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LETTER TO THE EDITOR

Are chemotherapy-associated symptoms underestimated? A view beyond common toxicity criteria

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To the Editor,

During the past decades, the prevalence of cancer is increasing as a result of the aging population and increasing cure rates. Quantity of life with a minimum of side effects during and after treatment is the primary goal for patients. Therefore, besides pursuing increasing disease-free and overall survival for patients, physicians should also pursue that patients can resume daily life, including work, as soon as possible. The aim of the medical treatment is not only prolongation of life, but also the preservation of its quality [1]. Simultaneously, a link has been observed between curation, or response in palliative treatment, and quality of life (QoL) [2]. Therefore a good balance between response and toxicity has to be found.

Consider this case and a non-oncologist physician's view on chemotherapy issues in daily practice outside clinical trials. A 47-year-old piano teacher has colorectal cancer (CRC) stage III, guidelines recommend adjuvant treatment with an oxaliplatin containing regimen [3]. Nevertheless, chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially severe side effect of oxaliplatin which may increase the risk the patient would not be able to play piano anymore. After thorough discussion between patient and clinician the decision was made to start treatment with capecitabine-monotherapy. Right or wrong? "*To be good physicians, we must all fight against the battle against cancer*" [4]. This illustrating letter by a non-oncologist physician mocks how the medical oncologist even would like to continue with chemotherapy after death in a 90-year-old woman with heart and kidney failure, hemiparesis and metastatic breast cancer [4]. Being medical oncologists, are we really that persuasive to our patients and reluctant to withhold tumor-directed treatment at any stage of cancer? And are we deaf for patients' desires or do we ignore them?

How do we determine which level of toxicity on the short- and long-term is acceptable in the light of curation or better response rates? What absolute survival advantage justifies persistent toxicity? In addition, what is acceptable to clinicians can be unacceptable to patients and limit them in their daily activities. In clinical trials toxicity is mostly based on Common Toxicity Criteria for Adverse Events (CTCAE), and mainly grade 3 or 4 are reported. However, those levels of toxicity are mainly based on the judgement of the clinicians, and patient-reported outcomes (PROMs), which may be helpful in determining what is acceptable to patients, have hardly been used and should be encouraged [5,6].

The toxicities of treatment should be justified by the benefits. Taxanes are often used in the adjuvant treatment of breast cancer patients. A meta-analysis of randomized controlled trials reported the absolute eight-year overall survival advantage of taxane containing treatment to be only 2.8% [7]. Nonetheless, patients with early breast cancer who are often treated with taxanes experience substantial toxicity [8]. Moreover, a French study investigating adding oxaliplatin to 5-fluorouacil/leucovorin to the first line treatment of stage IV CRC showed no significant benefit in overall survival [9], and the median overall survival in those patients was 16 months. Nevertheless, it is likely that the use of oxaliplatin in next line is responsible for the lack of survival benefit. However, oxalipatin is often used in those patients and accompanied by potentially severe and persistent adverse events, such as CIPN [10], which may influence patients' QoL [1]. Another option for treatment in those patients with similar response rates is irinotecan containing therapy. However, these regimes are also often accompanied by severe side effects. Therefore, informing patients properly about possible side effects and the average survival advantage for certain treatment options is important. In that way, a shared decision between the patient and clinician can be made regarding the treatment they prefer. The availability of information on PROMs would be valuable in this decision as it informs patients about the expected side effects. When more profound and toxic regimens result in small or no overall survival advantage, toxicity and the influence on patients' QoL should outweigh the potential benefit.

As a result of application of adequate anti-emetics and hematopoietic colony stimulating agents for side effects like

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chemotherapy-induced nausea and hematotoxicity, other toxicities, such as CIPN and fatigue, nowadays become more apparent and therefore subject of investigation in clinical trials. However, it is also described that subjective side effects are often underreported by clinicians [5,6]. This is emphasized by a recent study that confirmed that common adverse events of CRC, like cognitive functioning and fatigue, are often underestimated [11]. In addition, we investigated the incidence and severity of the common side effect CIPN, and reported that CIPN was still often experienced by CRC survivors up to 11 years after diagnosis with a negative influence on their QoL [10,12]. Similar results were reported up to 12 years after the end of treatment in women with ovarian cancer who received chemotherapy [13]. The side effect that is most neglected is alopecia [14]. It is not life threatening, temporary and 'only' cosmetic. However, it is the stigma of fighting cancer, it often has high impact for the patient and it is regularly a reason for rejecting chemotherapy [15]. Also this side effect is highly underestimated by clinicians and nurses [16]. Therefore measuring and preventing alopecia deserves attention.

Moreover, not only the underreporting by clinicians of subjective adverse events is of concern, also the timing of toxicity assessment during treatment is crucial. Toxicity is most frequently reported before the subsequent treatment, however, adverse events are most severe shortly after chemotherapy administration. Consequently the burden of the adverse events for patients is probably even more than reported. Therefore, we believe that common side effects, such as fatigue, CIPN and alopecia, are underreported and the more thoroughly a specific adverse event is examined, the higher the burden appears to be. Self-monitoring of adverse events by patients and customized coaching on how to report concerns to clinicians [17] should positively contribute to future research.

Furthermore, fatigue is a common determinant of overall functioning and QoL. Therefore, it is not unlikely that it is associated with other adverse events. Recently studies have reported that fatigue is associated with other common adverse events, such as CIPN, and greater levels of fatigue were associated with greater symptom severity [11,18,19]. Additional analysis of data of a previous study [12] showed significantly ($p < 0.0001$) more fatigue, measured by the total score of the fatigue assessment scale, in patients with the 10% highest CIPN scores ($N = 141$, mean = 25.38, SD = 8.43) compared to those with lower CIPN scores ($N = 1348$, mean = 19.41, SD = 5.84). This observation may suggest not only that certain toxicity items are interrelated, but also that they may aggravate each other, and how would this relate to a patients' QoL? Given the fact that mainly grade 3 or 4 adverse events are reported in randomized clinical trials, we believe that adverse grade 1 and 2 events are not only underreported [6], but therefore also underestimated, especially if they are related. The burden of treatment with chemotherapy is not only determined by the severity of the adverse events, but also by the combination of all experienced side effects together.

To provide optimal care and find the right balance between response and toxicities we should overcome the mentioned drawbacks. First, personalized medicine should be integrated in daily care, not only to achieve the best response rates, but also to prevent toxicity. Identifying patients at risk of developing toxicities is of major importance. The findings of recent studies demonstrate that certain patients, who are treated with oxaliplatin, might be more at risk of developing CIPN due to variants in encoding genes of ion channels in the central nervous system [20–22]. Therefore a clinician might decide to restrain oxaliplatin for that patient. Furthermore, as toxicities are often underreported by clinicians [5,6], self-reported questionnaires or self-monitoring should be incorporated in daily clinical practice. In addition, the burden of treatment with chemotherapy is determined by the combination of all experienced side effects together, and over time the patient is confronted with varying grades of these side effects until the next chemotherapy cycle. The burden of treatment should be expressed in the number and level of toxicities (including grade 1 and 2) multiplied by the days between cycles they experience those side effects. In daily clinical practice this is difficult to determine, however, a tool to define the total burden would be valuable. Consequently, clinicians should consider applying dose modifications earlier in patients with many adverse events, especially in the case of the side effects as CIPN with no proper available treatment [23]. As a result of the assumed interrelation between toxicities, and the increasing prevalence of fatigue and CIPN in cancer patients, management is warranted. Physical activity is associated with a better health-related QoL, less fatigue and CIPN among CRC survivors [24] and should therefore be encouraged.

In summary, the gains of treatment with chemotherapy must outweigh the disadvantages. Identifying patients at risk of developing adverse events is warranted. Common adverse events of cancer and its treatment are often underreported and underestimated and the use of PROMs are therefore encouraged. As adverse events might be interrelated and accumulative, it is important that also moderate side effects are reported and treated as possible. Future studies should not only focus on the CTCAE-grades, but also on the total burden of adverse events and the impact of these adverse events on patients' QoL.

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