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Is CBOP/BEP an alternative to BEP for patients with poor prognosis metastatic germ cell tumours?

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The management of metastatic germ cell tumours (GCTs) with platinum-based chemotherapy represents a major success story. However, patients with poor-prognosis[1] non-seminomatous GCTs (NSGCTs) with high tumour markers, non-pulmonary visceral metastases, or a mediastinal primary site at presentation have a less certain outcome. This group achieved cure rates <50% in an international pooled analysis despite being treated with standard bleomycin, cisplatin and etoposide chemotherapy (BEP).[2]

There have been no clear improvements in the efficacy of first-line chemotherapy since the introduction of BEP in the mid-1980s. Four cycles of BEP given every 3 weeks remain the internationally accepted, standard of care for intermediate-prognosis and poor-prognosis patients,[3] and three cycles of BEP given every 3 weeks[4] is the most commonly endorsed regimen for good-prognosis patients.[5] Attempts to improve survival have included use of multiagent regimens (eg, cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide (POMB/ACE);[6] bleomycin, vincristine, cisplatin/etoposide, ifosfamide, cisplatin, and bleomycin (BOP/VIP-B));[7] newer drugs such as ifosfamide,[8] paclitaxel and high-dose chemotherapy.[9–11] None have proved superior to BEP for overall survival (OS) in randomised trials and all are more toxic.[12] Although the chemotherapy sensitivity of GCTs is a strong rationale for testing high-dose chemotherapy, this approach has been hampered by greater toxicity and some early deaths.[13 14] An alternative approach has been to shorten the interval between courses of chemotherapy rather than increase the doses,[15] but even this has been limited by toxicity.

In order to improve survival for patients with poor-prognosis disease there is a need to better understand which patients will respond well to BEP and which patients need more intensive treatment. A retrospective study with 653 patients proposed that a subgroup with poor-prognosis NSGCT and an improved outcome could be identified based on tumour marker decline assessed 3 weeks after the start of chemotherapy. Patients with an unfavourable decrease had a 4-year progression-free survival (PFS) of 38% and those with a favourable decrease had a 4-year PFS of 64% (p=0.01): 4-year OS was 58% in patients with unfavourable decrease and 83% in those with a favourable one (p=0.02).[16] Based on this the randomised phase III GETUG 13 trial was designed for patients with poor-prognosis GCTs. After one cycle of standard BEP, patients' human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) concentrations were measured. Patients with a favourable decline in HCG and AFP, calculated from a logarithmic formula using baseline and day 18–21 marker values, continued BEP (Fav-BEP group) for three additional cycles. Patients with an unfavourable decline were randomly assigned (1:1) to receive either BEP (Unfav-BEP group) or a sequential dose-dense regimen (Unfav-dose-dense group), consisting of two cycles of paclitaxel (T)-BEP-oxaliplatin followed by two cycles of cisplatin, bleomycin and ifosfamide. Of the 263 patients recruited 254 were evaluable for tumour marker decline. Fifty-one patients had a favourable marker assessment, and 203 (80%) had an unfavourable decline; 105 were randomly assigned to the Unfav-dose-dense group and 98 to the Unfav-BEP group. Three-year PFS was 59% (95% CI 49% to 68%) in the Unfav-dose-dense group versus 48% (38% to 59%) in the Unfav-BEP group (HR 0.66, 95% CI 0.44 to 1.00, p=0.05). Three-year PFS was 70% (95% CI 57% to 81%) in the Fav-BEP group (HR 0.66, 95% CI 0.49 to 0.88, p=0.01 for PFS compared with the Unfav-BEP group). More grade 3–4 neurotoxic events (7% vs 1%) and haematological

toxic events occurred in the Unfav-dose-dense group compared with the Unfav-BEP group.

While the GETUG 13 study confirmed that early tumour marker decline might predict more or less favourable poor-prognosis groups dose intensification led to only modest improvements in PFS. All patients received the first cycle of standard BEP and it may be that patients with the greatest burden of disease require earlier identification and immediate intensification of treatment.

The Royal Marsden Testicular Tumour Unit developed an intensive induction regimen (BOP/BEP) based on Wettlaufer *et al*.[5 11] Features included weekly cisplatin for 4 weeks with weekly bleomycin and vincristine for 6 weeks. In weeks 2 and 4, bleomycin was administered as 5-day infusions[17] rather than bolus injections.[18] Three courses of BEP were administered, followed with bleomycin at 15 000 IU/week. Later, carboplatin was added (weeks 2 and 4), and cisplatin was given over 2 rather than 5 days (weeks 1 and 3). The resulting carboplatin, BOP/BEP (CBOP/BEP) regimen differed from BOP/VIP in early dose intensity, use of infusional bleomycin, and use of BEP in the second treatment phase with higher dose etoposide than VIP.[19] Three centres within the UK participated in a phase II trial where 54 patients with metastatic NSGCT poor-prognosis group were recruited and treated with CBOP/BEP. The 3-year PFS was 83.2% and the OS rate after a median follow-up of 48.5 months was 91.5% at 3 years and 87.6% at 5 years. A single-arm European Organisation for Research and Treatment of Cancer (EORTC) phase II trial of CBOP/BEP found similar results with 1 year PFS of 81.8% and 2-year OS of 84.5% in 29 patients with poor-prognosis disease.[20]

To date a phase III trial of CBOP/BEP versus BEP has not been conducted. However, a randomised phase II study of CBOP/BEP[21] compared to standard 5-day BEP recruited 89 patients from 16 UK centres. After a median follow-up of 58 months the 1 year PFS was 65% for CBOP/BEP and 43% for BEP (HR 0.59, 95% CI 0.33 to 1.06). Two-year OS was 67% versus 61% respectively (HR 0.78, 95% CI 0.41 to 1.50). As expected the intensive treatment with CBOP/BEP led to more immediate toxicity. This was mostly haematological with 84% of patients treated with CBOP/BEP experiencing grade 3 or 4 neutropenia compared to 54% of patients treated with BEP. Thirty per cent of patients in the CBOP/BEP arm developed neutropenic fever versus 15% in the BEP arm. Overall 79% of patients treated with CBOP/BEP had at least one dose modification or omission. Concern was raised about the potential effect of bleomycin on lung toxicity with two on treatment deaths in the CBOP/BEP arm compared to one patient who died 3 months after completing the BEP arm. Bleomycin toxicity possibly contributed to two further deaths in the patients treated with CBOP/BEP and one with BEP.

CBOP/BEP is certainly an alternative to BEP in patients with poor-prognosis disease with early intensification potentially being beneficial for patients with the poorest outcomes. Ideally, personalised treatment with dose intensification, such as CBOP/BEP with the risk of greater toxicity, would only be offered to patients identified as having an unfavourable outcome at the outset rather than all patients with poor-prognosis disease. The GETUG 13 study indicates it is possible to identify an unfavourable group but this only occurred after 3 weeks of standard BEP. Research is required to identify robust molecular predictors that provide earlier classification of poor-prognosis patients into favourable and unfavourable groups.

For example gene methylation patterns in tumour tissue can be indicative of tumour aggressiveness and likelihood of recurrence,[22] and numerous studies correlate tissue methylation of individual genes and gene panels[22–24] with patient survival. Methylation can facilitate tumour progression by silencing genes that directly regulate cell growth and metastatic potential, and this can reflect tumour subtypes, which in turn link to prognosis. Since tumours shed DNA into the blood, the methylation status of a tumour can be non-invasively assayed by analysing circulating tumour DNA (ctDNA). A particular cancer-specific methylated sequence may not need to be identified in order for ctDNA presence in the blood to be informative. Detection and quantification can simply be indicative of the amount of ctDNA present in the circulation, which in turn reflects tumour burden.[25] As such detection of target methylated sequences in serum or plasma may be indicative of a more aggressive phenotype and/or larger volume of tumour, both of which could correlate with poor prognosis. Studies are required to evaluate the potential for this technique to provide earlier prediction of prognosis in patients with metastatic GCTs.

In conclusion CBOP/BEP represents a valid alternative to BEP in patients with poor-prognosis GCTs. Owing to the initial intensive weekly induction schedule treatment should only be given in specialised centres. However, not all poor-prognosis patients will require treatment intensification, with a significant proportion being cured by standard BEP. While tumour marker decline after one cycle of treatment provides some information about outcome there is an increasing need to identify the group of patients who need to intensify therapy upfront. Use of molecular markers and techniques such as measurement of ctDNA should be explored in prospective trials.

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