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Editorial Comment

Physical activity in long-term survivors of germ-cell cancer

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The treatment of patients with disseminated testicular cancer has been one of the major breakthroughs in oncology. Since the introduction of cisplatin in chemotherapeutic regimens for testicular cancer in the late 1970s, the majority of these mostly young patients achieve durable complete responses. This even accounts for more than 90% of patients who are deemed good-prognosis metastatic disease according to the International Germ Cell Cancer Collaborative Group classification. Today, the combination of bleomycin, etoposide, and cisplatin (BEP) is considered standard therapy. However, this treatment is associated with sometimes severe toxic side-effects such as bleomycin-induced pneumonitis and fibrosis, Raynaud's phenomenon, neurotoxicity, ototoxicity and nephrotoxicity, during or shortly after treatment. Therefore, especially in patients with good-prognosis disease, trials have been performed aiming to identify chemotherapeutic regimens with an improved toxicity profile compared with the BEP-regimen. From these trials, it can be concluded that three cycles of BEP, with a total dose of etoposide of 500 mg/m^2 per cycle either in a 3- or 5-day schedule, should be regarded as standard chemotherapy for patients with good-prognosis disease [1,2]. Although a randomised trial of four cycles of etoposide and cisplatin (EP) versus three cycles of BEP designed to assess therapeutical equivalence has not been implemented, in view of updated data from two Eastern Cooperative Oncology Group (ECOG) studies, it can be assumed that four cycles of EP is a valid, alternative treatment option [3]. In intermediate- and poor prognosis disease, four cycles of BEP remains standard therapy [1].

Because an increasing number of patients with disseminated testicular cancer obtain long-term survival, attention has focused on the long-term sequelae of treatment. One of the most disturbing long-term effects identified is the increased risk for cardiovascular morbidity. Meinardi and colleagues previously reported that patients who were in remission for more than 10 years after receiving cisplatin-containing chemotherapy had a 7.1 times increased risk for coronary disease compared with the general male population [4]. In their and other studies [4–7], several risk factors were identified, including hypertension, hypercholesterolaemia, micro-albuminuria and hormonal alterations. An increased body mass index (BMI), a well-known risk factor for developing cardiovascular disease, has also been established in these patients [5]. In addition, in other cancers, breast cancer in particular, an increase in BMI after receiving chemotherapy has been observed among patients. The mechanisms responsible for this effect are not exactly known, but decreased physical activity has been suggested to be involved [8]. Furthermore, besides being a risk factor for increased BMI, decreased physical activity as such has been shown to be an important risk factor for increased cardiovascular morbidity. Because of the notable risk for cardiovascular events in long-term survivors of testicular cancer, it is important to obtain more insight into the level of physical activity that these patients have.

In this issue of the *European Journal of Cancer*, Thorsen and colleagues report on this topic [9]. The authors' hypothesis was that patients who were treated with chemotherapy would have a reduced physical activity compared with patients who did not undergo chemotherapy. This hypothesis was based on observations that after receiving chemotherapy patients reported more fatigue, more psychological problems, and suffered from somatic sequelae such as neurotoxicity and decreased testosterone levels, all factors which would presumably compromise their ability to undergo physical activity. Besides comparisons between the treatment groups, the level of physical activity of the patients was also compared with the general population.

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The study used data from 266, 530 and 480 testicular cancer patients treated with surgery alone, radiotherapy and chemotherapy, respectively, which were compared with data from 20 391 men from of the general population aged between 18 and 59 years. The level of activity was established by a questionnaire-based assessment.

Contrary to the hypothesis, no difference was found in the level of physical activity between patients who were given chemotherapy compared with the other treatment groups. Moreover, testicular cancer survivors appeared to have a higher level of physical activity than the general population. The authors speculate about explanations for these findings, but the exact reasons are not clear. Of note, it appeared that the most of the patients, as well as of the control population, were inactive or minimally active according to the definitions used in this study. Unfortunately, the authors do not present data on BMI in the several treatment groups that would enable us to get more insight into the relationship of physical activity and BMI in these patients.

Nevertheless, it can be concluded from this study that a lower level of activity does not seem to play an important role in the underlying mechanisms responsible for the increased cardiovascular risk in testicular cancer patients treated with chemotherapy. Since the risk for developing cardiovascular diseases in these patients appears to be greater than the risk of a relapse or the occurrence of a secondary malignancy, it is clinically relevant to pay attention to this problem.

As indicated above, both three cycles BEP and four cycles EP can be regarded as standard treatment in patients with good-risk disease. Which of these two regimens leads to more cardiovascular risk is not known. Obviously, the advantage of four cycles EP is the omittance of bleomycin, which is, however, at the price of the increased cumulative doses of etoposide and cisplatin associated with the fourth cycle, that may lead to more nephrotoxicity and neurotoxicity. Whether this, and other unknown factors, may result in more cardiovascular risk is not yet known. The advantage of three cycles BEP is the lower total dose of etoposide and cisplatin, but bleomycin can induce bleomycin-induced pneumonitis, that has been reported to be fatal in between 1 and 3% of patients treated in testicular cancer trials. Most of the patients, however, do not experience any lung toxicity. Moreover, in those patients who developed signs or symptoms of pulmonary toxicity, these were mostly found to be reversible over time [10]. Bleomycin-mediated effects on the vasculature, also reflected in, e.g. Raynaud's phenomenon, are probably involved in the pathogenesis of bleomycin-induced pneumonitis [10]. Hypothetically, these bleomycin-induced vascular effects may also contribute to the increased cardiovascular risk. Therefore, more research is needed to elucidate the pathogenesis of the increased cardiovascular risk in testicular cancer survivors and exactly which treatment factors are responsible for this. Until then, no firm recommendations can be made as to which of these two treatment options should be used, except for patients that are at an increased risk of developing bleomycin-induced pneumonitis [11] for whom four cycles EP may be the preferred regimen.

Today, physicians involved in the long-term follow-up of these patients should consider screening regularly, e.g. yearly, for cardiovascular risk factors such as hypertension, hypercholesterolaemia, micro-albuminuria, and increased BMI, and treat these if they are abnormal. Another important preventive measure may be to encourage physical activity in these patients. Increasing physical activity has been clearly shown to attenuate cardiovascular risk in men, also in the presence of other unfavourable coronary risk factors [12,13]. This beneficial effect of intensive physical activity has been described to result in a relative risk of approximately 0.6 compared with those with the lowest level of activity [12,13]. Although testicular cancer patients may self-report increased physical activity compared with the general population, which is encouraging, most are not physically active on a regular basis according to today's report.

Therefore, because of the substantial cardiovascular risk for patients with disseminated testicular cancer who have received chemotherapy and because of the demonstrated benefit of physical activity with regard to this risk in men, we should consider encouraging our patients to exercise. So, long-term survivors of testicular cancer should take inspiration from Lance Armstrong and "Get up and be more physically active (e.g. take a bike ride)" [14].

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