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Original Paper

Very High-dose Chemotherapy with Autologous Peripheral Stem Cell Support in Advanced Ovarian Cancer

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20 patients with stage III–IV ovarian cancer were submitted to induction chemotherapy (ICT) (40 mg/m² cisplatin, days 1–4; 1.5 g/m² cyclophosphamide, day 4; every 4 weeks for 2 cycles) followed by intensified CT (100 mg/m² cisplatin, day 1; 650 mg/m² etoposide, day 2; 1.8 g/m² carboplatin by 24 h infusion, day 3). Haematological support consisted of autologous peripheral stem cells (APSC) and bone marrow (ABM) transplant (T) in 16 and 4 patients, respectively. All patients were evaluable for toxicity and 19 for pathological response (PR), one patient dying of systemic mycosis after ABMT. Severe (grade 3–4) non-haematological toxic effects were gastrointestinal (100%), neurological (10%) and hepatic (10%). PR was observed in 84% of patients (complete response 37%, partial response with microscopic residual disease 26%, partial response with macroscopic residual disease 21%). Five year overall survival was 60% and progression-free survival was 51% with 9 patients still disease-free (DFS). APSCT significantly reduced the duration of aplasia compared with ABMT, and toxicity was acceptable in those patients undergoing APSCT. The prolonged DFS in patients showing PCR suggests that this new approach may have a therapeutic impact.

Key words: ovarian carcinoma, high-dose chemotherapy, autologous peripheral stem cell transplantation
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INTRODUCTION

OVARIAN CANCER is the fifth leading cause of cancer death in women, and the majority of patients have advanced stage disease at the time of diagnosis. Although clinical responses can be achieved in over half of all patients with current platinum-based chemotherapy regimens, only a minority enjoy prolonged disease-free survival (DFS). In particular, median survival is longer than 3 years only for patients who have residual tumour less than 0.5 cm after primary surgery. Clearly, there is an urgent need for innovative strategies to improve prognosis, especially in patients with larger postoperative residual disease.

In recent years, the concept of the dose–response relationship has formed an integral part of the principle of treatment of haematological and solid tumours. In fact, virtually all anticancer agents have shown both therapeutic and toxic endpoints [1]. With regard to ovarian cancer, high-dose cisplatin has proved to be effective in some patients failing standard-dose regimens and response rates seem to be increased by dose escalation of platinum in phase I–II studies [2–6]. Moreoever, preliminary data on the use of combinations further suggest that dose intensification may produce superior results [5, 7–9].

Therefore, the use of platinum dose intensification regimens with haematological support has been suggested in previously untreated selected patients [10, 11]. In particular, according to our previous results with high-dose cisplatin [12], dose intensification programmes seem to be worthwhile in patients with minimal macroscopic residual disease rather than in those with large tumour burdens [13]. Unfortunately, prohibitive peripheral neurotoxicity occurs when cisplatin is escalated to very high doses [12]. Carboplatin has shown similar activity in ovarian carcinoma to cisplatin [14], but it causes less nausea and vomiting, neurotoxicity and nephrotoxicity, with the dose-limiting toxicity being myelosuppression, in particular thrombocytopenia. Combination cisplatin and carboplatin therapy may permit the administration of higher doses of platinum than a single analogue, as these agents have non-overlapping toxicities [15, 16]. Moreover, the lack of non-haematological toxicity makes carboplatin a potentially useful drug in a high-dose chemotherapy setting, when recovery from myelosuppression can be accomplished by use of adequate haematological support [17–19]. Among the other alkylating agents, etoposide may be

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selected for combination with platinum compounds. In fact, etoposide has shown synergistic activity both *in vitro* and *in vivo* with cisplatin [20]. Furthermore, its dose-limiting myelosuppression makes etoposide an ideal agent to be administered when means for restoring bone marrow are used. In this respect, autologous peripheral blood stem cell harvesting and transplantation have proved to be effective in rapidly restoring haematopoietic function after high-dose treatment [18, 19]. Hence, dose escalation of platinum up to very high doses may be possible by a clear-cut reduction of the prolonged aplasia-related toxicity.

On the basis of the considerations above, a phase I–II study was conducted to test the feasibility and activity of very high-dose chemotherapy with autologous peripheral blood stem cell (APSC) or bone marrow (ABM) support in selected advanced ovarian cancer patients after primary surgery.

PATIENTS AND METHODS

Patient characteristics

Patients with histological diagnosis of moderately to poorly differentiated adenocarcinoma of the ovary and 0.5–2 cm residual disease (RD) after initial or interval surgery were eligible for the study. Age less than 55 years, a performance status of 0–1 [21], and written informed consent were also required, together with adequate bone marrow function (WBC count $> 4000 \times 10^6$/l; platelet count $> 100 \times 10^9$/l), liver function (bilirubin <2 mg/dl; alkaline phosphatase and serum glutamic-oxalacetic transaminase <2.5 times normal), and renal function (creatinine level <2 mg/dl; creatinine clearance >50 cc/min). The study was approved by the Hospital Human Investigations Review Board.

Between June 1989 and June 1991, 20 consecutive patients were entered into this study. The characteristics of patients are detailed in Table 1. It should be noted that the majority of patients (80%) presented with stage IIIC disease, and 85% of cases had poorly differentiated tumours. One stage IV patient had metastasis to the abdominal wall. Initial surgery was classified according to Wharton and Herson [22] and, despite extensive disease at laparotomy, it was possible to achieve a less than 2 cm RD in the majority of patients (cytoreductive surgery: 80%). In order to debulk the tumour as much as possible, intestinal resections were performed in 7 cases (35%). In 3 patients (15%) primary surgery was limited to explorative laparotomy due to massive tumour extent, and in one (5%) consisted of simple tumour removal. Thus, 4 patients (20%) were suitable for very high-dose chemotherapy since a minimal RD has achieved interval surgery.

Table 1. Patient characteristics

No. of patients entered	20 (100%)
Median age	
52 years	(range 28–55)
Performance status (WHO): 0–1	20 (100%)
FIGO stages:	
IIIB	3 (15%)
IIIC	16 (80%)
IV	1 (5%)
Histotype:	
serous	17 (85%)
endometrioid	3 (15%)
Grade of differentiation:	
moderately good	3 (15%)
poor	17 (85%)
Residual disease after primary surgery	
0.5–2 cm	16 (80%)
2–5 cm	1 (5%)
>5 cm	3 (15%)
After interval surgery	
0.5–2 cm	4 (20%)

Treatment plan and supportive care

After initial surgery, two courses of induction chemotherapy (ICT) consisting of 40 mg/m^2 intravenous (i.v.) cisplatin (CDDP) daily from day 1 to day 4 and 1500 mg/m^2 i.v. cyclophosphamide (CTX) on day 4 were given. CDDP was administered in 3% hypertonic saline by 2 h infusion with adequate pre- and posthydration. Intravenous mannitol ± furosemide was routinely used daily to promote diuresis. An alizapride-based anti-emetic treatment was given. Patients were treated on an inpatient basis, and body weight, fluid intake and output, serum electrolytes (including magnesium), urinalysis and creatinine were determined daily. Clinical chemistry and complete blood count were repeated twice a week. A second cycle was given after a 28 day interval provided that the WBC count and haemoglobin were above 3500×10^6/l and 10 g/dl, respectively, and the creatinine level was less than 2 mg/dl. If on the day of retreatment, haematological recovery had not occurred, the second cycle of therapy was delayed for up to 2 weeks. Patients underwent autologous peripheral blood stem cell (APSC) harvesting by repeated leukaphereses 2–3 weeks from the start of each course of ICT, when the recovery from transient myelosuppression became evident (platelets $>50 \times 10^9$/l, WBC $>1000 \times 10^6$/l). Leukaphereses were performed according to the procedure previously reported [23]. ABM harvesting was included in the treatment plan to ensure availability of a haematological support in case of inadequate APSC harvesting, and was performed within 6 weeks of the second course of ICT according to the procedure previously reported [24]. Of the patients initially undergoing explorative laparotomy, those who clinically responded underwent intervention surgery and, if a less than 2 cm postoperative RD was achieved, were eligible for ABM harvesting followed by very high-dose chemotherapy (VHDCT). All patients initially undergoing cytoreductive surgery or simple tumour removal and with no progressive disease after ICT and with CA125 serum levels decreasing were eligible to receive one cycle of VHDCT. VHDCT was administered within 2 weeks of the ABM harvesting, and consisted of 100 mg/m^2 i.v. CDDP over 4 h on day 1, 650 mg/m^2 i.v. etoposide (VP-16) over 2 h on day 2, and 1800 mg/m^2 i.v. carboplatin (CBDCA) as a continuous infusion over 24 h on day 3. APSC or ABM were infused on day 5. Six to eight days before receiving the VHDCT, all patients were placed on prophylactic trimethoprim-sulphamethoxazole and ketoconazole. The patients were given a low bacterial content diet and received total parenteral nutrition during periods of low oral intake. During the period of neutropenia, patients were started immediately on broad-spectrum antibiotics when body temperature exceeded 38°C, and amphotericin-B was added when fever persisted for more than 5 days in spite of antibiotic treatment. Irradiated erythrocytes and platelets were transfused to maintain the platelet count $>25 \times 10^9$/l and haemoglobin level >8.5 g/dl. Toxicity was graded according to the World Health Organization (WHO) criteria [21].

Definition and assessment of response

Clinical and pathological responses were defined according to the WHO criteria [21]. In patients with no measurable RD, clinical response was assessed on the basis of CA125 serum levels. Four to six months after the VHDCT, patients showing complete clinical remission had a second-look laparotomy. Multiple biopsy procedures, including sampling of all previously involved sites, and peritoneal cytology were required to assess pathological response.

Survival analysis

Survival time was measured from the day of histological diagnosis to the date of death. Progression-free survival (PFS) was calculated from the day of first surgery to the date of clinical or pathological progression or death, whichever came first. DFS was calculated from the day of second-look surgery. All medians and life tables were computed using the product-limit estimate by Kaplan and Meier [25]. Median follow-up times of 60 (range 44–64) and 52 months (range 35–52) from diagnosis and second-look operation have been reached, respectively. Analysis was as of October 1994.

RESULTS

Toxicity and feasibility

Haematological toxicity induced by the two cycles of ICT is detailed in Table 2. All patients except one showed WBC nadir values below 2×10^9/l, and granulocytopenia less than 0.5×10^9/l occurred in 5 patients (25%). 6 (30%) and 5 (25%) patients developed platelet and haemoglobin nadir values corresponding to WHO grades 3 and 4, respectively. However, there were only two cases of transient neutropenic-induced fever, and no cases of thrombocytopenic bleeding. Haematological toxicity did not seem to accumulate during the first two cycles. In fact, the grade of myelosuppression appeared to be similar. Because of leuco- and/or thrombocytopenia and anaemia, the second course was postponed for 1 and 2 weeks in 12 and 3 patients, respectively. A total of 128 leukaphereses were performed in 16 patients, 59 after the first and 69 after the second course. Each patient underwent a median number of eight leukaphereses (range 7–11). The patients were not hospitalised during the first 2 weeks after each cycle of the induction phases, but were re-admitted 48–72 h after the WBC nadir, and underwent leukaphereses on an inpatient basis. 4 patients underwent ABM harvesting only: one refused the aphereses procedure, 2 had fever and 1 did not regularly attend haematological controls after ICT courses. In accordance with the results previously reported [23], ABM harvesting yielded an average of 0.7×10^8/kg body weight MNC (mononuclear cells) and 1.7×10^4/kg body weight CFU-GM (colony forming unit–granulocyte macrophage) which was remarkably lower than that yielded by repeated leukaphereses (6.7×10^8/kg body weight MNC and 22.1×10^4/kg body weight CFU–GM). All 20 patients, including the 3 patients who underwent successful intervention surgery after the ICT, showed no signs of progression and received VHDCT.

VHDCT was given within the planned time in 8 of the 20 patients (40%), with an overall median interval from the second cycle of ICT to the VHDCT of 9 weeks (range 6–12). In 12 cases, VHDCT was postponed because of severe anaemia (<8.5 g/l) due to ABM harvesting. As expected, haematological toxicity induced by the VHDCT was severe in all cases (Table 3). The median durations of granulocytopenia less than 0.5×10^9/l and platelet count less than 50×10^9/l were 10 and 6 days, versus 16 and 15 days, for patients receiving APSC and ABM infusion, respectively. Petechiae developed in 5 patients and epistaxis in 2 patients, all but 1 having undergone ABMT. Neutropenic-induced fever was observed in all patients. Severe infections with documented pulmonary infiltrates developed in 2 patients, 1 of whom received ABMT. One treatment-related death occurred in a 42-year-old woman undergoing ABMT. Blood culture-documented candida sepsis was diagnosed, and the patient died 35 days after the start of VHDCT. The median numbers of transfused platelet and erythrocyte concentrates were 3 (1–4) and 1 (0–1), respectively. The additional time required by ABM harvesting, the related anaemia and, more importantly, the satisfying results of the APSCT procedure suggested elimination of the ABM harvesting from the protocol in the last 6 patients (median interval from the end of ICT to VHDCT: 7 weeks, range 6–8). After VHDCT, gastrointestinal toxicity was observed in all patients. Severe diarrhoea (2 cases) and vomiting (grade 3: 18; grade 4: 2 cases) occurred respectively in 10% and 100% of patients and required total parenteral nutrition in 6 (33%). Hepatic toxicity, consisting of transient elevation of transaminase (grade 1: 7; grade 2: 3; grade 3: 2

Table 2. Haematological toxicity induced by induction chemotherapy

Nadir	1st cycle No. (%)	2nd cycle No. (%)
WBC ($\times 10^9$/l)		
2.0–2.9	0 (–)	1 (5)
1.0–1.9	17 (85)	16 (80)
<1.0	3 (15)	3 (15)
PLT ($\times 10^9$/l)		
>100	6 (30)	6 (30)
75–99	2 (10)	2 (10)
50–74	4 (20)	6 (30)
25–49	7 (35)	5 (25)
<25	1 (5)	1 (5)
Hb (g/dl)		
9.5–10.9	1 (5)	4 (20)
8.0–9.4	5 (25)	9 (45)
6.5–7.9	10 (50)	6 (30)
<6.5	4 (20)	1 (5)

PLT, platelets; Hb, haemoglobin.

Table 3. Haematological toxicity following very high-dose chemotherapy

	APCT (16 pts) Days	ABMT (4 pts) Days
WBC <1.0 × 10^9/l	8 (8–10)	17 (15–21)
Granulocytopenia		
<0.5 × 10^9/l	10 (9–12)	16 (15–19)
<0.1 × 10^9/l	7 (5–8)	9 (8–10)
Thrombocytopenia		
<50 × 10^9/l	6 (2–16)	15 (13–19)
<20 × 10^9/l	2 (0–4)	7 (5–15)

Results are expressed as the median value (range) obtained in the different series.

cases), was manifested in 12 patients (60%). A grade 2 serum creatinine elevation was detected in 8 patients (40%), and was reversible within 2–3 days of the completion of chemotherapy in all cases. All patients experienced ototoxicity defined as mild to moderate clinical hearing loss. However, tinnitus and "roaring" were observed in only 5 patients. These disturbances improved slightly over time, but mild (3 cases) and moderate (3 cases) hypoacusia is still present many months after the completion of treatment. Peripheral neuropathy, as grade 1 distal sensory deficit, developed in all patients 4–6 weeks after the VHDCT. In 13 cases (65%), numbness and tingling in the distal extremities were also recorded. More severe neurological toxicity, defined as gait disturbances, developed in 2 cases. However, no patient became wheelchair-dependent. 2 of the 14 (14%) long-term survivors demonstrated a mild to moderate degree of residual functional sensory-motor deficit, which persists more than 2 years after therapy. Non-haematological toxicity is reported in Table 4. The median hospital stay from the start of VHDCT for patients receiving APSCT and ABMT was 28 days (range 27–30) and 38 days (range 32–42), respectively.

Dose intensity

Assuming the conventional concept that 400 mg of CBDCA are equivalent to 100 mg of CDDP [14], the projected dose intensity (DI) of CDDP was 54.4 mg/m²/week [26]. As described in the treatment protocol, each patient was intended to receive 870 mg of platinum divided by 16. Given the delay due to toxicity, the median actual DI was 48.3 mg/m²/week, corresponding to 88.8% of the projected DI [26]. It is worthwhile noting that for the last 6 patients who did not undergo ABM harvesting, the median actual DI corresponded to the projected DI.

Response and survival

All 20 patients received VHDCT and were evaluable for survival, and all except 1 were assessable for tumour response. 19 patients had no evidence of disease and decreasing CA125 serum levels 3 months after VHDCT. Therefore, according to the study design, all these patients underwent second-look laparotomy (median interval from the VHDCT: 5 months, range 4–6). Pathological complete response (PCR) was found in 7 of the 19 patients (37%) (Table 5). Of interest is that among the 9 (47%) patients with pathological partial response (PPR), 5 (26%) had microscopic RD only. In 3 (16%) of these cases, microscopic disease was found in one to three nodes removed in the aortic area, and in two the only RD was retroperitoneal tumour. The remaining 3 patients had no change to their disease. 12 of the 20 enrolled patients (60%) are still alive at the time of the present analysis. The median survival has not yet been reached, but it exceeds 47 months (range 9–64+). Apart from the toxic death, 6 patients died of progressive tumour and 1 patient, in complete remission, died of intercurrent disease, 7–38 months and 13 months from the second-look, respectively. 6 of the 7 patients with PCR, 2 of the 5 with microscopic RD and 1 of the 4 with macroscopic RD are currently disease-free, while the remaining 3 patients are alive with clinical evidence of disease. The median PFS has not yet been reached, but it exceeds 24 months (range 9–64+). The 5-year survival analysis showed an overall survival and PFS estimates of 60% (95% CI: 35.7–52.5) and 51% (95% CI: 26.3–46.2), respectively (Figure 1).

Table 4. Non-haematological toxicity

Toxicity	WHO grade				
	0	1	2	3	4
Nausea and vomiting	–	–	–	18	2
Diarrhoea	–	6	12	2	–
Hepatic	8	7	3	2	–
Renal	2	10	8	–	–
Ototoxicity	–	13	6	–	–
Peripheral neurotoxicity	–	16	1	2	–
Infections	17	–	–	2	1*

*Patient dead of mycotic septicaemia. In this case, neurotoxicity could not be evaluated.

Table 5. Pathological response

Initial FIGO stage	No. of patients	CR	PR (Micro)	PR (Macro)	NC
IIIB	2	2	0	0	0
IIIC	16	5	4	4	3
IV	1	0	1	0	0
Total	19	7 (37%)	5 (26%)	4 (21%)	3 (16%)

CR, complete response; PR, partial response; NC, no change.

DISCUSSION

Few studies have been performed to determine the effect of high-dose intensity and short-duration chemotherapy as a possible determinant of outcome in ovarian carcinoma [4, 6, 9–11, 27]. As expected, patients with minimal RD may have greater improvement of the remission rate and DFS than those with massive and/or refractory disease. To our knowledge, no study has yet been reported on very high-dose platinum-based chemotherapy with APSC support in previously untreated ovarian cancer patients. Therefore, the results presented are the first data published in this respect.

First, it is worthwhile mentioning that, given the unfavourable characteristics of this selected series of patients, the therapeutic approach adopted should be considered a salvage combination of both aggressive surgery and chemotherapy. A maximum surgical effort was pursued in all cases, and a 0.5–2 cm RD was achieved by primary surgery in 80% of patients and by intervention surgery in the remaining 20%. Moreover, it is to be noted that the average platinum delivered DI approached the projected DI, and that 48.3 mg/m²/week is one of the highest

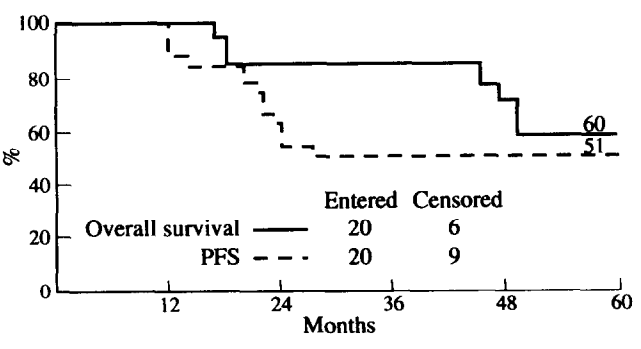

Figure 1. Five year progression-free survival (PFS).

doses of platinum compounds administered so far. Thirty-seven per cent of our patients achieved a PCR, and microscopic disease was the only residual tumour in a further 26%. However, the PCR obtained would not seem to be as high as the increased platinum DI could lead one to hypothesise. In fact, this figure does not substantially differ from those reported for combination chemotherapy regimens using CDDP in a standard dose range of up to 100 mg/m^2/cycle in patients with minimal RD. Nevertheless, some considerations are to be made: (a) in the absence of macroscopic intraperitoneal RD at second-look, aortic and pelvic lymphadenectomy was routinely performed, and in 2 cases retroperitoneal tumour was the only detectable RD; therefore, if microscopic tumour in the lymph nodes was not considered, the PCR rate would be higher; (b) subsets of patients with <2 cm RD generally include those with no RD, while our patients all presented with macroscopic (≥0.5 cm) RD; (c) initial stage—according to the new FIGO classification—is still rarely reported, as is the kind of surgery required to achieve minimal RD; in spite of the presence of 0.5–2 cm RD in 79% of our evaluable patients, 89% of these initially presented with stage IIIC–IV, and their prognosis may have been worse than that of patients with minimal RD after simple tumour removal. More interesting, it should be emphasised that neither the 7 pathologically complete responders nor the 2 patients with only microscopic tumour in the lymph nodes have so far relapsed in the absence of any further treatment, and with a median follow-up from second-look of 52 months (range 35–52). Forty to seventy per cent recurrence rates could have been expected, as reported in pathologically complete responders following standard-dose CDDP-based chemotherapy, who, in the majority of cases, received further therapy after second-look. The respectively 60% and 51% 5-year survival and PFS rates observed in our series further support the hypothesis of a possible increase in therapeutic efficacy, if compared to the 28.1% 3-year overall survival reported in 1961 stage IIIC patients treated from 1982 to 1986 [28]. More recently, results from a meta-analysis of randomised trials comparing standard-dose single-agent platinum versus platinum-based combinations and CDDP versus CBDCA-based regimens in advanced ovarian cancer show 4-year overall survival rates never above 30% [29]. Although our results are not directly comparable with those from the aforementioned studies, and the phase I–II nature and size of this study precludes conclusive analyses, it can be suggested that some improvement in DFS may be achieved by combining an aggressive surgical approach with a brief, very intensive platinum-based chemical cytoreduction.

Repeated leukaphereses timed on the recovery phase from myelosuppression after the two induction courses yielded the harvesting and storage of significantly higher quantities of MNC and CFU-GM than ABM harvesting. Therefore, in accordance with previous publications [23], patients who underwent ABMT had a delayed engraftment with a significantly longer duration of granulocytopenia and thrombocytopenia than those undergoing APSCT. The only case of toxic death was caused by systemic candida infection, and occurred despite antimycotic prophylaxis and ABMT. Moreover, the anaemia induced by the ABM harvesting was often the cause of delay in VHDCT administration. Consequently, these drawbacks, together with the good results of APSCT, made it possible to abandon ABM harvesting in the last 6 patients. The clear advantage of APSC compared with ABM support has also been confirmed in terms of adherence to the protocol. In fact, the median actual DI corresponded to the projected dose only in the 6 patients who did not undergo ABM harvesting. Non-haematological toxicity mainly consisted of gastrointestinal side-effects, experienced by all patients despite the routine anti-emetic treament. Ototoxicity and peripheral neuropathy, although observed in all cases, were mild to moderate, and improved slightly over time.

In conclusion, this study has demonstrated that the combination of aggressive surgery and VHDCT with APSCT is a feasible treatment in previously untreated patients with advanced ovarian cancer. In particular, the induced toxicity proved to be manageable in those patients undergoing APSCT. The observation of a prolonged disease-free interval in complete responders suggests that this new approach could have a therapeutic impact in chemosensitive tumours. Hence, a decision has been made to continue this approach in patients with minimal macroscopic RD after cytoreductive surgery using a modified regimen, incorporating granulocyte-colony stimulating factor and erythropoietin [30] in both the induction and intensification phases, melphalan in the intensification phase, and having APSC support only. The use of cytokines and the exclusion of ABM harvesting might shorten the treatment time, further lowering the costs of therapy, in terms of hospitalisation and patient quality of life. Updated results of this new ongoing trial will be reported in the near future.

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