comorbidities, BMI 32

2/2014 Locally advanced, non-operable pancreatic corpus Adenocarcinoma, pT4 cN0 (0/2), cM0; biliodigestive Anastomosis Roux-Y

4-9/14 6 x FOLFIRINOX, PR; wait; 5/15 CT PR; 6/15 PD

9-9/15 6 x FOLFIRINOX, PR, Hepatosteatosis

9-11/15 4 x FOLFIRINOX, PD primary Tumor under Chemo well tolerated, minimal fatigue, no febrile NP

12/15-3/16 3 x Gem/nab-Paclit., PT 9→3 cm², liver met 1→3

3/16-5/16 3 x Gem/nab-Paclit., PT 3.2 cm², liver multiple PD adequately tolerated, fatigue

CA19-9 8.4.16: 28, 22.4.: 56, 20.5.: 145, 31.5.: 356

PDL1-Expression membranous <1%, DNA mismatch repair preserved

→ Palliative Oncology referral in refractory disease
5-6/2016 5 Visits Palliative Oncology Outpat in 4 weeks; CA19-9 7.6. 544, 14.6. 702

Pain 6/10, Fatigue 7/10 (emotional, physical), Anorexia 8/10, Nausa 2/10, Anxiety 2/10, Depression 4/10, no breathlessness

Pain syndrome abdominal (6/10), no risk factors, eating-related
→ Increasing doses Oxycodone/Naloxone, Oxyc, Novamin

Cachexia, weight loss 8%/5 mts, anorexia (8/10), no dysgeusia, early satiety, minimal nausea, CRP 12, Alb 32
→ combination laxatives, prokinetics, education eating

Illness- / prognosis-understanding moderate, unknow liver mets
→ education spectrum wks to many mts, pat wants «all» if QOL

Preparation for end-of-life
→ Legacy work, finish business, living will, testament
→ marriage daughter in 7/16 italy, family important

What would you do next? 6/2016 PS1
6/2016  St.Gallen no Phase I option, consider capec/gem
Second opinion Zurich: consider nal-Iri, SIRT

23.6.  FOLFIRINOX, cachexia & inflammation-adapted dose
  Physical activity & strength training, protein-rich food

5./18.7.  FOLFIRINOX, 14.7. Opioid stop, CA 19-9 412, CINP 1

20.7.-7.8. Marriage in Italy, dancing, eating; 8.8. CA19-9 215

8./24.8.  FOLFIRINOX (#20/21), G1 Fatigue, Tc nadir 59

5.9.  CA19-9 582, CT PT SD, liver PD, LN retrop PD; PS1

7.9.  Discussion phase I (SAKK 67/15), required 1 mts wait

13.9.  New pain cervical, CA 19-9 856, MRI Clivus metastasis

21.9-6.10. Radiotherapy Skull Base 12x3 Gy. CA 19-9 7400

12.10.  More pain, Oxycodone/Naloxone 40, Pregabaline 50, Dexamethasone 4mg
  PS 2, 9% weight loss in 1 month, Fatigue, if Dexam reduced 2mg → Pain
  Good illness understanding, PS2.

What shall we do? Will symptoms improve again with Chemo?
13.10. FOLFIRINOX (4000/600, 200, 100), CA19-9 7400>4680
   Fatigue G2 day 4-9, CINP G1, sweating better

27.10. FOLFIRINOX (Dose Reduction: 3500/500, 100, 50), CA19-9 7520>9830

11.11. FOLFIRINOX (4000/700, 250, 160), CA199 13100>5130

25.11. no opioids, 1 mg Dex, weight stable (min. edema), PS1
   CINP G1, Tc 53, Bili 21; 4 KCL → aldosterone 25mg;
   Pat wants celebrate family christmas → wants chemo

25.11. FOLFIRINOX (4000/700, 280, 100) CA199 6650>3700

1.-10.12. Hospital for Cholangitis, Gc nadir 2.9, Tc 39; Liver diffuse metas, Bili 94,
   Antibiotics, Ascites punction, no opioids

14.12. outpat, KPS 50, pain abdominal right, Bili 117, CRP 84
   CA19-9 11400; Ciproflox/Metronidazol. Fenta td 12mcg
   alert, clear, wants again anticancer treatment (helped), Fatigue 9/10
   Husband, daughter prepared both for death & christmas
15.12. FOLFIRINOX (#26) (3000/500, 140, 100)

20.12. Hospitalisation Pain abdominal, weakness
   Ascites 2000ml (relief), Dexamethasone (no relief)
   hepatorenal syndrome (Bili 222, Crea-Cl 36), worsening
   CRP 77 → 51, CA 19-9 11’400 → 3200 (day 8)
   no neutropenia, no bleeding

23.12. Family from Italy (mother, brother) visit dying patient

24.12. Psychooncology support for family

26.12. Patient dies peacefully with family members around

Would we (who is we?) do this same management again? YES / NO
Was this aggressive End-of-Life Care? YES / NO
Was this Patient-Centered Integrated Oncology & Palliative Care? YES / NO
Palliative Oncology (double boarded)? YES / NO
F1 Sarcopenia → OAS

Impact on Survival

- **Performance Status** (abundant data, various tumors)
- **Weight Loss** abundant data\(^1\) (mixed with starvation)
- **Weight loss & BMI**\(^2\) (BMI: available reserves)
- Low **MiniNutrAss**\(^3\) (intake, WL, mobil, psych, Di, BMI)
- **Muscle mass** (SarcoPenia)\(^4\)
- **Muscle Attenuation**\(^4\) (catabolism, hypo-anabolism)
- **Inflammation** (CRP) & Albumin\(^5\) / Lymphocytes\(^6\)

- CRP ≤ 10mg/L = 0
- CRP > 10mg/L = 1
- CRP > 10mg/L and albumin < 35 g/L = 2


\(\rightarrow\) worse OAS
Cancer-Associated Weight Loss: Survival, Grading System

8160 cancer pts, multivariable analysis (age, sex, cancer site, stage, PS). Independent validation sample 2963 pts. Survival mts depends both on WL% and BMI.

Gastroesophageal cancer n=942

<table>
<thead>
<tr>
<th>Weight Loss (%)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 25 22 20</td>
</tr>
<tr>
<td>1</td>
<td>1 1 1 3</td>
</tr>
<tr>
<td>2</td>
<td>2 2 2 3</td>
</tr>
<tr>
<td>3</td>
<td>3 3 3 4</td>
</tr>
<tr>
<td>4</td>
<td>4 4 4 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight Loss (%)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.5</td>
<td>25 22 20</td>
</tr>
<tr>
<td>14.2</td>
<td>19.9 15.7</td>
</tr>
<tr>
<td>10.7</td>
<td>13.5 8.4</td>
</tr>
<tr>
<td>8.1</td>
<td>17.3 10.6</td>
</tr>
<tr>
<td>4.4</td>
<td>11.3 7.8</td>
</tr>
<tr>
<td></td>
<td>15 22 20</td>
</tr>
<tr>
<td></td>
<td>17.3 10.6</td>
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<tr>
<td></td>
<td>11.3 7.8</td>
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<td></td>
<td>15 22 20</td>
</tr>
<tr>
<td></td>
<td>17.3 10.6</td>
</tr>
<tr>
<td></td>
<td>11.3 7.8</td>
</tr>
</tbody>
</table>

Cumulative Survival (probability) vs. Time to Death (months)

Skeletal muscle density (SMD) is an independent predictor of diffuse large B-cell lymphoma outcomes treated with rituximab-based chemoimmunotherapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>R-IPI score 1–2</td>
<td>1.29</td>
<td>0.29–5.75</td>
</tr>
<tr>
<td></td>
<td>R-IPI score 3–5</td>
<td>4.20</td>
<td>0.98–17.88</td>
</tr>
<tr>
<td></td>
<td>Sex, male</td>
<td>0.98</td>
<td>0.60–1.61</td>
</tr>
<tr>
<td></td>
<td>Low SMD</td>
<td>1.56</td>
<td>0.90–2.71</td>
</tr>
<tr>
<td>OS</td>
<td>R-IPI score 1–2</td>
<td>2.18</td>
<td>0.28–16.74</td>
</tr>
<tr>
<td></td>
<td>R-IPI score 3–5</td>
<td>6.26</td>
<td>0.84–46.4</td>
</tr>
<tr>
<td></td>
<td>Sex, male</td>
<td>1.23</td>
<td>0.76–2.02</td>
</tr>
<tr>
<td></td>
<td>Low SMD</td>
<td>2.52</td>
<td>1.40–4.54</td>
</tr>
</tbody>
</table>

In DLBCL patients, watch protein intake and physical function. May consider also early Pall Care.

Chu MP J Cachexia Sarcopenia Muscle 2016 Nov 21
Sarcopenia is associated with anticancer tx toxicity and perioperative complications

Why is this association?
- Pharmacokinetics?
- Inflammation (hepatic fct)?
- Other cachexia mediators?

Another example (of many):
84 NSCLC pts afatinib
(55% 2\textsuperscript{nd}, 38% 3\textsuperscript{rd}, 7% 4\textsuperscript{th} line)
G3/4 diarrhea 39%, mucositis 29%, overall GI-Tox 56%
Lower LBM & BMI: DLT 71% vs 19%

Arrieta O Oncologist 2015;20:967-74
F3 Anticancer treatment → Impact on Muscle

Folfox/Folfiri causes
- mitochondrial depletion
- activation of ERK1/2 & p38 MAPKs-dependent pathways

Barreto R Oncotarget 2016; 43442-60

MEK-1 Inhibitor

Soluble Activinin Rec 2B

Cisplatin (& tumor) causes muscle atrophy
- downregulate Akt, myoD, myogenin
- upregulate proteolysis (UbP), Myostatin
- Ghrelin may partially reverse effects

Chemo → inflammation, oxidative stress
Sultani M Chemother Res Pract 2012;490804
Chen JA J Cach Sarcop Musc 2015;6:132-143
# Muscle wasting associated with the long-term use of mTOR inhibitors

<table>
<thead>
<tr>
<th>Drug use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus alone</td>
<td>12</td>
</tr>
<tr>
<td>Temsirolimus alone</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>18</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior to the start of the treatment</th>
<th>Following at least 6 months of treatment</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>55.5</td>
<td>54.4</td>
<td>-2.9 to 0.8</td>
<td>0.262</td>
</tr>
<tr>
<td>SAT index (cm²/m²)</td>
<td>35.1</td>
<td>36.4</td>
<td>-6.3 to 8.8</td>
<td>0.722</td>
</tr>
<tr>
<td>VAT index (cm²/m²)</td>
<td>31.5</td>
<td>43.8</td>
<td>-0.2 to 24.7</td>
<td>0.053</td>
</tr>
<tr>
<td>TAT index (cm²/m²)</td>
<td>66.6</td>
<td>80.2</td>
<td>-6.0 to 33.1</td>
<td>0.163</td>
</tr>
<tr>
<td>SMT area at (cm²)</td>
<td>137.3</td>
<td>124.6</td>
<td>-22.0 to -3.3</td>
<td>0.011a</td>
</tr>
<tr>
<td>SMI (cm²/m²)</td>
<td>50.2</td>
<td>43.8</td>
<td>-11.7 to -1.0</td>
<td>0.022a</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>47.2</td>
<td>43.1</td>
<td>-6.9 to -1.3</td>
<td>0.007a</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.7</td>
<td>3.5</td>
<td>-0.6 to 0.0</td>
<td>0.091</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.8</td>
<td>5.3</td>
<td>-0.6 to 5.5</td>
<td>0.105</td>
</tr>
</tbody>
</table>

SMT: skeletal muscle tissue; SMI: SM index (corrected for height)

Also data for sorafenib: promote muscle wasting (8% in 12 mts) by proteolytic systems

Toledo M J Cach Sarcop Musc 2016;7:48-59

→ Indication for monitoring protein intake, physical activity

Gywali B Molec Clin Oncol 2016;5:641-6
Anticancer treatment → causing Secondary Nutrition Impact Symptoms

Anticancer treatments can cause a lot of secondary nutrition impact symptoms, these data are not well reported, but clinical reality
- Stomatitis, Xerostomia, Taste alterations
- Nausea/vomiting, stomach pain
- GI mucositis, Diarrhea, Constipation
- Endocrine abnormalities, etc,

Systematic review (Medline 2005-16: n=24)
Chemotherapy-related digestive symptoms likely to impair nutritional status:
dry mouth, nausea/vomiting, stomach pain, diarrhea and constipation

Caillet P Clin Nutr 2016 Dec 18

Clinical trials with primary endpoint cancer-related symptoms & syndromes are still rare

Cholangio-Ca
Patient-derived clinical benefit response
PR: 7/10
SD: 16/24
PD: 2/5

Köberle D JCO 2008;26:3702-8
Tumor-Response and Symptom-Alleviation example: Lung cancer (Cisplatin & Vindesin vs Gemcitabine)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Response (N = 34)</th>
<th>Stable disease (N = 44)</th>
<th>Progression/non eval (N = 91)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N_{eval}</td>
<td>N_{impr}</td>
<td>N_{eval}</td>
</tr>
<tr>
<td>Cough</td>
<td>33</td>
<td>22 (67%)</td>
<td>39</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>31</td>
<td>17 (55%)</td>
<td>35</td>
</tr>
<tr>
<td>Pain</td>
<td>26</td>
<td>13 (50%)</td>
<td>34</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>19</td>
<td>13 (68%)</td>
<td>24</td>
</tr>
<tr>
<td>Anorexia</td>
<td>34</td>
<td>20 (59%)</td>
<td>44</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>17 (50%)</td>
<td>43</td>
</tr>
<tr>
<td>Overall symptom control</td>
<td>32</td>
<td>19 (59%)</td>
<td>40</td>
</tr>
<tr>
<td>Normal daily activities</td>
<td>32</td>
<td>15 (47%)</td>
<td>40</td>
</tr>
<tr>
<td>Overall quality-of-life</td>
<td>32</td>
<td>13 (41%)</td>
<td>40</td>
</tr>
</tbody>
</table>

Symptoms better: 41-67%  39-62%  2-23%

→ Individual improvement of symptoms despite tumor-growth
→ Symptom deterioration despite tumorshrinking

Vansteenkiste J
Lung Cancer
2003;40:191-9
7 Anticancer treatment → improvement of Cancer Cachexia

Systematic Literature Review

Eligible: ≥18y; RCT n ≥ 100; chemotherapy or targeted therapy; locally adv or met pancreatic adenocarcinoma; patient-reported QOL, pain or cachexia (weight loss) as endpoints

Eight studies reported on weight change, data were inadequately reported. No studies significant differences in favor of one treatment arm.

“The effect on cachexia (weight loss) was rarely and inadequately evaluated, and cannot be determined from the current literature”

→ May be true for other tumor types


<table>
<thead>
<tr>
<th>Health-related quality of life issue</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conceptual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A priori hypothesis stated</td>
<td>5</td>
<td>22%</td>
</tr>
<tr>
<td>Rationale for instrument reported</td>
<td>5</td>
<td>22%</td>
</tr>
<tr>
<td>Measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychometric properties reported</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Cultural validity verified</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Adequacy of domains covered</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Methodology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrument administration reported</td>
<td>7</td>
<td>30%</td>
</tr>
<tr>
<td>Baseline compliance reported</td>
<td>12</td>
<td>52%</td>
</tr>
<tr>
<td>Timing of assessments documented</td>
<td>23</td>
<td>100%</td>
</tr>
<tr>
<td>Missing data documented</td>
<td>19</td>
<td>83%</td>
</tr>
<tr>
<td>Interpretation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical significance addressed</td>
<td>8</td>
<td>35%</td>
</tr>
<tr>
<td>Presentation of results in general</td>
<td>16</td>
<td>70%</td>
</tr>
</tbody>
</table>
Muscle mass (Sarcopenia) is associated with more toxicity, poorer OAS & poor QoL.

Oncologist «promise» anticancer treatment improves cancer-related symptoms.

1 Case challenge of anticancer treatment and palliative interventions patient value based

7 Facts Sarcopenia → OAS → Tox
Anticancer Tx → Muscle → S-NIS
   → Goals → RR & QoL
   → Cachexia

3 Questions and state-of-the-art answers
   . Dose reduction in SP because of worse OAS?
   . Dose reduction in SP preventing toxicity?
   . How give anticancer treatment in cachexia?

“You’ve got six months, but with aggressive treatment we can help make that seem much longer.”
12'472 pts 2012, 10% DR <60d start. 15-17% taxanes & cDDP, 11% 5-FU, 7% Capecit.

(Neo-) adjuvant breast cancer tx (n=123). 40% needed DR (73.4% [68-94], 17% for CINP. Risk fct: diabetes, african-amer, paclitaxel.

Dose reduction (DR): paucity of data

- DR seems to be performed usually in many patients responding to toxicity.
- DR in curative Tx: done after toxicity → important to maintain Dose Intensity.
- DR may be in-vivo dose optimization → toxicity as signal of individual effect, no impact on survival.
- Primary DR
  - in older cancer pts due to Sarcopenia?
  - in palliative pts when co-morbidity
  - not performed according to KPS.

86 pts DLBCL ≥ 6 x R-CHOP. Relativ avg dose intensity (±85%) 2y OAS 67% vs 93%, p=.011.

Primary DR in 500 pts (73y [65-91]; 36% curative) 15% curative, 25% palliative chemotx (p=.005). Factors: age, pall only: comorbidity (cancer, liver/kidney), NOT KPS.

55/76 mNSCLC pts erlotinib skin rash ≥G2, retrospective Data. 24 DR vs 31 no DR. PFS 341 vs 70, OS 566 vs 202 d (p<.001). DR: no smoker, female, EGFR mutated, G3 rash.

1: Casadei GA Oncotarget 2016;7:40719-24
2: Bhatnagar B Springerplus, 2014;3:366-72
4: Gajra A J Geriatr Oncol, 2015;6;133-40
5: Takashima, N Onkologie 2012;35:747-52
Q1 Primary dose reduction in sarcopenic / cachectic patients if survival is the main goal?

- Currently not recommended, paucity of data (needs trials)

To do practically:
- Monitor weight (and edema), BMI, nutritional intake
- Monitor Symptoms (ESAS) and Toxicity
- Prescribe protein-rich food, maybe Oral Nutritional Supplements
- Prescribe Physical Activity and Strenght Training
- Educate Patient (and family)

Q2 Primary dose reduction in sarcopenic / cachectic patients if quality of life / minimizing toxicity is the main goal?

- In adjuvant settings currently not recommended, needs clinical trials
- In palliative intent anticancer treatment: consider secondary uptitration
  - age *over-treatment risk*
    64% elderly pts solid tumor: severe toxicity by polychemotherapy\(^1\)
  - under-treatment risk
    Advanced NSCLC el-pts less tx despite clear evidence (OAS, Sy)\(^2\)
  - PS
    PS3/4 NSCLC pts not recommended, but performed often\(^3\)
  - CRP
    may consider DR if CRP high and suspected hepatic dysfunction
  - CoM
    Comorbidities, renal function (too low s-crea in sarcopenia)

Q3 How to give and monitor anticancer treatment in the sarcopenic / cachectic patient?

- Assess and treat malnutrition (S-NIS) before you start anticancer tx
- Assure patient & family member understanding of cachexia mechanism
- Careful decisonal process (session 1)
  - define expected effect (symptom, weight, function) as goal
  - prediscuss how to deal with toxicity & burden of anticancer treatment
- Prescribe physical function (2-3 x / week, 15min moderate) and strenght training (2-3 x/week, upper & lower extremity, 12 repetitions x 2 80% max)
- Every visit (weekly) check on nutritional intake, # meals, type of food
- Monitor proactively toxicity (session 1)
- Prevent toxicity: nausea/vomiting, mucositis, constipation, diarrhea
- Monitor effect (tumormarker if any, physical fct, symptoms, tumor size)
Assess always risk factors for toxicity: weight loss (& edema), low BMI, CRP/NLR, anorexia.

Include in the decisional process of anticancer treatment clear, measurable goals and illness & prognosis understanding.

May empower patients, if chemo, also physical activity and protein-rich food, but this is also a research question (MENAC).
Thank you

florian.strasser@kssg.ch