Testicular cancer (TC) is the most common neoplasm in males aged between 15 and 40 years and the majority of patients are diagnosed without evidence of metastatic disease, i.e. clinical stage I (CSI) [1, 2, 3]. Adjuvant chemotherapy in form of one or two cycles of BEP reduces the risk of relapse by ~90%. However, the majority of patients with metastatic nonseminoma are within the good-prognosis group according to the International Germ Cell Collaborative Group (IGCCCG) and are cured by three cycles of BEP. In light of tumor burden, two cycles of BEP might represent overtreatment of patients with only micrometastases and many experts prefer to recommend one cycle of BEP when adjuvant chemotherapy is to be given.

The controversy surrounding adjuvant BEP chemotherapy in stage I testicular cancer rests more on fear of as yet unknown late toxicity than on concerns about efficacy and known immediate toxicities. Ethically, any risk of harm without a certain benefit is particularly problematic as is always the case in patients receiving adjuvant chemotherapy when the existence of micrometastases is uncertain in any individual patient [4]. Therefore, the article by Vidal et al. ‘Long term outcome of patients with clinical stage I high-risk nonseminomatous germ cell tumors 15 years after one adjuvant cycle of Bleomycin, Etoposide and Cisplatin chemotherapy’ is a timely report [5].

This principle of nonmaleficence is part of the Hippocratic Corpus and ‘Primum non nocere’ represents unethical backbone, meaning, ‘first, do no harm.’ More broadly, this bioethical precepts suggests: ‘given an existing problem, it may be better not to do something, or even to do nothing, than to risk causing more harm than good’ [6].

does adjuvant chemotherapy cause more harm than benefit?

So, were any of the 40 consenting nonseminoma high-risk stage I patients harmed by exposure to one modified-BEP cycle?

No, long-term data do not indicate relevant long-term toxicities. This is in concordance with other studies, which reported most serum parameters as well as lung function, audiometry, sexual function, and fertility rates as unaffected by adjuvant treatment with one to two cycles of BEP [7–9]. A Philadelphia-positive acute lymphoblastic leukemia occurred in one patient after additional three cycles of BEP for subsequent metastatic contralateral testicular cancer. This type of leukemia is not known to be related to chemotherapy, as opposed to the etoposide-induced acute myeloblastic leukemia with 11q23 abnormalities. This complication usually occurs after high cumulative etoposide doses exceeding 2000 mg/m² [10].

The study by Vidal is far from perfect: only 40 patients were finally eligible, the BEP dosing was experimental and the one arm design does not allow a comparison between outcomes following different management options. Further, embryonal carcinoma >50% is not a standard risk factor and apparently challenging for pathologists since 3 of the initial 44 patients (6.8%) had to be excluded from this study since the proportion of embryonal carcinoma was below 50% at re-evaluation. Lymphovascular invasion (LVI) is the most widely accepted risk factor for relapse and its presence is associated with a relapse rate of 50% compared with 15% in patients without LVI [11–13]. The experimental BEP schedule using a daily dose of 20 mg/m² of bleomycin, 120 mg/m² of etoposide, and 40 mg/m² of cisplatin administered i.v. on days 1–3 has no clear benefit over standard BEP, which remains the recommended regimen [14].

Only 1 of 40 patients (2.5%) experienced recurrent TC. Without active treatment, i.e. surveillance, one would expect about 20 recurrences (50%). The relapsing patient received three salvage BEP courses for pulmonary metastases and died of a pulmonary distress syndrome within 4 weeks. This is a rare complication of metastatic TC patients within the good-risk group according IGCCCG and there is no indication that the previous adjuvant BEP contributed to this outcome [15]. Subsequent salvage chemotherapy is generally well tolerated and of similar efficacy as in patients during active surveillance. Of note, autopsy of the deceased patient showed no signs of active tumor.

In total, three patients (7.5%) developed a contralateral TC and the indicated lack of prevention of subsequent progression of carcinoma in situ has recently been reported by SWENOTECA [16]. Two additional patients required treatment of colorectal cancer which is unrelated to TC or its treatment, as opposed to cancers of the kidneys, thyroid or abdominal soft tissue [17].

In conclusion, BEP ×1 is a well-tolerated means to abolish micrometastases and should be considered the standard treatment when adjuvant chemotherapy is to be given. Patients should be encouraged to consider their individual risk of recurrence on surveillance and all the consequences of this, both medical and socioeconomic, against the short-term toxicities of adjuvant chemotherapy. Only then can they make a balanced, informed choice. Physicians failing to present risk-adapted treatment strategies may harm their patients by infringing their autonomy and exposing them to a high risk of requiring salvage chemotherapy and possibly retroperitoneal lymph node dissection, with well-established long-term toxicities [18].
disclosure

The authors have declared no conflicts of interest.

references