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EDITORIAL

What is the appropriate use of palliative docetaxel in castration-resistant prostate cancer?

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Those of us who believe we can do much more for the well-being of men destined to die of their prostate cancer applaud the effort by Lissbrant and co-authors, published in this issue of ActaOncologica [1]. They fetch their data from the Swedish quality registers – a rich source both for knowledge that can be used to improve clinical practice and to learn more about the biology of prostate cancer [2]. Possibly the data are relevant for countries with similar conditions as those in Sweden. We learn from the article that 21% of men with castration-resistant prostate cancer (with specific restrictions, including disease severity and comorbidity) receive cytotoxic or cytostatic chemotherapy, treatment occurrence follows an age-gradient and a socio-economical gradient and Sweden holds a large geographical variation of the clinical practice for this group of men. The article presents important new information and we can discuss how to move forward based on the outlined reality.

Concerning the suffering among men during the last year before they die of prostate cancer, we have no registers until recently. The dramatic changes during the 1970s and 1980s are documented in narratives from physicians and patients only. Before the days of a rational use of opioids, or palliative radiotherapy against lesions, skeletal metastases could result in a long-lasting frightful pain. Before the days of nephrostomy, continuous growth of malignant cells into the ureter caused to symptom-giving uremia. Before the days of prompt actions with a radiological examination and operation to relieve the pressure on the spinal cord, paraplegia with secondary bedsores led to months of hospitalization. Today, with cutting-edge palliative care, the death of prostate cancer often implies an increasing tiredness until the final sleep follows. Other symptoms can be relieved or eliminated.

So, today, given a cutting-edge palliative care, what is the role of chemotherapy in castration-resistant prostate cancer? We know that men contracting metastases typically respond for 1–2 years to medical or surgical castration – the pain stops bothering them and tumor shrinkage may lead to improved well-being. But, ultimately the malignancy resists the castration and proliferates. At that point, when should we consider chemotherapy to increase survival? When should we offer it to the patient with the intention to improve quality of life?

A modest improvement in survival, say three months, for a group of men treated by chemotherapy (as compared to non-treated men), may be evenly or unevenly distributed. That is, either most men gain about three months, or a smaller group have a larger benefit while the majority has a limited or no influence on the length of life by their treatment. If the gain is evenly distributed, the man can weigh side effects against the expected delayed onset of death with reasonable certainty. The man has possibilities to imagine an area under the curve with time on the x-axis and quality of life on the y-axis. Cytotoxic and cytostatic treatment requires time, presence in hospital, economical expenses and results in chemotherapy-induced side effects; all these negative consequences must be subtracted from any survival gain. But, can we give the patient considering chemotherapy the

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tools to understand his future alternative scenarios? Do we have the science to measure this area under the time-quality-of-life curve, or do our methods blur the reality? And, if measured, do we have a science that allows us to fully communicate the two scenarios, with and without chemotherapy? Those of us answering no on one or both of these questions should hesitate to make specific recommendations – to the patient with castration-resistant prostate cancer in front of us as well as to the population in standards-of-care programs. The same reasoning goes if the agents are given with the aim to relieve skeletal pain only.

Tannock and co-authors have published a randomized study of men with castration-resistant prostate cancer [3]. The median survival was 16.5 months among 337 men planned for mitoxantrone, 18.9 months in the group with 335 men allocated to receive docetaxel every three weeks and 17.4 months in 335 men randomized to be given weekly docetaxel. In an up-date of this study, the survival differences remained (median 19.2 vs. 16.3 months, hazard ratio 0.79 (95% CI 0.67–0.93). A similar survival gain of close to median three months was also found in another phase III trial [4]. The appropriateness of the control group in these two trials (mitoxantrone-prednisolon), as well as the combination with extramustine in [4] have been much discussed. A longer median survival gain [nine months, from 18 (95% CI 15.2–20.8) to 27 (95% CI 19.8–34.1) months] was seen in a prematurely broken study (109 eligible patients included), using prednisolone alone as control group [5]. No data are presented indicating an uneven distribution of the survival benefit in the three studies, which could be interpreted as that most men live about three months longer with the chemotherapy than without. This is, however, not likely. In a review [6], it is stated that about half of the patients have some benefit from docetaxel in [3]. If this is true and based upon experience in other tumor types like colorectal cancer [7,8], any survival gain is probably limited to that half. Side effects of docetaxel include neutropenic fever, diarrhea, dehydration, nausea and vomiting. The corticosteroids needed to be given concomitantly with docetaxel can result in psychosis, insomnia and provoke the onset of diabetes mellitus.

We are not aware of any data on the success of communicating reasons for giving chemotherapy without curative intention in castration-resistant prostate cancer. A study throughout the US revealed that as high proportion as 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer [9]. Paradoxically, patients who reported higher scores for physician communication were also at higher risk for inaccurate expectations. That is, patients satisfied with their physicians were more often unrealistic about the possible treatment effects. If these data are relevant for prostate cancer, many men receive chemotherapy based on an illusion.

In recently released (March 2013) Swedish guidelines about the care of patients with breast, prostate and colorectal cancer from the National Board of Health, indicators of quality are defined and desired cut-off values, above or below which every hospital or county should aim at, are provided. The proposed minimum level for the use of docetaxel in castration-resistant prostate cancer is 60%, i.e. considerably higher than the present situation [1]. The results of the study by Lissbrant and co-authors are important in these discussions to illustrate the "substantial underuse" of palliative chemotherapy in prostate cancer patients. What is then an appropriate level of use of a non-curative therapy that may prolong life median three months, improve the probability to live at three years a few percentage points, relieve tumor-related symptoms or delay their appearance in let us say 50% of the patients at the level of toxicity docetaxel has in a society with a tax-financed healthcare with a clear aim to be equal to all? Or is it at all possible to define a minimum appropriate level for use of palliative treatments? We do not think so, particularly not when it is possible that high quality palliative care can reduce its use [10], as Lissbrant and co-authors discuss. Reference is given to apparently higher use in, e.g. metastatic colorectal cancer, where presently about 60% in the three Scandinavian countries and the Netherlands receive chemotherapy [11,12]. This level of use was reached at specialized centers actively running clinical trials. Again, strong age dependence was seen, but it was not possible to detect any influence from education in the Scandinavian study [13]. Again, it is not possible to state whether a 60% level is appropriate. It is, however, not acceptable if the use differs between different diagnoses depending upon traditions; only the magnitude of the gains, toxicity and other inconvenience levels, and costs should matter.

We are not aware of any study including the patient's preferences presenting data saying we underuse chemotherapy in the palliative setting the six months preceding death. The literature contains publications describing the prevalence of use, predictors of the use and investigations to what extent the indications had been discussed with the patient. Randèn and co-authors [14] outline the situation in 2009 at one center in Stockholm, Sweden. Among 346 persons who died of disseminated cancer during 2009, and had had at least one contact with the Department of Oncology, Karolinska University

Hospital, 54% had been treated with chemotherapy with non-curative palliative intent. The figure for prostate cancer was as high as 26 of 35 (74%). Moreover, they found that in only 43% of patients were discussions about ending chemotherapy documented in the patient file. Näppä and co-authors [15] studied 374 patients who had received chemotherapy and died 2008 in northern Sweden; 87 (23%) received chemotherapy the last month. Similar findings have also been reported by others [16]. Such figures indicate an overuse of side effect producing agents during the end of life. Major reasons may include the lack of scientific data as a basis to weigh beneficial versus harmful effects during the different stages of disease progression from being incurable to the obvious near-death stage. We overestimate the expected survival time [17], have no clear definitions for the disease stage apart from being metastatic and incurable, and have no clear criteria for assessing outcome during the different disease stages. Thus, reading the literature with this perspective in mind, available data, including those from Lissbrant and co-authors, it tells us we need to be better of abstaining from, and ending when started, chemotherapy at the end of life in men with prostate cancer. This is likely true for most other solid malignancies as well.

Some believe the palliative setting will change dramatically when we learn to efficiently use abiraterone and other new drugs [18]. Roughly, we can picture the effect by abiraterone and similar drugs as an intra-cellular castration; the molecule breaks the autocrine loops giving the resistance of the malignant cells to an environment with low levels of testosterone. Fizazi and co-authors documented a 4.6-month survival gain (15.8 months vs. 11.2 months) in men with a median age of 69 years, and having been treated with chemotherapy for their castration-resistant prostate cancer [19]. A clear gain was more recently reported also in castration-resistant prostate cancer patients who had not received prior chemotherapy (median not reached vs. 27.2 months, hazard ratio 0.75; 95% CI 0.61–0.93) [20]. The spectrum, occurrence and intensity of side effects differ markedly from chemotherapy, reflecting varying mechanisms of action. All evidence say the negative influence of the men's well-being is markedly less than for conventional chemotherapy. Future use of these drugs will be determined by clinical research but also on the structure of healthcare and health-economic issues. Like most other new drugs, they cost a lot.

Until July 1, we were all welcome to respond to the proposed Swedish guidelines for prostate cancer. In the guidelines, one of the highest recommendations is for usage of docetaxel in men having castration-resistant disease. Whether the present situation, with 21% of men in Sweden with castration-resistant prostate cancer receiving chemotherapy is appropriate, too low, or too high is not known. We need to do much better studies than we have done. Can the side effects of chemotherapy be outweighed by a (median) three month survival gain for men with castration-resistant prostate cancer? Moreover, when we consider a man for palliative treatment, we must learn to communicate a realistic scenario about wanted and unwanted treatment effects [21]. We cannot treat him on the basis of an illusion.

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