

410

POSTER

Platinum (II) complexes with phosphine-ferrocene containing ligands and their *in vitro* activity against leukemia

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Purpose: Platinum-amino complexes, e.g., cisplatin, carboplatin (paraplatin), oxaliplatin, etc. were known to have anti-tumour activity against certain types of tumour cell lines. In this study, a new class of heterobimetallic platinum-iron complexes with mixed phosphine and sulphur containing ligands were synthesized and screened against leukemia cell line P₃₈₈.

Methods: The complexes $cis-[Pt((Fer)PhP)(DMSO)_2X_2]$, where $X_2 = Cl_2, C_2O_4, O_2(CO)_2(C_6H_{11})_2$ and $O_2(CO)_2C-CH_2CH_2$ have been synthesized and characterized physicochemically and spectroscopically. These complexes were tested *in vitro* against leukemia cell line P₃₈₈ using the MTT-assay, and compared with those for both cisplatin, carboplatin, oxaliplatin & 5-fluorouracil (5-FU).

Results: Two of these complexes showed significant cytotoxic activity against P₃₈₈ cells which possess one order of magnitude better activity than cisplatin & 5-FU and two and three orders of magnitude better activity than carboplatin & oxaliplatin.

Conclusion: The present results are encouraging since these complexes are novel and represent new analogues to cisplatin & carboplatin, however, further *in vitro* tests are required using other cell lines like the human breast (T_{47D}) & the non-small-cell lung (A₅₄₉) to confirm the above results before any *in vivo* tests.

411

POSTER

Prospective analysis of factors affecting CD34+ cells mobilization in breast cancer patients

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Purpose: To analyze clinical (age, stage, regimens and cycles of prior chemotherapy (CT), interval from the last CT, radiotherapy) and biological (% and count of CD34+ cells/mL in steady-state bone marrow (BM) and blood) factors influencing CD34+ cell mobilization in breast cancer pts.

Methods: One hundred and two pts with breast cancer received 3 different mobilization programmes: 24 pts Cyclophosphamide (Cy) 4 g/m² or FEC (Fluorouracil 600 mg/m², Epirubicin 75 mg/m² and Cy 600 mg/m²) + G-CSF 5 µg/Kg/d s.c. from d + 1 (G5) and 78 pts G-CSF 10 µg/Kg/d s.c. alone (G10). Daily leukapheresis (LK) were started when CD34+ cells/mL count in blood was >2500. The objective was a minimum collection of 2×10^6 CD34+ cells/Kg.

Results: Median age was 42 yrs (26–59). Median number of prior CT cycles 6 (3–14). Median days from the last CT until mobilization 30 (18–147). Median blood and BM steady-state CD34+ cell % were 0.012% (0–0.2) and 0.9% (0.1–6), respectively. Median BM CD34+ cell count was 3.3×10^5 /mL (0.1–44.1). A high correlation was observed between preLK CD34+ blood cell count and CD34+ cells collected ($r = 0.78$; $p = 0.000$). A median of 2 (1–7) LK per pt was performed.

	Max. peak	CD34+/Kg/m	%CD34+ in bag	Failures
CT + G5	113300 ± 9571	648 ± 503	1.6 ± 1.36	0/24 (0%)
G10	66547 ± 58492	279 ± 170	0.66 ± 0.31	3/78 (4%)
	$p = 0.0084$	$p = 0.000$	$p = 0.000$	n.s.

Number of previous chemotherapy cycles had an inverse correlation with both maximum peak of CD34+ cells and CD34+ cells collected ($r = -0.22$, $p = 0.023$ and $r = -0.23$, $p = 0.022$ respectively).

	BM CD34+/mL		Prior cycles:	
	< percentil 25	> 25	<5	>5
Peak CD34 ($\times 10^5$ /mL)	3.6 ± 2	9.1 ± 8.7 ($p = 0.0056$)	15 ± 16.2	6.7 ± 4.7 ($p = 0.002$)
CD34+ (kg/mL)	317 ± 414	389 ± 301 ($p = 0.37$)	637 ± 496	328 ± 272 ($p = 0.001$)

Correlation analysis of maximum blood CD34+ cells/mL with BM CD34+ cells/mL was significantly positive ($r = 0.35$, $p = 0.001$). Prior CT cycles had an inverse correlation with BM CD34+ cells/mL ($r = -0.15$, $p = 0.145$) and differences between ≤5 and 6 or more previous chemotherapy cycles was significant ($p = 0.031$).

Conclusions: CT+G5 mobilizes better than G10 and provides a purer cell yield that might facilitate a further cell manipulation. Extensive prior CT might decrease CD34+ cells in BM and compromise mobilization results.

412

POSTER

Idarubicin in advanced or relapsed multiple myeloma treatment in elderly

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Idarubicin (IDA) is an analogue of doxorubicin with elevate cytotoxic activity. Bone marrow toxicity is dose-limiting; the drug is claimed to be less toxic than doxorubicin. It is active when given by mouth because of its lipophilia. We report our experience about IDA treatment of relapsed or progressive Multiple Myeloma (M.M.) in elderly. We studied 18 patients (10 M – 8 F, aged 67–80 years) with M.M. st. II–III (12 A – 6 B) and M component: Ig G-k = 8; Ig A-k = 4; Ig G-λ = 2; Ig A-λ = 1; B.J. = 3. All pts. were previously treated with melphalan + prednisone; 10 pts. in maintenance with α-IFN. Our schedule was the following: IDA 10 mg/m² + PDN 80 mg/m² 4/28 days for 6 cycles, os, at home.

Exclusion's criteria were: age <65 years; st. I; heart and renal failure; diabetes. We obtained good response on 16/18 pts. with seric M.C. of 50% and urinary of 65% decrease (respectively range 20–70% and 50–80%). Two non responder pts. were Ig A M.M. Performance status was 0 on 7 and I on 9 pts; neutropenia was II on 9, III on 8, IV on 1 pt.; nausea on 2 and alopecia on 3 pts.

Conclusions: IDA + PDN association is good effective and tolerated, with excellent control of advanced M.M. in elderly, prolonged survival, quality life improvement and easy treatment schedule.

413

POSTER

Incidence of delayed infections after high-dose chemotherapy with peripheral blood stem cell support

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High-dose chemotherapy (HD-CHT) with autologous bone marrow rescue (ABMR) induces profound and persistent immune disturbances. In the period following neutrophil recovery, opportunistic infections associated to cellular and antibody-mediated immune deficiency have been reported in a significant number of pts treated with ABMR. Reinfusion of peripheral blood stem cells (PBSCs) after HD-CHT induces faster neutrophil and platelet recovery than ABMR. We have studied the incidence of infections after neutrophil recovery in pts treated with HD-CHT+PBSCs and whether incidence correlated with the number of CD34+ PBSCs reinfused. Fifty-three of 59 pts with solid tumors or lymphoma treated with HD-CHT + PBSCs at a single institution (1995–1996) survived after neutrophil recovery. Nine (16.9%) had late infections (operatively defined as infections presenting after neutrophil recovery). Late infections appeared in 3 of 10 pts (30%) with non-Hodgkin's lymphoma, 3 of 33 pts with breast cancer (9%) and 3 of 16 pts with other malignancies (18%). Type of infection: interstitial pneumonitis (5 pts), superficial candidiasis + fever (2 pts), herpes zoster (1 pt), *Mycobacterium avium* infection (1 pt). Median time from PBSC infusion to infection was 26 days (range 6–210). One pt with interstitial pneumonitis died. All others recovered after a median period of 7 (0–21) days on antimicrobial agents and 7 days (0–21) in hospital. The median number of CD34+ cells reinfused ($\times 10^6$ /Kg) was 2.9 (1–5.7) in 9 pts who had late infections vs. 4 (1.9–16.5) in 41 pts who did not develop late infections ($p < 0.05$). Infections presenting after neutrophil recovery cause substantial morbidity in pts treated with HD-CHT+PBSCs. The number of CD34+ cells reinfused is inversely correlated with the risk of late infections.

414

POSTER

Use of the delta assay of plastic adherent progenitors (PD) to measure early haemopoietic precursors in peripheral blood harvests

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Purpose: To determine the relationship between plastic adherent early stem cell progenitors and engraftment following peripheral blood progenitor cell (PBPC) rescue.

Methods: 30 patients (pts) undergoing high dose chemotherapy and PBPC rescue were studied for relationship of harvest CD34+ cell count, granulocyte-macrophage colony forming units (CFU-GM) and plastic adher-

ent progenitor-derived CFU-GM to recovery. Pts were treated in remission from multiple myeloma (9), breast cancer (10), lymphoma (8) and teratoma (3). Harvests were analysed for CD34+ cell count by flow cytometry. Apheresis products on the first day were tested in CFU-GM and a delta assay (PΔ) performed with progeny from the plastic-adherent fraction of 10^7 mononuclear cells incubated for 7 days and enumerated by CFU-GM assay.

Results: A median 3.69×10^6 CD34+ cells/kg were reinfused (range 0.25–51.9), 6.1×10^4 CFU-GM/kg (range 0.10–79.0) and 10.4×10^4 pΔ CFU-GM/kg (range 0.27–603.8). Median time to platelet count of $50 \times 10^9/l$ was 14 days (range 9–gt; 80) and to neutrophil count of $0.5 \times 10^9/l$ was 13 days (range 9–27). Inverse correlation was seen between CD34+ count and time to recovery of platelets ($p = 0.002$) and neutrophils ($p = 0.005$). Correlation was also seen between CFU-GM and platelet recovery ($p = 0.031$). There was positive correlation between CD34+ count and PΔ CFU-GM numbers ($p = 0.037$) but no correlation between PΔ CFU-GM count and engraftment time.

Conclusion: The delta assay of plastic adherent progenitor cells is capable of quantitating a primitive population in PBPC harvests but the CD34+ cell count remains superior as a means of predicting engraftment, suggesting that committed progenitors are more influential in the early phase of recovery.

415

POSTER

High-dose chemotherapy (HDC) and autologous peripheral blood stem cell support (PBSC) in patients with metastatic breast cancer (MBC)

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Purpose: The aim of this phase I/II study was to determine therapeutic efficacy and toxicity of a tandem (T)- or triple (TR)-HDC with PBSC in 38 patients with MBC as first line chemotherapy.

Patients and Methods: From 9/92 to 12/95 25 patients with MBC were enrolled onto the study with a tandem HDC-regimen and since 1/96 13 patients to the study with a triple HDC-regimen. Conventional chemotherapy (CC) consisted of two cycles epirubicin (120 mg/m²) and ifosfamide (7.5 g/m²) in case of (T)-HDC and one cycle Taxol (135 mg/m²), epirubicin (90 mg/m²) and ifosfamide (6 g/m²) in case of (TR)-HDC. Following (T)-HDC was composed of 2 cycles epirubicin (180 mg/m²), ifosfamide (12 g/m²) and carboplatin (900 mg/m²). In case of (TR)-HDC Taxol (180 mg/m²), etoposide (1.5 g/m²) and thiotepa (600 mg/m²) was added as third cycle. Only patients with CR or PR during CC were admitted to HDC ($n = 21$ in case of (T)-HDC).

Results: Patients with (T)-HDC were evaluable for both response and toxicity and patients with (TR)-HDC only for toxicity in case of short-term follow up. With a median follow up of 37 months the probability of the progression free survival amounts 20% and of the overall survival 30% in patients with (T)-HDC. Severe non hematologic toxicities were not observed in both regimens. Patients with (TR)-HDC showed prolonged thrombocytopenia following HDC. Improved response rates were observed in patients with few metastatic sides.

Conclusion: Both HDC-regimens were well tolerated. Only a selected group of patients may have a benefit of HDC

416

POSTER

Cyclosporin A in the treatment of myelodysplastic syndromes (MDS)

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Purpose: Enhanced apoptosis is considered one of the main causes of cytopenia in MDS. Since Cyclosporin A (CyA) is known as an inhibitor of the apoptosis some authors used CyA for treatment of MDS patients (pts) with certain success. The aim of this study was to evaluate the efficiency of the CyA in the MDS treatment.

Methods: 8 pts with MDS (3 RA, 3 RAEB, 1 RAEBt and 1 CMML) in age from 16 to 67 years (median age – 50) received oral CyA in following doses: 10 mg/kg for the first 10 days, then 5 mg/kg for all period of the treatment (1–9 months). During the treatment the CyA level in blood was not more than 340 ng/ml

Results: A positive effect was achieved in 7 pts: in 6 cases PLT count increased, RBC-transfusion requirements decreased in 3 of 6 transfusion-dependent pts, WBC count increased in 3 of 6 pts with leukopenia. In one case there was a reductions of blast cells in bone marrow from 11% to 5%.

The duration of positive effect was no longer than 6 months. Two pts (one with RAEB and one with RAEBt) developed progressive disease to frank AML.

Conclusion: The treatment of MDS pts with CyA can be successful but improvement is transient.

417

PUBLICATION

Persistent lymphopenia six months after intensification with peripheral blood progenitor cells (PBPC)

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Purpose: Long term follow-up of hematological recovery after PBPC.

Methods: 31 consecutive breast cancer patients aged 28–50 years were treated by autografting with PBPC. All were given 3 g/m² cyclophosphamide as priming followed by daily 5 µg/kg of G-CSF. PBPC were harvested with a Fresenius AS 104 apheresis machine. A minimum of 1×10^6 CD-34+ cells/kg of the patient were given after myeloablative treatment. The 31 breast cancer patients had the same treatment being cyclophosphamide 5 g/m², melphalan 50 mg/m² and carboplatin 900 mg/m². The non-cryopreserved PBPC were returned to the patient within 36 h of the harvest. Thereafter G-CSF is given at a dose of 5 µg/kg.

Results: All patients recovered reaching >1000 neutrophils/mm³ and >50.000 platelets/mm³ after a median time of 14 days. Blood counts were checked before priming and at 6 months on 28 patients. On the average the platelet count was decreased from 272.000 u³ to 202.000 u³, the neutrophil count from 3.333 u³ to 3.229 u³ and the lymphocyte count from 1.070 u³ to 788 u³. Only 3 patients had >1.000 total lymphocytes count at six months post-PBPC.

Conclusions: Mostly T-lymphocytes were decreased. The 4 patients (15%) with the lowest B-lymphocyte count (<200 u³) have persistent hypogammaglobulinemia. The results were independent from age, previous therapy and stage of disease. Measurements of HLA-DR and Thy-1 markers may allow better cell count prediction.

418

PUBLICATION

Economic costs of high-dose chemotherapy with peripheral blood stem cell rescue

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Purpose: When compared to bone marrow (BM) rescue, infusion of autologous peripheral blood stem cells (PBSCs) after high-dose chemotherapy (HD-CHT) allows faster hematologic recovery, less extrahematologic complications, shorter admission and lower mortality. This might result into lower cost. However, the increasing use of expensive drugs, p.e. colony-stimulating factors (CSFs) makes cost estimations based solely on the duration of admission unreliable.

Methods: The cost of PBSC mobilization and admission for HD-CHT (including both direct (wages, pharmacy, diagnostic tests) and indirect (overhead) costs of hospital stay) was evaluated in 27 consecutive pts treated at our institution (1995–6).

Results: Tumor types: breast cancer (15 pts), non-Hodgkin's lymphoma (6 pts) and other solid tumors (6 pts). Median hospital stay was 21 days (range 15–40). Mean cost was 3.5 million pesetas (ptas) (= 21959 ECU = 27665 US dollars). Median cost was 3.1 million ptas (range 1.9–6.7). Distribution of expenses: wages 37%, pharmacy 35%, PBSC mobilization 7%, blood bank 7%, fixed hospital costs 5%, diagnostic tests 3%, Hickman catheter 2%. Drugs causing the highest expense: paclitaxel (28% of all pharmacy expenses), carboplatin (11%), mesna (9%), imipenem (7%), fluconazole (6%), telicoplanin (5%), parenteral nutrition (5%), G-CSF (4%), granisetron (4%) and GM-CSF (2%).

Conclusions: The cost of HD-CHT+PBSC rescue found in this direct cost evaluation is similar to that reported in other European centers, and lower than for HD-CHT + BM rescue. Wages and pharmacy expenses represent 72% of the total cost. Since CSFs are not the drugs generating the highest expense, measures to limit the pharmacy cost should not focus exclusively on them.