There are several reasons why drugs may not reach therapeutic levels within cancer cells. Since the drug concentration in the cell is limited by the dosage that can be usually given, the increased number of target molecules means that many of the targets are not affected by the drug: there are just too many for the number of drug molecules present [1]. Consequently, oncologists thought that just increasing the dosage of active drugs would increase the cell kill. Therefore, as soon as autologous bone marrow transplantation became available, they started to give high-dose chemotherapy (HDCT) with stem cell support. The most-used drugs are etoposide and alkylating agents.

Connolly and McCaffrey [2] presented a well-written and well-documented review paper on HDCT supported by autologous stem cell transplant in advanced or relapsed male germ cell tumours (GCTs). They performed an accurate search in the English language literature of the last 20 yr for HDCT with SCT in first-line treatment for poor prognosis and in the salvage setting for relapse after failure of first-line standard chemotherapy. While several phase 2 studies claimed a therapeutic advantage of HDCT over conventional chemotherapy in high-risk patients, phase 3 trials failed to confirm such results. There were only two randomised studies for each clinical situation, and the authors correctly expressed some criticism. As for HDCT in the first-line treatment of poor-prognosis patients, the authors expressed some difficulties in interpreting the French study because of low dose intensity in the high-dose arm and the use of a nonstandard regimen (references 22 and 23 in Connolly and McCaffrey [2]). Furthermore, the phase 3 American study did not achieve the patient accrual and complete overall responses were not different in the two arms; however, in a subanalysis of patients with slow marker decline, HDCT was superior to standard bleomycin, etoposide, and cisplatin (BEP; reference 29 in Connolly and McCaffrey [2]).

As for phase 3 trials in the salvage setting, the IT94 European study unequivocally documented no difference in overall survival in the two arms (reference 47 in Connolly and McCaffrey [2]). A discussion arose about an unplanned analysis of subgroups and the amount of HDCT given. German oncologists started a new randomised study comparing three high-dose courses (arm A) versus one high-dose course (arm B) after standard induction chemotherapy. After recruiting 230 patients in 5 yr, the study was closed for 4% and 16% mortality in arms A and B, respectively (reference 49 in Connolly and McCaffrey [2]). Nevertheless, we have to remember that the first drug to be tested in HDCT versus low-dose chemotherapy in metastatic GCTs was cisdiamminodichloroplatinum (cisplatin). In 1984, the Southwest Oncology Group (SWOG) published a randomised study comparing 120 mg/m² with 75 mg/m² monthly cisplatin in combination with standard-dose vinblastine and bleomycin in 114 patients with advanced testicular cancer [3]. There was a clear advantage in favour of 120 mg/m² over 75 mg/m², both in complete response rate (63% vs 43%) and in survival (p = 0.03).

Four years later, Ozols et al [4] reported on a small randomised study comparing double–standard-dose cisplatin (200 mg/m²) combined with vinblastine, bleomycin, and etoposide (PVeBV) versus standard-dose cisplatin, vinblastine, and bleomycin (PVB) in 52 consecutive poor-risk patients with large abdominal masses, multiple pulmonary metastases, liver metastases, brain metastases, α-fetoprotein (AFP) >1000 mIU and/or human chorionic gonadotrophin (hCG) >10 000 mIU, unfavourable histology.
expression of multifunctional efflux transporters from the adenosine triphosphate (ATP)–binding cassette (ABC) gene family. It has been known for >25 yr that these same transporters also play a role in multidrug resistance of tumour cells. An exciting outcome of the concept of the cancer stem cell is that the tumour-initiating cell may be innately resistant to many standard therapies. This hypothesis provides one mechanism by which cancer stem cells could survive cytotoxic or targeted therapies and lead to tumour regrowth or relapse [9].

The logical consequence is not to increase dose therapy beyond even the tolerance of the human body but to use new active drugs that can overcome cancer cell resistance. Furthermore, such drugs would be administered in sequences that would maximise cancer cell damage. Sequential paclitaxel (which binds to microtubular breakdown), cisplatin (an alkylating agent), and gemcitabine (an antimetabolite) in combination with resection of residual disease, for example, enabled disease-free survival in patients who were treated in third- and fourth-line therapy [10].

**Conflicts of interest:** The authors have nothing to disclose.

**References**


