Quality of Life – The Ultimate Endpoint

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SHORE-C
Sussex Health Outcomes Research & Education in Cancer
Aims of all metastatic cancer treatments

- To improve a patient’s well-being by:
  - increasing overall survival
  - delaying metastatic spread
  - ameliorating worst symptoms of disease

- Need to balance improvements in disease control with iatrogenic harms of therapy

- Quality not just quantity of life an important consideration

*Fallowfield, SHORE-C, 2015*
Advances in modern cancer treatment

- Many advances made in diagnostics, surgical & radiotherapy techniques, molecular biology and systemic therapy
- Patients cured of their disease and/or surviving longer
- Substantial psychosocial and iatrogenic harms created by diagnosis, symptoms of disease and treatment
- Unfortunately many acute and long-term SEs under-recognised, under-reported and consequently undertreated

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Patients and clinicians may have different values

- Many treatments offer improved PFS and OS
- Some also have unpleasant toxicities, others serious AEs
- True benefits often modest/uncertain
- Desirable benefits/acceptable costs may differ between patients and HCPs

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Decision-making

- Is lengthier survival worth treatment SEs?
- How much survival benefit is needed to trade off the disadvantages and SEs?
- Much research suggesting that pts will accept high toxicity for minimal benefits flawed
- If no clear survival benefits exist between treatments then QoL information crucial and influences patient preferences
- 459 pts with advanced cancer (Merepol et al, Cancer, 2008) 55% QoL and LoL equally important, 27% preservation QoL, 18% LoL

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Are there data for optimal decision-making?

- Can only talk about things systematically recorded
- Veracity of safety data (mainly trials) doubtful, initially most novel therapies appear to have better profiles than standard
- AEs and SEs not collected reliably, studies show SEs often underestimated
- Bias in 164 trials with poor reporting of toxicity (67%) especially RCTs with positive 1° endpoints (Vera-Badillo, Ann Onc, 2013)
- HCPs’ toxicity assessments maybe more subjective!

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Adverse event reporting in clinical trials

- Review of 175 publications of RCTs involving >96,000 patients for completeness of reporting AEs *(Sivendran et al, JCO, 2014)*

- Reporting suboptimal, characterised by substantial selectivity and heterogeneity

- Majority (96%) only reported AEs above certain threshold rate or severity

- 37% did not specify criteria for selection

- 88% grouped together AEs of varying severity

*Fallowfield, SHORE-C, 2015*
Concordance – clinician/patient

- Symptom burden collected from PROs often higher than physician reported CTC AEs (Greimel, Supp Care Ca, 2011)

- Frequency and severity may differ (Fallowfield, 2007)

- Little concordance between pts and HCPs ratings of QoL rather than life-threatening AEs (Ruhstaller, Oncology, 2009)

- Toxicity assessments made by proxy raters provide different information from that provided by patients (Basch et al, NEJM, 2010)
Cumulative incidence AEs in 467 pts

Pts report AEs earlier and more frequently than drs and nurses on CTCAE

Estimated 38% of AEs in BC labels are symptoms best reported by pts

(Basch et al, NEJM, 2010)
Under-reporting SEs

• >1000 breast and NSCLC pts enrolled in 3 RCTs receiving cisplatin +/- gemcitabine and rofecoxib, erlotinib, CMF and docetaxel (Di Maio et al, JCO, 2015)
• toxicity recorded by pts (grade 0 by physicians on CRF)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>%</th>
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<tbody>
<tr>
<td>alopecia</td>
<td>65.2</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>50.8</td>
</tr>
<tr>
<td>constipation</td>
<td>69.3</td>
</tr>
<tr>
<td>vomiting</td>
<td>47.3</td>
</tr>
<tr>
<td>nausea</td>
<td>40.7</td>
</tr>
<tr>
<td>anorexia</td>
<td>74.4</td>
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</tbody>
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Reasons for differences?

• Poor communication skills of HCPs eliciting information
  - leading & multiple questions
  - ascertainment bias
• Reluctance of patients to admit to presence and/or severity of symptoms
  - fear treatment maybe stopped
  - embarrassment
  - no wish to appear ungrateful or complaining
• Lack knowledge about CTCAE definitions
  - 3rd party transcribing info onto CRF from medical record
Proxy ratings patients/nurses
(To, J Pall Med, 2012)

- Symptom Assessment Scale used to self-report sleep, appetite, nausea, bowels, breathing, fatigue and pain
- Completed weekly by patient and treating nurse in hospice
- Poor – moderate correlations across all 7 domains (Pearson’s $r$)
- Nurses systematically under reported symptoms especially appetite, nausea and fatigue
- Proxy assessment even by experienced nurses a poor surrogate for patient self-report

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Why this matters

- If SEs under-recognised and under-reported then invariably under-treated

- SEs: peripheral neuropathy, diarrhoea, fatigue, mouth soreness, skin rashes etc more than minor inconvenience, and can lead to suboptimal adherence

- Without good quality PRO data little impetus to drive research into ameliorative interventions

- Little evidence in initial reports from RCTs of novel drugs of toxicities that matter to patients

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AVALPROFS  (Fallowfield et al, ECC poster-P280)

- Many therapies approved on PFS alone

- Predicting likelihood of benefit and life expectancy not easy but important to discuss

- 32 oncologists treating 90 pts (metastatic lung, breast, ovarian, cervical, colon, renal, H&N, melanoma)

- Estimated % pts in general who might derive benefit from drug and likelihood of benefit for their own pt with/without treatment

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Some results

- % pts expected in general to derive any medical benefit from drugs given for specific cancers variable 10-80%

- Drs thought 46/90 (51%) of their own patients would derive some medical benefit

- No likely benefit 5/90 (6%) or uncertainty for 39/90 (43%) who were nevertheless prescribed treatment

- Estimations of life expectancy were variable and inconsistent but 56/90 (62%) pts were predicted longer survival with treatment

Fallowfield, SHORE-C, 2015
AVALPROFS  (Fallowfield et al, ECC poster-P305)

- 90 pts (51 female, 39 male; mean age 65yrs range 32-85) all had progressive disease about to start novel therapies with only PFS or very modest OS benefits demonstrated

- 45/90 (50%) pts thought the therapeutic aim was "to help me live longer" and 35/90 (39%) pts expected that this would be achieved

- 35/90 (39%) thought the aim was "to help me feel better/improve QoL" and 40/90 (44%) had an expectation that this would be a benefit of treatment

- > half 49/90 said that having treatment "gives me hope"
Denial of death

• Modern Western cultures have inclination to deny death celebrating instead new medical advances

• Consequently HCPs and patients often harbour unrealistic expectations about likely therapeutic benefits of modern medicine

• ‘Doing something’ behaviours result instead of the honest but painful conversations needed
Shooting the messenger

“I HATE BEING THE MESSENGER AROUND HERE.”
Prognostication

• Failure to prognosticate not just unpredictability

• Prediction accuracy poor, direction of error (90%) in the overly optimistic direction

• Better doctor knows patient in length and intensity of contact more likely to overestimate survival (Christakis, BMJ, 2000)

• Patients become ‘twice removed’ from prognosis as
  - foreseeing – (unexpressed cognitive estimate about survival) likely to be optimistic
  - foretelling - communication of it subject to conscious and unconscious ambiguity or deliberate evasion

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Blurring of boundaries in the dr/pt relationship
(Fallowfield et al, Lancet Oncology, 2014)

I find it hard to be truthful about prognosis with patients whom I like

ESMO Survey N= 338

- 58% women
- 62% men

hard to be truthful

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Being truthful

- Some doctors seem to need to believe in the same sorts of miracles as do their patients.

- Many are nihilistic about the genuine benefits of good quality palliative care.

- Many data showing that patients with advanced disease benefit from early discussions about PC.

- True therapeutic aims and likely harms and benefits of treatment need to be expressed honestly surely reducing sometimes inappropriate toxic and invasive procedures near the end of life is important.

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Patients’ expectations (1)

- In study of 1193 pts with metastatic stage IV lung (n=710) colorectal cancers (n=483) 69% lung and 81% colorectal cancer pts did not understand chemotherapy was unlikely to offer cure. (Weeks et al, NEJM, 2012)

- Veracity of consent given questionable

- This was independent of educational level, performance status or pts’ role in decision-making

- These results together with the unlikelihood that end-of-life-care discussions take place may mean that too many pts are embarking on aggressive treatments prior to death

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Patients’ expectations (2)

• In CANCORS study pts who rated communication with doctors most favourably also more likely to harbour inaccurate expectations

• A follow-on study examined if optimistic expectations of cure led to receipt of chemotherapy in last month of life and less enrolment in hospice care (Mack et al, Cancer, 2015)

• 33% of 722 pts who died knew chemo was unlikely to cure their cancer but were just as likely to have treatment as those with inaccurate perceptions

• But understanding prognosis was significantly associated with hospice care before death

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Why defer discussing and integrating palliative care?


- Primary interest is to improve patient/family well-being; there are also good economic arguments (May et al, JCO, 2015)

- ASCO has offered a clinical opinion that PC should be integrated into standard oncology care (Smith et al, 2012)

- ASTRO likewise as part of their “Choosing Wisely” campaign in context of radiotherapy

Fallowfield, SHORE-C, 2015
They said **“nothing more can be done”**

- Be truthful about prognosis and likely outcomes with and without further treatment important
- Know the data, question own motives for recommendations
- Focus on positive deliverables of good palliation rather than implausible outcomes from more anti-cancer drugs
- Stress that something can always be done to relieve many of the worst symptoms
- Be positive about pain relief, stopping nausea, improving appetite etc etc

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“Rare are the cases where making or offering a carefully considered and framed prognosis results in choices that are harmful to the patient.....

As a result of a failure to prognosticate, let alone prognosticate accurately, patients may die deaths they deplore in locations they despise.

They may seek noxious chemotherapy rather than good palliative care, enrol in clinical trials of experimental treatment that offer more benefit to the researchers than to themselves, or reassure loved ones that it is not yet time to pay a visit only to lapse into a coma before there is time to say goodbye”

(Christakis, Death Foretold, 1999)
Conclusions

• New advances in therapeutics that extend patients lives obviously welcome

• If we are genuinely concerned about making quality of life the ultimate endpoint in metastatic disease:-
  - Communication about prognosis needs to improve dramatically
  - Disease & treatment related symptoms and SEs need better monitoring using validated PRO measures
  - Nihilism about benefits of good quality palliative and supportive care must be challenged

Fallowfield, SHORE-C, 2015
Acknowledgements

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