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Schuurhuizen, C.S.E.W.

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Summary and General discussion

The general aim of this thesis was to improve overall well-being and quality of life (QOL) for patients with advanced cancer undergoing anticancer treatment by optimizing psychosocial support and symptom management. More specifically, the first aim was to study the (cost-)effectiveness of a combined screening and treatment program in reducing psychological distress in patients with metastatic colorectal cancer (mCRC) receiving first line systemic treatment. Further, we intended to increase our understanding of the relatively low use of psychosocial support during first line treatment despite high rates of patients screening positive for psychological distress. Our second aim was to critically appraise the clinical value of QOL and toxicity reporting in randomized controlled trials (RCTs) in patients with cancer.

In this final chapter, the main findings of Chapters 2 through 8 will be summarized. Subsequently, the main findings will be discussed in relation to other studies, and clinical implications of our findings and recommendations for future research will be presented.

Summary of the main findings

Chapter 2 described the study protocol of a cluster randomized controlled trial by means of which we examined the effectiveness of a combined screening and stepped care intervention program (TES program) on psychological distress in patients with mCRC receiving first line palliative treatment.

In Chapter 3, the results of our cluster randomized controlled trial were presented. The combined screening and treatment (TES) program targeting psychological distress in patients with mCRC was not effective in improving psychological distress. The absence of effect could be explained by the low uptake of psychological treatment in the intervention (TES) group. Patients in the TES group did report higher satisfaction with the received treatment and better cognitive functioning.

In Chapter 4, we evaluated the cost-effectiveness and cost-utility of the TES intervention program. This economic evaluation did not show a statistically significant improvement in costs between the TES program and usual care.

In Chapter 5, we aimed to identify predictors for use of psychosocial services in patients with mCRC receiving first line treatment. We found that approximately one in five patients used these services at any point during their 48 weeks clinical follow-up. In this sample of patients with mCRC, the following predictors for psychosocial support use were identified: being younger, reporting higher levels of pain, being higher

educated, expressing a need to talk to a professional and the absence of progressive disease within the first weeks of treatment.

Chapter 6 consisted of a systematic literature review to assess whether treatment-related toxicity affects global QOL in patients with mCRC receiving systematic treatment. Evidence from 30 RCTs was reviewed, these were evaluated on the basis of global QOL scores, toxicity during treatment (assessed by scoring relevant adverse events) and primary outcomes. Our results showed that global QOL was similar between treatment arms despite consistently higher severe treatment-related toxicity of the experimental compared to the standard treatment arms. In addition, global QOL seemed to be unaffected by benefit in overall survival or progression free survival.

In Chapter 7, we evaluated whether cumulative toxicity can be used to predict treatment burden in patients with mCRC receiving chemotherapy, as opposed to measures only considering high-grade adverse events (AEs). Our results showed that cumulative toxicity scores, comprising all grades AEs are predictive for a clinically relevant decrease in physical QOL. Our findings indicate that future RCTs should include cumulative toxicity measures, as well as physical QOL instead of global QOL only.

In Chapter 8, we examined the predictive impact of cumulative toxicity on QOL reported by both patients and clinicians, for patients with metastatic castrate-naïve prostate cancer (mCNPC) enrolled in a large French RCT, the GETUG-AFU 15 trial. The results showed that clinician-based cumulative toxicity scores comprising all grades AEs provide a better measure of treatment burden than a toxicity score comprising high-grade AEs only. Further, it was shown that to predict the impact of toxicity on QOL, patient-based cumulative toxicity scores are to be preferred over clinician-based toxicity scores.

Discussion of the main findings – part I

Before starting this thesis, it was known that patients with cancer suffer from elevated levels of psychological distress¹⁻⁷. Psychological distress had been proven to be an unfavorable outcome in itself, and in addition was shown to be a risk factor for a poor outcome in the physical, mental and social domain of QOL^{6,8-11}. Studies suggested that a program relying on targeted selection of patients and enhanced care would be an effective approach towards screening and treatment of psychological distress in cancer patients. However, the true benefit of screening and subsequent treatment of psychological distress was far from being definitively proven¹²⁻¹⁵.

Because of the improved life expectancy, providing treatment for psychological distress in patients with CRC is an important issue. For these reasons, there was a strong ground for an intervention aimed at decreasing psychological distress in patients with (m)CRC. The cluster randomized controlled trial as described in Chapters 2 through 4, in which we tested a combined approach consisting of targeted selection and stepped care treatment of distress, showed that this program was not (cost-)effective in treating psychological distress in patients with mCRC receiving first line systemic treatment. Despite the optimal conditions created for a standardized screening and treatment program, marked contrasts between the intervention and the control group, high protocol adherence and the relatively high prevalence rate of psychological distress, the uptake of the stepped care program in the intervention arm was very limited. Of the patients assigned to the intervention condition, 60.3% screened positive for elevated distress on at least one of the screening moments. Strikingly, only 26.1% of patients entered the stepped care program, with only 11.4% choosing to receive active treatment to address their symptoms of psychological distress, and 14.7% choosing 'watchful waiting' only. In a recent meta-analytic study reporting on uptake of psychological interventions targeting distress in more than 12000 patients with cancer, uptake of care was as high as 60.1%¹⁶. However, as already well commented by Schellekens et al.¹⁷, the majority of the patients analyzed in that study were recruited by self-referral. This so called convenience sampling resulted in a higher uptake rate of interventions, since patients recruited in this manner are by definition very likely to be more intrinsically motivated to actually participate in such programs than patients invited by their clinician. In our study a more realistic estimate of uptake of interventions was obtained, since all potentially eligible patients were asked to participate (i.e. we used consecutive sampling).

The uptake of active psychological treatment in our study was only 11.4%. In other recent studies with this more realistic recruitment method, low acceptance rates of psychological treatment ranging from 3-10% were seen as well^{10,18-21}. Even though psychological treatment itself has been shown to effectively reduce psychological distress²², it seems that offering psychosocial interventions to patients scoring above a cutoff for distress does not result in higher uptake of these interventions nor reductions in distress levels, since the majority of patients decline such professional intervention²⁰. As already has been observed in patients with hematological cancers by Braamse et al.¹⁹, it seems that the presence of psychological distress does not necessarily equate the presence of treatment needs.

The finding that many patients with elevated levels of distress did not have a need for treatment and that other

patients without signs of distress did have the need to enter the stepped care program in our study, is consistent with other recent studies^{16,20,23-26}. These observations challenge the empirical basis for routine distress screening in cancer care, even when combined with triage and referral for treatment. However, patients that were screened for psychological distress and discussed this with trained nurses did report higher satisfaction levels with the received treatment, and reported better cognitive functioning. In addition, these patients tended to have better QOL scores in general compared with patients in the control group. Indeed, it has been shown previously that offering patients a chance to discuss their emotional concerns, regardless of distress levels or screening, can improve their well-being²⁷. Rather than implementing resource intensive routine screening programs for distress, patients could be simply asked whether they would like to discuss any psychosocial concerns with oncologic or psychosocial staff, regardless of the presence of distress²⁸. The finding that emotional support itself, consisting of empathy, concern, caring, affection and encouragement, improves both health and well-being outcomes^{29,30} further emphasizes the importance of clinicians providing such emotional support to their patients.

Since routine screening does not ensure identification of patients in need of support, it may in clinical practice be hard to recognize which patients may benefit from or are in greater need of emotional support. The majority of patients in our RCT seemed to have a low need for additional psychosocial care during their first line systemic treatment. However, the characteristics of patients that did use psychosocial support had not been investigated in a homogeneous group of patients with mCRC. These observations led us to study possible predictors for the use of psychosocial support, as described in Chapter 5.

Previous research in patients with cancer already demonstrated the relationship between certain sociodemographic characteristics and self-report assessments of patients' physical and psychosocial well-being and the use of psychosocial services^{15,23,25,31-35}. In line with these findings we showed that age, pain levels before start of treatment, level of education and the expressed need to talk to a professional at baseline were associated with more frequent use of psychosocial services. Interestingly enough in this group of patients with mCRC, clinical factors such as disease burden, time since diagnosis (of metastasis), type of systemic treatment, severe side effects and subsequent admissions were not associated with use of psychosocial services. The exception was disease progression during treatment; patients with progressive disease were shown to use psychosocial services less frequently, indicating that patients with advancing disease are *less* willing to address

or less capable of addressing psychosocial issues. Patients' focus when facing disease progression may shift towards end-of-life issues, in which energy is more likely to be spent on preparation for death and achieving a sense of completion than in using psychosocial support services^{36,37}. These findings suggest the following; 1) patients' sociodemographics and their self-reported well-being before start of treatment predict which patients will use psychosocial services and, 2) patients with progressive disease less often use psychosocial interventions aimed at distress reduction.

Clinical implications and future perspectives – Part I

It seems that even when facing life-threatening disease and intensive treatment, many patients are resilient. Resilience is characterized *by the ability to maintain relatively stable or experience only transient symptoms, minimal impairment, and a relatively stable trajectory of healthy functioning when exposed to potentially highly disruptive events*^{38,39}. With resilience occurring so frequently, screening necessarily aims at a minority of patients. Even if treatment would be highly effective, screening and subsequent treatment has limited impact on the entire sample, as the majority of the patients is not distressed nor in need of treatment³⁹. However, a major improvement in routine cancer care would be the provision of emotional evaluations with professionals and access to psychosocial services for all patients without patients having to score above a cutoff point for distress. Implementing optimal psychosocial care in routine cancer care may require active involvement of the entire staff of the ward, the support by an expert team, and policy maker promotion. Based on our study results and previous literature the following recommendations should be considered. As mentioned above, there is a significant role for the treating clinical staff (both oncologists and nurses) in providing emotional support. An essential requirement in providing emotional support seems to lie in effective communication, which has been associated with improved psychological functioning in patients⁴⁰ and a higher QOL and satisfaction⁴¹. In order to do this, clinical staff may have to improve their communication skills by training⁴². Second, a trained nurse or case manager could be assigned to selected patients that enter the oncology ward. This nurse accompanies the patient throughout the entire care process, helps in identifying social needs, and matches the patient between different hospital services and therapies based on intake information about specific problems and patient characteristics⁴³. It has been demonstrated before that trained nurses are able to manage psychosocial complaints in patients with cancer in the context of an organized multidisciplinary team^{44,45}, and that this is highly valued by patients⁴⁶. Finally, all patients should be informed about cancer-

related issues and must be offered the opportunity to attend psychosocial support services. Third, patients with disease progression during treatment should be monitored closely, since these patients are in general less likely to use offered psychosocial treatment and therefore might benefit more from psychosocial support from their treating clinicians. Especially when anti-tumor treatments are no longer available, clinicians can help patients have a better QOL (in their final days) by offering emotional comfort, concern and preventing unnecessary hospital admissions.

Discussion of the main findings – part II

In the second part of this thesis we focused on the apparent association between QOL and toxicity (reporting) during systemic treatment. Patients with advanced cancer have a poor prognosis and treatment is given to reduce tumor-related symptoms and to prolong survival to some extent. Especially in those patients where cure is not an option anymore, maintaining QOL is an important objective. For over almost four decades, there has been increased attention for systematic and quantitative ways to evaluate the impact of cancer and its treatment on health-related QOL⁴⁷. Originally, the purpose of QOL assessment was to provide an accurate estimation of a patients' well-being and of the benefits or losses that may result from treatment. However, it was shown to be difficult to widely agree on the definition of health-related QOL, as it consists of multiple dimensions such as physical, emotional, social, and cognitive functioning and seems to be an individual construct^{48,49}. Therefore, an overall quantified value of QOL, global QOL, that refers to life as a whole and could serve as an index, was added to the majority of QOL questionnaires^{47,50-52}. In many RCTs including QOL as an endpoint, indeed this quantified overall measure of global QOL is used to compare different treatment arms. Yet, previous research has already shown that patients with severe health problems and intrusive toxicities do not necessarily have global QOL scores that seem to match their health⁵³⁻⁵⁶. This is consistent with the findings from our systematic review described in Chapter 6, which indicated that the presence of severe toxicity does not seem to relate to global QOL. Nonetheless, this is often how QOL results are interpreted and explained in RCTs comparing different treatment regimens. The findings of our systematic review, however, indicate that one should be cautious by concluding that toxicity from a certain treatment is acceptable and tolerable because of the absence of global QOL deterioration.

Previous studies that already raised concern about the sensitivity of global QOL suggested that functional

scores of QOL, like physical QOL, may be more profound in detecting changes over time than global QOL^{53,57}. To further explore the observed discrepancy between treatment-related toxicity and QOL, we examined the impact of cumulative toxicity on global and physical QOL in Chapter 7. In line with our expectations we showed that the total of toxicity experienced by patients with mCRC during 10 weeks of treatment did not affect their global QOL scores. On the contrary, cumulative toxicity was shown to be associated with lower physical QOL. A finding just as interesting was the fact that cumulative toxicity measured as the total of severe toxicity only, i.e. the total of grade 3-4 AEs, did not seem to affect global or physical QOL, while measuring cumulative toxicity including the often longer lasting, lower grade 1-2 AEs, did seem to have an important impact on patients' physical QOL.

The accuracy of assessment and reporting of toxicity by clinicians has been questioned lately⁵⁸, as it seems that toxicity is frequently underreported by clinicians^{59,60}. The cumulative toxicity scores described in Chapter 7 were based on clinician-reported AEs, whereas there is a recent and growing emphasis on using patient-reported outcomes in conjunction with toxicity⁶¹. In Chapter 8 we aimed to validate our previous findings on cumulative toxicity and QOL in patients with mCNPC. In addition, we aimed to examine whether cumulative toxicity reported by patients was more predictive for QOL than cumulative toxicity reported by clinicians. It appeared that patient- and clinician-based cumulative toxicity scores comprising all grades AEs better reflect the impact on patients' physical QOL than a toxicity score comprising high-grade AEs only. Additionally it was shown that patient-reported cumulative toxicity scores are to be preferred when to predict the impact of toxicity on QOL.

The combined findings of these studies imply that the standard methods for reporting on QOL and toxicity should be questioned. We have shown that instead of global QOL, physical QOL may better reflect potential benefits and harms of treatments in patients with mCRC and mCNPC receiving treatment. However, the original purpose of QOL evaluation was not to obtain a subjective report of treated-related toxicity burden by patients. Since overall QOL, or even health-related QOL, by definition is more than just toxicity burden and physical functioning, the real question is: What are we measuring when patients complete their "QOL" assessments? It is questionable to which extent standardized QOL measures adequately quantify a patient's actual QOL^{62,63}. Subsequently, are clinicians then capable of preserving or improving patients' overall QOL? Sure, by alleviating symptoms or halting disease progress they help in improving physical functioning, but that

does not necessarily equals improving patients' overall health-related QOL.

Further, it seems that clinicians and patients seem to differ in their evaluation of toxicity and subsequent burden of treatment. The clinical toxicity evaluation mainly focuses on occurrence and severity, while patient-reported toxicity focuses more on the duration and relative burden. A description of severe toxicities by clinicians is important and relevant to determine drug tolerability, while patients themselves may provide a more representative overview of how toxicity including the (re)occurring, longer-lasting grade 1 or 2 AEs throughout therapy may impact their day to day lives.

Clinical implications and future perspectives – Part II

We should no longer try to monitor, interpret and understand global QOL in relation to treatment, an outcome that is unlikely to improve by symptom relief. Conversely, clinicians should no longer attempt to improve an outcome that is unlikely to be properly measured. Recent interest has grown in including patient-reported toxicity in clinical oncology care to improve symptom detection and management^{64,65}. Not only do clinicians often underestimate many of the symptoms experienced by patients, also the reliability between different clinicians is low^{59,66}. Patients self-reporting of toxicity has been found to intensify symptom management, improve communication, satisfaction and well-being^{67,68}.

With the ultimate aim of providing patients with the best-care, incorporating patient-reported toxicity into routine cancer care is of major importance, since these may potentially serve as the best correlates for patients' QOL we have^{69,70}. In addition, our outcomes suggest that improvement of treatment-related toxicity management by clinicians should include emphasis on the lower grade AEs as well, as this may result in clinically relevant improvements in patients' physical functioning. Physicians should become increasingly aware that addressing lower grade AEs in RCTs is just as important as the higher ones for optimizing physical health status.

Conclusion

Patients with advanced cancer receiving first line systemic treatment may suffer from a variety of side effects, both emotional and physical. This thesis provides several directions to improve these broad range of effects. First, a combined screening and treatment program for psychological distress is not effective; instead, it seems that enhanced care in the form of providing emotional support, close monitoring and access to psychosocial

support services may improve patients' well-being. Second, the reporting of toxicity by patients with advanced cancer and the acknowledgement of impact of less severe but multiple side effects, may improve overall management of toxicity during treatment by clinicians. Taken together, the findings presented in this thesis indicate that even in absence of cure, clinicians may still positively and significantly influence the lives of their patients.

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