

The recurrence of germ cell tumours (GCT) after radical treatment still gives the possibility of successful treatment. There are some objective difficulties in the optimization of therapy, however, which are mostly related to the deficiency of highly reliable clinical data. Studies carried out in the 1980s revealed that ifosfamide- or cisplatin-based therapeutic protocols are efficient in the cases discussed. Their application may result in a recovery rate slightly higher than 20%. Many hopes are pinned on attempts with so-called “new drugs” – particularly paclitaxel and gemcitabine – used together with cisplatin in second-line treatment. There are some reports which suggest the predominance of such programmes over the classical ifosfamide- and cisplatin-based therapies. An alternative attitude is the application of high-dose chemotherapy (HDCT) with subsequent bone marrow or – currently more frequent – stem cell transplantation. Markedly over-treated patients (second recurrence) were qualified to early phase I/II trials, however, which was reflected in their results (low efficiency and poor tolerance of HDCT). The results became more promising when more restrictive qualification criteria were used (only patients with first recurrence, exclusion of subjects with primary mediastinal location) and the transplantation techniques improved. Unfortunately, a phase III trial (IT 94) did not prove the advantages of HDCT over non-myeloablative treatment of recurrent GCT. There is some new evidence, however, according to which HDCT is advisable in certain groups of patients.

Key words: germ-cell tumour, recurrence, prognostic factors, chemotherapy, high-dose chemotherapy.

Recurrence of testicular cancer – only VeIP?

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Introduction

The recurrence of germ cell tumours (GCT) after radical treatment always constitutes a serious clinical challenge. On one hand, it evidently reflects the failure of primary treatment. On the other, however, there is still a good chance to achieve a satisfactory therapeutic effect, including recovery. Consequently, there is a need for a particularly precise definition of the therapeutic goal and the optimal route to achieve it.

The aforementioned tasks face numerous objective difficulties, however. Firstly, marked heterogeneity exists in the group of patients discussed. Secondly, a precise definition of prognostic factors and possible predictive factors is necessary. Thirdly, we do not have enough reliable scientific data on the methods of effective treatment.

Heterogeneity of the group

In many studies on GCT management, patients in whom there was an actual recurrence after they showed CR due to first-line therapy were analyzed together with those who did not show CR after first-line treatment. Besides that basic non-homogeneity, there are some other discrepancies, which concern:

- the location of recurrence,
- the mass of recurrent tumour,
- the serum concentration of biological tumour markers,
- the histological structure of recurrent tumour (non-mature malignancy vs. *teratoma maturum and seminoma vs. non seminoma*),
- the possibility of efficient postoperative treatment,
- time to recurrence,
- the type of first-line treatment,
- the performance status of patients.

The aforementioned facts complicate both the planning and the interpretation of trial results, which are necessary for clinical decisions in everyday practice.

Identification of prognostic (and predictive) factors – the basis for rational therapeutic decisions

Prognostic factors defined by the International *Germ Cell Cancer Collaborative Group* (IGCCCG) refer to newly-diagnosed (primary) forms of GCT [1]. We do not have such a precise tool, however, in case of recurrent disease.

Fossa et al. [2] analyzed the treatment results of 164 patients with recurrent non-seminomatous germ-cell tumours (NSGCT), who were treated with conventional – cisplatin-based – chemotherapy. The authors defined the prognostic factors for that group of patients (the study included both patients with recurrence after CR and those who failed to respond to first-line treatment). The following factors were found to be associated with poor prognosis in one-way analysis: shorter than 2 years time to progression after first-line treatment, initially unfavourable prognostic factors, the lack of CR after first-line therapy. Characteristically, the prognosis was worse in patients

who were initially treated by a “small” oncology clinic or who underwent therapy a relatively long time ago (in the 1980s). Three factors were found to have prognostic value for multiple analysis: time to progression, response to first-line treatment and the levels of tumour markers (AFP, beta-HCG). Considering these three prognostic factors, two categories were distinguished within the group studied: patients with worse (co-existence of three negative factors) or better prognosis (no more than two negative factors). About 50% 5-year survival was noted in the better prognosis group, while there was no such long survival in the other group.

Sammler et al. [3] attempted to transfer the results of Fossa et al. [2] to patients treated with high-dose chemotherapy (HDCT). The authors proved the usability of prognostic factors proposed by Fossa et al. [2] and the resulting categorization of high-dose chemotherapy patients into groups with better or worse prognosis. Moreover, nearly 30% 5-year survival (OS – 28%; EFS – 26%) was noted in the worse prognosis group during the retrospective analysis of 176 recurrence patients who were treated with HDCT. These results suggest that HDCT may improve the outcomes of patients with worse prognosis (5-year OS in the better prognosis group was 47%).

Beyer et al. [4] identified negative prognostic factors during the analysis of HDCT treatment results in 300 patients with recurrent GCT. The following factors were related to poor prognosis: progression prior to the induction of HDCT, mediastinal onset of NSGCT, resistance to cisplatin, and chorionic gonadotropin level over 1000 U/l prior to HDCT.

The results of previous studies (performed in the 1980s) enumerated the following factors among the potential negative ones: the location of metastases (central nervous system, liver, skeleton), large size and number of metastatic foci, and elevated levels of tumour markers [5]. Moreover, extra-testicular location of primary malignancy was related to poor prognosis [6].

Therapeutic options

There are many treatment options for recurrent GCT. Therapeutic decisions must be based on an analysis of the entire – usually multi-aspect – clinical situation.

Classical approach – conventional cisplatin- and ifosfamide-based chemotherapy

The effectiveness of multi-drug combinations with ifosfamide in the treatment of recurrent testicular cancer were proved already in the 1980s [7, 8]. Currently, the following protocols are considered as the referral ones: VeIP (vinblastine, ifosfamide, cisplatin) or VIP (etoposide, ifosfamide, cisplatin). Due to their application it is possible to achieve long-term survival which slightly exceeds 20%. The tolerance of therapy is also acceptable [7, 8].

Attempts with new drugs in conventional chemotherapy

The implementation of new drugs, which are efficient in GCT treatment and do not exhibit cross-resistance with the

drugs used in first-line chemotherapy, brings the possibility of their effective application in the management of recurrent GCT. Among them, the protocols which include the combination of platinum derivative with paclitaxel and gemcitabine seem particularly promising.

Many authors have studied the usability of TP protocols that combine paclitaxel and two drugs of established efficiency in second-line GCT treatment: ifosfamide and cisplatin [9–12]. In a study the results of which were published in 2005 [10], including 46 patients with recurrent GCT (only with testicular primary and with CR after first-line treatment), 4 cycles of TIP resulted in 70% CR and 65% 2-year PFS. Similar optimistic results were obtained in the earlier study of Motzer et al. [9], who searched for the optimal dose of paclitaxel used in the TIP protocol. Both the aforementioned studies, however, have restrictive inclusion criteria (only patients with good prognosis). In both groups of patients haematological toxicity predominated, followed by neurotoxicity. Slightly worse results (CR – 41%, 2-year DFS – 47%) were obtained by a small Slovak study [11]. The TIP protocol was also applied as an introduction to high-dose chemotherapy [13]. All the aforementioned results suggest the advantage of the TIP protocol over the conventional approach (VeIP/VIP) in the treatment of recurrent GCT. Nevertheless, this must be confirmed by phase III clinical trials.

The combination of gemcitabine with oxaliplatin and paclitaxel [14] or with paclitaxel alone [15] seems to be a valuable therapeutic option in cases resistant to cisplatin. The main goal of a study by Bokemeyer et al. [14] was to assess the fraction of responders to GOP (gemcitabine, oxaliplatin, paclitaxel) treatment. Patients (n=41) with recurrent GCT resistant to cisplatin and subjects with recurrence after HDCT received at least 2 cycles of GOP. Resulting OR amounted to 51%. By a median 5-month follow-up (range: 0–20 months), CR (after chemotherapy ± surgical resection of residual mass) persisted in 15% of patients. The tolerance of treatment was acceptable with the predominance of haematological toxicity. The profile of patients subjected to the study is worthy of attention: 78% of them had recurrence after high-dose chemotherapy and the median of cisplatin-based lines of chemotherapy was 2 (range: 1–3). Similar results were obtained in a study of a comparable group of patients who underwent a phase II trial (under the auspices of the Eastern Cooperative Oncology Group) with gemcitabine and paclitaxel [15]. The other efficient combination against recurrent GCT is the GEMOX protocol (gemcitabine + oxaliplatin). Its application in a study of the German Testicular Cancer Study Group resulted in 46% OR. Patients with CR have a chance of long-term survival [16]. Also the irinotecan plus cisplatin combination seems to be a promising protocol [17].

Although it is not always easy in clinical practice, the treatment of recurrent GCT that may result in recovery/long-term survival should be distinguished from an a priori palliative approach. If aggressive and burdensome treatment may be accepted in the first case, it does not seem reasonable in terms of palliative treatment.

High-dose treatment

The scant number of highly reliable data does not allow us to form an unequivocal opinion on the role of HDCT in the treatment of recurrent GCT.

Historically, the onset of high-dose (carboplatin- and etoposide-based) chemotherapy in recurrent GCT was based – as it turned out – on a mistaken assumption. Inclusion criteria for phase I/II and subsequently for phase II trials with HDCT allowed the qualification of markedly over-treated patients (even after three lines of conventional therapy, mostly cisplatin-resistant) [18, 19]. High-dose treatment included etoposide (1200 mg/m²) and carboplatin (initially at increasing dose, from 900 to 2000 mg/m²; in the phase II trial the dose was established at 1500 mg/m²). More than half of the patients received two cycles of HDCT. Low efficiency and high toxicity of HDCT were revealed in both the aforementioned studies. CR was noted in 8/33 and 9/40 patients, respectively, but it was prolonged in about half of these figures. Mortality due to treatment complications was 21% and 13%, respectively.

After these initial failures, however, there was marked progress in HDCT use for recurrent GCT cases. The rationalization of inclusion criteria, the development of transplantation techniques, the increased popularity of growth factors and the progress in the optimization of HDCT itself were reflected in the highly promising results (57% of long-term DFS in Indiana University results) of many subsequent studies (phase II, *matched-pair* analysis) [20–24]. These, in turn, resulted in the 1990s in the implementation of the most popular conditioning programme for GCT – CarboPEC (carboplatin, etoposide, cyclophosphamide) [25, 26].

More disappointing, however, were the results of a large, multicentre phase III study (IT 94) [27, 28]. Its initial results were published in 2002, while the whole report was made public three years later. A total number of 280 GCT patients with failure (lack of CR or recurrence) after first-line treatment were subjected to the study, including both cases with testicular (n=233) and cases with extra-testicular primary location (n=47). Subjects were qualified to arm A (4 cycles of conventional chemotherapy: PEI = cisplatin + etoposide + ifosfamide or Velp = vinblastine + ifosfamide + cisplatin) or to arm B (3 cycles of the same conventional chemotherapy as previously mentioned with subsequent high-dose CarboPEC chemotherapy and bone marrow or stem-cell transplantation). No significant differences in event-free survival (EFS) and overall survival as well as in the response to treatment rates were noted after median observation of 45 months. Objective responses in arms A and B were 65.7 and 67.9 %, respectively, whereas OS equalled 53% and 46% for arms A and B, respectively. Subgroup analysis revealed some advantages, however, which were related to high-dose treatment. Three-year DFS was more frequent in patients in whom there was complete remission after high-dose treatment compared to those with CR who received non-myeloablative therapy (75% and 55%, respectively, p<0.04). Unfortunately, the toxicity of the experimental arm was higher, as well as the number of treatment-related deaths (9 versus 2 in arm B). The main weak point of the study

discussed, however, was too small a difference in dose intensity between the arms analyzed [29].

Controversies dealing with the role of HDCT in the treatment of recurrent GCT still exist. In their study, whose results were published in 2007, Einhorn et al. [30] administered two cycles of high-dose chemotherapy (carboplatin + etoposide) in most cases (n=173), while only 11 were given one cycle of HDCT. By a median observation of 48 months, disease-free survival was noted in 94 (of 135 in total) patients treated by second-line and in 22/49 patients who received third- and further-line therapy. Treatment-related mortality was 1.63% (3 patients). Moreover, three patients developed acute leukaemia.

Questions on the role of HDCT in the therapy of recurrent GCT will be answered satisfactorily only by further large phase III trials.

Role of surgical treatment

Surgical resection of residual masses left after chemotherapy and – in selected cases – primary resection of single metastatic lesions (very often of both therapeutic and diagnostic character) is an integral part of the treatment of recurrent GCT. The possibility of resection may be the most important factor determining prognosis in cases in which the structures of mature teratoma have survived first-line treatment. It should be remembered that during the studies performed – both with high-dose and conventional chemotherapy – surgical treatment was a constant component of therapeutic procedures. Surgery should also be considered in every case of chemoresistant, but potentially resectable, disease [31–33].

Conclusion

Further extensive clinical trials – mostly phase III ones – are necessary in order to optimize the treatment of recurrent GCT. The role of conventional chemotherapy protocols which are based on cisplatin derivative combined with new generation drugs is the main question that should be clarified by phase III trials. Moreover, many doubts are associated with the application of high-dose chemotherapy. Hence, either the purpose of use of that form of therapy in selected cases of recurrent GCT, or the type of optimal cytoreductive chemotherapy that precedes HDCT and the type and the number of courses of high-dose treatment should be clarified by future studies.

Although in the authors' opinion it is currently impossible to answer unequivocally the title question, undoubtedly there exist many attractive therapeutic options for recurrent GCT. Their optimal selection is mostly related to the precise identification of prognostic and predictive factors. The lack of proof for their predominance over platin- and ifosfamide-based protocols is associated with the lack of decisive phase III trials.

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