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High-dose chemotherapy with autologous haemopoietic support for advanced ovarian cancer in first complete remission: retrospective analysis from the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EBMT)

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Summary:

The majority of advanced ovarian cancer patients achieve an objective response following chemotherapy; however, only 20–30% are in remission after 5 years. Intraperitoneal or high-dose chemotherapy (HDC) may prolong disease-free and overall survival (OS) in patients with platinum-sensitive, small volume disease. To better define the subsets of patients who might benefit from HDC, we performed a retrospective analysis on 91 patients in 1st complete remission (CR) treated from 21 centres of the EBMT group. At a median follow-up of 48 months, median time-to-progression (TTP) and OS were 21.2 and 44.4 months, respectively. Tumour grade, stage, residual disease, disease status before HDC, type and year of transplant, source of haemopoietic progenitors and use of haemopoietic growth factors (HGF) after transplant were analysed for TTP and OS. The only significant parameter was the use of HGF: median OS for patients receiving or not receiving HGF was 46.2 *vs* 17.8 months, respectively (*P*: 0.035); this difference was maintained after multivariate analysis (*P*: 0.02). Our analysis does not identify any subgroup of patients in 1st CR who can benefit from HDC; however, median survival of patient with no residual disease has not been reached. The role of HGF after HDC deserves further investigation.

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Ovarian cancer is one of the leading causes of cancer death in women and epithelial ovarian cancer accounts for 80–90% of all ovarian malignancies. Approximately 70% of patients with ovarian cancer are diagnosed with advanced disease (FIGO stage III–IV) and the standard treatment includes cytoreductive surgery and platinum/taxanes-based chemotherapy.[1] First-line chemotherapy induces an objective response rate of 60–80% with 30–50% clinical complete remissions (CR); unfortunately, about 20–70% of complete responders develop recurrent disease after a median time of 14–30 months and the long-term prognosis is poor with overall 5-year survival of 20–25%.[2] Several investigators have explored the possibility of maintaining or consolidating the response with whole abdomino-pelvic radiotherapy,[3] intraperitoneal 32p,[4] more prolonged administration of drugs used upfront,[5] cross-over to other cytotoxics,[6,7] intraperitoneal chemotherapy[8] or biologic agents.[9] With few exceptions, these trials have produced negative results and, outside of clinical trials, no treatment is recommended to maintain or consolidate response to upfront chemotherapy.

In this setting high-dose chemotherapy (HDC) represents a potentially interesting approach for several reasons: the disease is responsive to frontline chemotherapy and, in most cases, retains chemosensitivity at relapse; alkylating agents are active in ovarian cancer and can be dose-escalated; four randomised trials have shown that upfront intraperitoneal chemotherapy (which provides significantly higher AUC) is superior to i.v. chemotherapy.[10–13] Unfortunately, i.p. chemotherapy is not devoid of catheter-related complications and is not applicable to many patients because of peritoneal adhesions following repeated surgeries. In contrast, several phase II studies have shown that high-dose i.v. consolidation chemotherapy is feasible with acceptable toxicities. The longer progression-free and overall survival (OS) in patients in clinical or pathological CR or with low tumour burden after induction chemotherapy[14–17] has encouraged further investigation. It has been difficult to conduct randomised trials and only one study comparing standard *vs* high-dose consolidation treatment in advanced ovarian cancer has been done and

this failed to show any improvement in survival for patients receiving HDC.[18]

We have used the EBMT Solid Tumour Registry database of ovarian cancer patients to investigate possible prognostic factors that might define subsets of patients who could benefit from high-dose consolidation.

Patients and methods

Between February 1986 and March 2000, a total of 218 patients from 58 centres in Europe were registered in the EBMT Solid Tumour Registry with a diagnosis of epithelial ovarian cancer in 1st CR treated with HDC with haemopoietic support. The registration details were reviewed and a questionnaire was sent to the physicians to collect further information. A total of 21 centres returned the questionnaire and we were able to collect data from 91 patients (41.7% of registered patients).

The following information was used: performance status, stage at presentation, residual disease after cytoreductive surgery, histology, histological grade, type of induction chemotherapy, response to induction treatment, status of disease after second look surgery (when performed), high-dose regimen and schedule (single *vs* multiple courses), the source of haemopoietic progenitors (bone marrow *vs* peripheral blood), year of transplant ($\leqslant$1993 *vs* $>$1993), status of disease after HDC, number of CD34+ cells transplanted, growth factor support after stem cell transplant and follow-up data.

Statistical analysis

OS and disease-free survival (DFS) were calculated according to the Kaplan–Meier method from the date of autologous stem cell transplantation to the date of death from any cause for OS or to the date of first event for the DFS. Multivariate analysis using, the Cox proportional hazards regression model, was performed to examine the association of clinicopathologic risk factors with disease recurrence and OS. Data were analysed using SPSS/PC+11.5 statistical software.

Table 1 Characteristics of patients

Age: median (range)	48 (18–65)
Performance status (WHO scale): median (range)	0 (0–2)
Histological subtype (no.)	
Papillary/serous	46
Endometrioid	7
Mucinous	5
Clear cell	3
Unknown	30
Grading (no.)	
1	2
2	12
3	27
Unknown	50
FIGO stage (no.)	
II	5
III	66
IV	20
Debulking surgery (no.)	
Yes	81
No	10
Residual disease after surgery (no.)	
No residual disease	16
$<$2 cm	30
$>$2 cm	31
Unknown	14
Status of disease before HDC (no.)	
pCR	24
Microscopic residual disease	8
cCR	59
HDC schedule (no.)	
Single transplant	65
Multiple transplants	26
Source of haemopoietic progenitors	
BM	22
Peripheral blood	69
Haemopoietic growth factor after transplant (no.)	
Yes	66
No	21
Unknown	4
Year of transplant	
$\leqslant$1993	23
$>$1993	68

Results

Patient characteristics

The characteristics of the patients are reported in Table 1. Median age was 48 years (range 18–65) and 4.4% of patients were older than 60 years; 72.6% of the patients had a PS 0 and 27.4% had a PS of 1 or 2. Tumour grade was available for 41 patients and 27 of them had G3 tumours; 94.5% of patients were in FIGO stage III–IV; 81 patients underwent debulking surgery and 51 of them had measurable disease after surgery. All the patients received platinum-based chemotherapy for a median of six courses (range 2–12); a total of 14 patients were treated with platinum-paclitaxel. After chemotherapy all patients were clinically disease-free. In all 32 patients (35.2%) underwent a 'second look' laparotomy: 24 were in pathological CR and eight had microscopic residual disease.

Graft and HDC regimens

A total of 26 patients (28.6%) received more than one course of HDC: median number was 2 (range 2–5); 65 patients (71.4%) received a single course of HDC. High-dose therapy included cisplatin/carboplatin-based regimens in 40 patients (43.9%), cisplatin/carboplatin-alkylating-containing regimens in 45 patients (49.5%) and carboplatin-paclitaxel-containing regimens in six patients (6.6%). Haemopoietic support was with bone marrow in 22

patients (24.2%) and peripheral blood stem cells in 69 patients (75.8%). After transplantation, 66 patients (73.3%) received granulocyte colony-stimulating factor (G-CSF) or granulocyte–monocyte colony-stimulating factor (GM-CSF) while 21 patients (23.3%) did not receive any haemopoietic growth factor (HGF). These data were unknown in four patients.

Outcome

At a median follow-up of 48 months (range 6–132), median OS of the entire population of 218 registered patients was 78 months (95% CI: 49–107). Median time-to-progression (TTP) and OS of the group of 91 patients whose data were available was 21.2 (95% CI: 11–31.7) and 44.4 months (95% CI: 32.3–56.4) respectively (Figure 1). Median TTP and OS (with 95% CI) according to tumour grading, FIGO stage, residual disease after primary surgery, disease status before HDC, type of high-dose treatment (single *vs* multiple courses), source of haemopoietic progenitors (peripheral blood progenitors *vs* bone marrow), year of transplant, and use of HGF after transplant (yes *vs* no) are reported in Table 2. The outcomes were not significantly different for the analysed parameters, in particular for residual disease after surgery (Figure 2) and status of disease before HDC (Figure 3), except for the use of HGF after transplant. However, median survival for patients with no residual disease after surgery has not been reached at the time of analysis.

Median TTP was 15.8 months (8–23.6) for patients not receiving HGF *vs* 24.7 months (13.7–35.7) for patients treated with HGF while median OS were 17.8 months

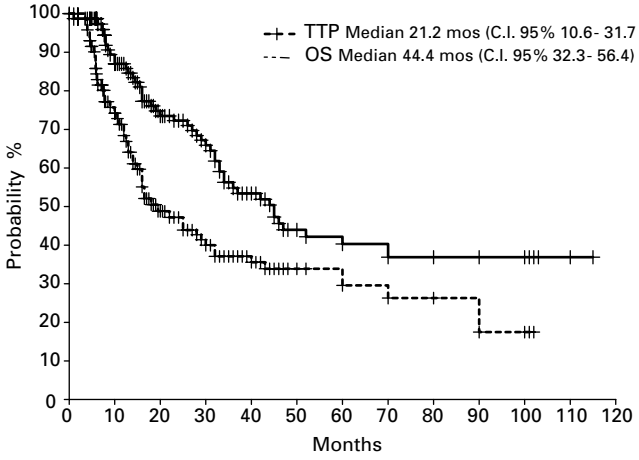


Figure 1 TTP and OS of entire group of patients.

Table 2 Univariate analysis – time-to-progression (TTP) and overall survival (OS)

	TTP months median (95% CI)	*P*	*OS months median (95% CI)*	*P*
Grading		0.6		0.6
G1 + G2	17.7 (10.4–25.1)		29.6 (15.7–43.4)	
G3	28.4 (19.6–37.2)		Not reached	
Unknown	18.9 (10.1–27.7)		43.5 (29.7–57.3)	
FIGO stage		0.2		0.5
II	Not reached		Not reached	
III	18.9 (13.0–24.7)		41.2 (29.4–53.0)	
IV	15.8 (0–42.1)		36.9 (0–86.3)	
Residual disease after surgery		0.5		0.7
No residual	21.2 (14.1–28.2)		Not reached	
<2 cm	18.9 (3.5–34.2)		43.5 (27.0–59.9)	
$\geqslant 2$ cm	16.0 (1.3–30.7)		33.2 (17.6–48.7)	
Unknown	29.5 (7.8–51.1)		Not reached	
Disease status before HDC		0.3		0.7
Microscopic residual disease	24.0 (3.4–44.6)		35.3 (29.8–40.9)	
cCR	16.4 (11.5–21.3)		44.4 (29.0–59.8)	
pCR	31.0 (24.3–37.8)		45.8 (22.4–69.3)	
Transplant		0.7		0.6
Single	21.2 (10.2–32.1)		43.5 (31.9–55.0)	
Multi	18.9 (4.0–33.7)		45.8 (n.d–n.d.)	
Use of HGF		0.2		0.035
No	15.8 (8.1–23.6)		17.9 (0–56.6)	
Yes	24.8 (13.9–35.6)		46.2 (31.9–60.5)	
Year of transplant		0.7		0.6
$\leqslant 93$	23.9 (6.3–41.6)		53.9 (38.0–69.8)	
>93	21.2 (10.6–31.8)		36.9 (24.5–49.3)	
Haemopoietic support		0.8		0.3
PBSC	21.2 (10.8–31.5)		45.8 (38.2–53.4)	
BM	17.8 (0.0–37.9)		32.4 (18.7–46.1)	

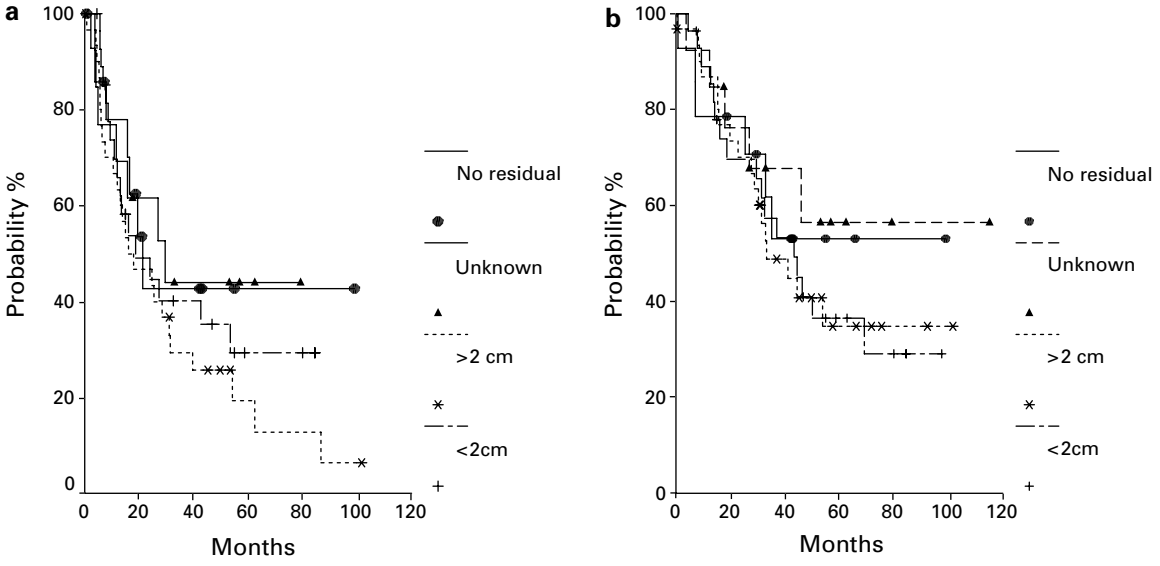


Figure 2 TTP (a) and OS (b) according to residual disease after initial surgery.

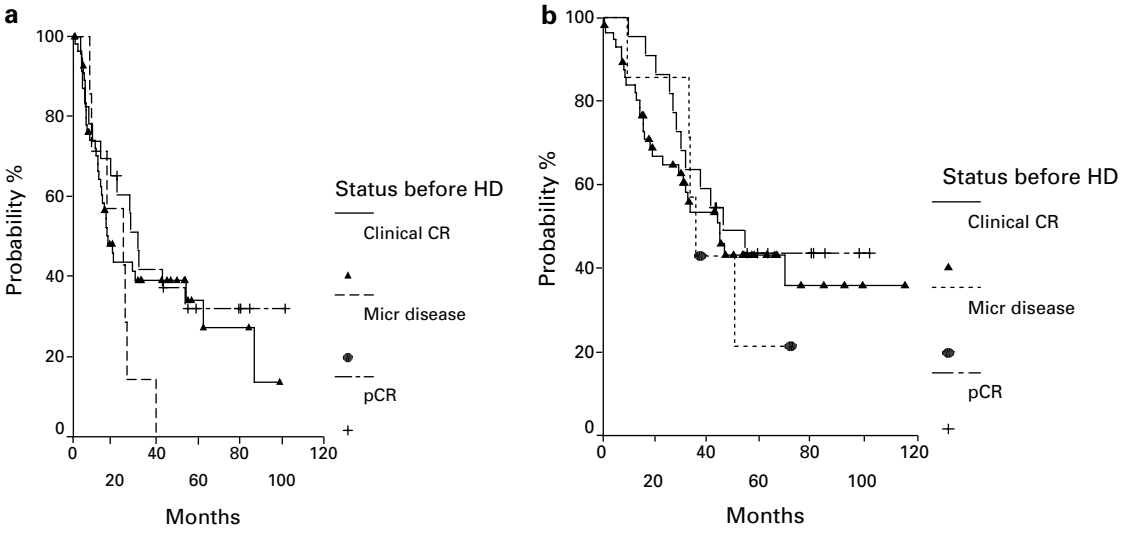


Figure 3 TTP (a) and OS (b) according to status of disease before HDC: clinical complete remission (cCR), microscopic disease, pathological compete remission (pCR).

(1–56.6) *vs* 46.2 months (31.9–60.5), respectively (Table 2). The difference was statistically significant for the OS (*P*: 0.035) (Figure 4). This difference was maintained also after multivariate analysis (*P*: 0.02) (Table 3b). However, in the group of the patients not receiving HGF, there were four deaths in the first six months. These early deaths were related to treatment toxicity (2 patients) and early progression of disease (2 patients).

Discussion

Ovarian cancer represents an interesting model to test HDC in solid tumours for several reasons: high chemosensitivity to first line chemotherapy, active drugs are suitable for dose escalation, randomised trials comparing i.p. *vs* i.v. chemotherapy show that a higher AUC is associated with better outcomes and, finally, chemosensitivity is retained at relapse. Unfortunately, data from randomised trials with HDC as first-line treatment are not available and only one small-size randomised trial, as consolidation, has been reported so far.[18] In this trial, patients with platinum-sensitive disease were randomised to either a single course of HDC or three courses of carboplatin and cyclophosphamide; the trial was closed for accrual in October 2000. In a preliminary report, a statistically significant improvement in PFS in favour of high-dose consolidation was observed; however, with a longer follow-up, the study failed to demonstrate any improvement in progression-free survival and OS. Stiff *et al*[19] have reported the largest single centre experience of high-dose consolidation chemotherapy for relapsed ovarian cancer. This study shows that the best

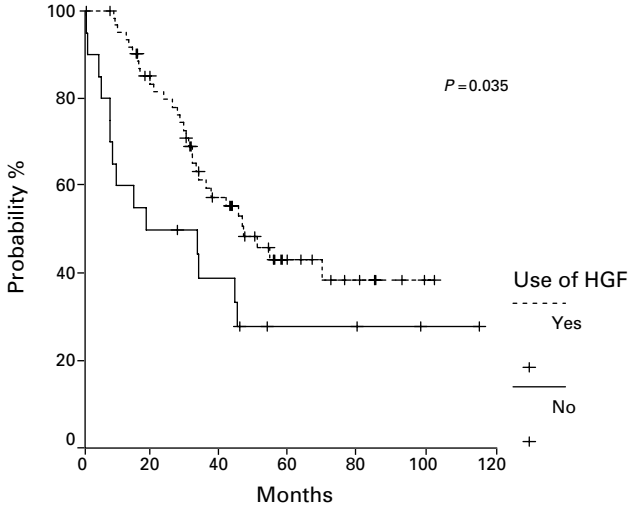


Figure 4 OS according to use of HGF.

Table 3 Multivariate analysis: (a) time to progression and (b) overall survival

	Hazard ratio	*95% CI*	χ^2	*df*	*P-value*
(a) Time to progression					
Grading					
G1+G2	1				0.4
G3	0.5	(0.2–1.5)			
Unknown	0.7	(0.2–2.0)	1.6	2	
FIGO stage					
II	1				0.3
III	4.6	(0.6–34.9)			
IV	3.9	(0.5–32.5)	2.3	2	
Residual disease after surgery					
<2 cm	1				0.5
⩾2 cm	1.4	(0.7–2.9)			
Unknown	0.7	(0.3–2.1)			
No residual	0.8	(0.3–2.2)	2.3	3	
Disease status before HDC					
pCR	1				0.8
Microscopic residual disease	1.4	(0.4–4.7)			
cCR	1.2	(0.5–2.7)	0.4	2	
Transplant					
Single	1				0.9
Multi	0.9	(0.4–2.2)	0.01	1	
Use of HGF					
No	1				0.2
Yes	0.5	(0.2–1.2)	2.0	1	
Year of transplant					
⩽93	1				
>93	1.1	(0.6–2.9)	0.01	1	
Haemopoietic support					
PBSC	1				0.9
BM	1.1	(0.4–2.4)	0.01	1	
(b) Overall survival					
Grading					
G1+G2	1				0.5
G3	0.6	(0.2–1.8)			
Unknown	0.5	(0.2–1.6)	1.3	2	
FIGO stage					
II	1				0.5
III	2.6	(0.3–19.6)			
IV	1.8	(0.2–15.5)	1.4	2	
Residual disease after surgery					
<2 cm	1				0.3
⩾2 cm	1.2	(0.5–2.6)			
Unknown	0.3	(0.1–1.0)			
No residual	0.9	(0.3–2.4)	3.9	3	
Disease status before HDC					
pCR	1				0.4
Microscopic residual disease	1.8	(0.5–6.8)			
cCR	1.9	(0.8–4.7)	2.0	2	
Transplant					
Simple	1				0.9
Multi	0.9	(0.4–2.2)	0.03	1	
Use of HGF					
No	1				0.01
Yes	0.4	(0.2–0.8)	6.4	1	
Year of transplant					
⩽93	1				0.2
>93	1.8	(0.8–4.1)	2.1	1	
Haemopoietic support					
PBSC	1				0.07
BM	2.5	(0.9–6.5)	3.3	1	

predictors of long-term outcomes were tumour bulk and platinum sensitivity. Similar results have been reported by the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EMBT)[20] and by Donato *et al*:[21] the survival of patients treated with high-dose chemotherapy in CR was significantly better than that observed in other groups of patients. Another recently published randomised trial showed a trend for a better outcome for patients in CR treated with i.p. cisplatin.[22] Intraperitoneal cisplatin produces significantly higher intraperitoneal AUC, supporting the concept that higher doses to the tumour lead to improved outcome. These studies clearly demonstrate that high-dose consolidation chemotherapy is not useful in patients with platinum resistant, bulky tumours. Our study was designed to see if there are subgroups of patients with drug-sensitive disease who may benefit from HDC. We have analysed the impact of several prognostic factors in patients with advanced ovarian cancer registered in the Solid Tumour Registry of the EBMT, transplanted in clinical or pathological CR after induction chemotherapy. There are limitations to this approach as data are often missing. Retrospective collection of data was possible for only 91 out of 218 registered patients as only 22 out of 58 centres returned the questionnaire. The information missing is mainly from centres that have transplanted ovarian cancer patients only

occasionally: this is certainly a major bias of the analysis. However, the median survival of the population of 218 patients registered as transplanted in 1st CR is longer than the median survival of the patients whose data were available for multivariate analysis. On the other hand, the major transplant centres in Europe have contributed with their data to the analysis and this could improve the quality of results.

At a median follow-up of 48 months, median TTP and OS of the group of 91 patients was 21.2 and 44.4 months, respectively, and the curves do not show any plateau. This is in agreement with the data of the GINECO trial that, updated with a longer follow-up, do not show any benefit of high-dose consolidation chemotherapy in chemoresponsive advanced ovarian cancer.[18]

In our study tumour grade, FIGO stage, residual disease after surgery and disease status before high-dose consolidation were not significantly associated with either TTP or OS; on the contrary, their importance as prognostic factors has been clearly demonstrated in other studies.[23–25] This discrepancy might be due to the ability of high-dose consolidation chemotherapy to overcome some negative prognostic parameters; the limited numbers of patients in each subgroup is, more likely, another explanation. However, the median survival of the 16 patients without residual disease after surgery has not been reached at the 48-month median follow-up and the TTP and OS curves show a plateau up to 8.3 years, suggesting that a fraction of patients might be cured.

We have analysed other transplant-related factors: single *vs* multiple transplants, the source of haemopoietic progenitors, the year of transplant, and the use of HGF after reinfusion.

The outcomes for the patients treated with single or multiple transplants were not different even if mathematical models had predicted better results with multiple cycles of HDC.[26–28] Moreover, the source of haemopoietic progenitors (peripheral blood progenitors *vs* bone marrow) and the year of transplant ($\leqslant$1993 *vs* $>$1993) were not associated with the outcome. The use of HGF (G-CSF or GM-CSF) after reinfusion of PBPC was associated with a significantly prolonged OS in both univariate and multivariate analysis (Table 3a, b). However, there was no statistically significant improvement in TTP. The improvement in OS but not in TTP may be explained by several factors including the fact that criteria for follow-up were not prospectively defined and definition of progressive disease might be different in different centres.

A possible beneficial role of HGF has been suggested by Pierelli *et al*.[29] These authors have shown that the administration of G-CSF after peripheral blood transplantation can induce higher CD3+ counts with a significantly longer TTP and OS, possibly because of an immunological antitumour effect. Moreover, they showed that GM-CSF after haemopoietic stem transplantation can induce an up-modulation of Fcγ receptor II and MHC class II molecule density on monocytes maintained until day 40 after transplant.[30] Although this possible explanation is very attractive, our data do not allow us to support this hypothesis. In fact, 20% of the patients who did not receive HGF died in the 1st six months. Moreover, a more rapid haemopoietic recovery in those patients who received growth factors could provide another explanation for the difference in survival between the two groups.

In conclusion, our data show that high-dose consolidation chemotherapy in ovarian cancer has been performed in several European centres outside of controlled clinical trials. None of the recognised prognostic parameters is able to identify subgroups that significantly benefit from high-dose consolidation. However, the small group of patients with no residual disease after surgery show a sustained progression-free benefit and OS benefit. The possible role of HGF to enhance the effect of treatment deserves further investigation.

These data and, even more, the complete absence of data for almost 60% of registered patients strictly reinforce the investigational nature of this procedure that is currently being tested in randomised trials.

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Appendix

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