In vitro drug sensitivity of normal peripheral blood lymphocytes and childhood leukaemic cells from bone marrow and peripheral blood

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Summary In vitro drug sensitivity of leukaemic cells might be influenced by the contamination of such a sample with non-malignant cells and the sample source. To study this, sensitivity of normal peripheral blood (PB) lymphocytes to a number of cytostatic drugs was assessed with the MTT assay. We compared this sensitivity with the drug sensitivity of leukaemic cells of 36 children with acute lymphoblastic leukaemia. We also studied a possible differential sensitivity of leukaemic cells from bone marrow (BM) and PB. The following drugs were used: Prednisolone, dexamethasone, 6-mercaptopurine, 6-thioguanine, cytosine arabinoside, vincristine, vindesine, daunorubicin, doxorubicin, mafosfamide (Maf), 4-hydroperoxy-ifosfamide, teniposide, mitoxantrone, L-asparaginase, methotrexate and mustine.

Normal PB lymphocytes were significantly more resistant to all drugs tested, except to Maf. Leukaemic BM and PB cells from 38 patients (unpaired samples) showed no significant differences in sensitivity to any of the drugs. Moreover, in 11 of 12 children with acute leukaemia of whom we investigated simultaneously obtained BM and PB (paired samples), their leukaemic BM and PB cells showed comparable drug sensitivity profiles. In one patient the BM cells were more sensitive to most drugs than those from the PB, but the actual differences in sensitivity were small.

We conclude that the contamination of a leukaemic sample with normal PB lymphocytes will influence the results of the MTT assay. The source of the leukaemic sample, BM or PB, does not significantly influence the assay results.

Differences in sensitivity to cytostatic drugs between normal and malignant cells are important for a number of reasons. In the first place, the clinical use of drugs with a preferential toxicity towards malignant cells is preferred. Secondly, the success of pharmacologic bone marrow (BM) purging of malignant cells before autologous BM transplantation, currently intensively studied and practised (Kluin-Nelemans et al., 1984; Rizzoli et al., 1990; Scholzel et al., 1986; Singer & Linch, 1987), depends on malignant cells being more sensitive to the drugs applied than normal hematopoietic stem cells. Finally, one should know the drug sensitivity of normal cells, to determine the influence of their presence in a malignant tumour sample of which in vitro drug sensitivity is assessed.

A tetrazolium-based assay to study in vitro antitumour activity of cytostatic drugs was described almost 40 years ago (Black & Speer, 1953). A similar assay is the MTT assay, in the English literature first described by Mosmann (1983). The MTT assay is a valuable drug sensitivity assay (Veerman & Pieters, 1990). In this assay no distinction can be made between different kinds of living cells in the sample tested (Pieters et al., 1988). Therefore, the presence of a substantial number of normal cells might influence the results (Kirkpatrick et al., 1990).

In studies of drug resistance in leukaemic patients, both BM and peripheral blood (PB) samples are investigated. Prior to the collective evaluation of the results, one should rule out the possibility that BM and PB leukaemic cells differ in drug sensitivity. Therefore, we determined and compared the in vitro sensitivity of normal PB lymphocytes and leukaemic cells from BM and PB of children with acute leukaemia to 16 cytostatic drugs.

Materials and methods

Reagents

Prednisolone disodiumphosphate (PRD), dexamethasone disodiumphosphate (DXM), daunorubicin (DNR), L-asparaginase (L-Asp), mustine hydrochloride (MUST), cytosine arabinoside (ara-C), vindesine (VDS), vincristine (VCR), mitoxantrone (Mitox), methotrexate (MTX), and teniposide (Teni) were obtained from our hospital pharmacy, together with acidified (0.04 N HCl) isopropanol, 6-thioguanine (6-TG), 6-mercaptopurine (6-MP), and doxorubicin (Dox) from Sigma; mafosfamide (Maf, 4-hydroxycyclofosfamide) and 4-hydroperoxy-ifosfamide (4-HI), active derivatives of cyclofosfamide (CFM) and ifosfamide (IFM) respectively, were kindly provided by ASTA Pharma AG (Dr M. Peukert, Bielefeld, Germany).

PRD (of which 75% corresponds to pure prednisolone) was dissolved in saline. DNR, L-Asp, Must, VDS, and Dox were dissolved in distilled water, 6-MP and 6-TG in 0.1 N NaOH, Maf in PBS, and 4-HI in DMSO/distilled water (1:1). DXM, Ara-C, VCR, Mitox, MTX and Teni were obtained in soluble form.

Cells were suspended in RPMI 1640 (Gibco, Dutch modification), containing 20% fetal calf serum, 2 mM L-glutamine, 100 IU ml⁻¹ penicillin, 100 μg ml⁻¹ streptomycin, 0.125 μg ml⁻¹ fungizone, 200 μg ml⁻¹ gentamycin, all obtained from Flow Laboratories, and 5 μg ml⁻¹ insulin, 5 μg ml⁻¹ transferrin, and 5 ng ml⁻¹ sodium selenite from Sigma. MT3 (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium-bromide) was obtained from Sigma.

Cells

Normal PB was obtained from 13 healthy adult volunteers. Mononuclear cells were isolated by density gradient centrifugation with Ficoll Isopaque (Lymphoprep; density 1.077 g ml⁻¹; Nyegaard, Oslo). Immunological phenotyping was done as described (Veerman et al., 1983). BM and/or PB samples from 38 children with acute lymphoblastic leukaemia.
(ALL) at initial diagnosis were mostly obtained from the laboratory of the Dutch Childhood Leukemia Study Group. From 11 of 38 children with ALL and from one child with acute non-lymphocytic leukaemia (ANLL), paired BM and PB samples were collected and investigated simultaneously. The cells were freshly tested.

**MTT assay**

Storage and preparation of the drug solutions was done as previously described (Pieters et al., 1990). Eighty µl cell suspension — 2 × 10^6/ml in case of leukaemic cells, 1 × 10^6/ml in case of normal cells — was added to the wells of 96-well microculture plates. The optical density (OD) is linearly related to the cell number in this range, as described by Pieters et al. for ALL cells (1990), and as shown in Figure 1 for normal PB lymphocytes. In the wells, 20 µl of the various drug solutions was dispensed already. Each drug was tested in six concentrations, in duplicate (Table I). Because we observed evaporation in the outer wells, these were filled with RPMI. Six wells containing medium only were used for blanking the reader, another six wells containing cells and medium used to determine the control cell survival. The plates were incubated in humidified air containing 5% CO₂ for 4 days at 37°C. Then 10 µl MTT solution (5 mg ml⁻¹) was added and after shaking the plates until the cell pellet was dissolved, they were incubated for 6 h. The formed formazan crystals were dissolved with 100 µl isopropanol. The OD of the wells was determined with a microplate spectrophotometer (Titertek Multiskan MCC 340) at 565 nm. The cell survival (CS) was calculated by the equation: CS = (OD treated well/mean OD control wells) × 100%. The LC₅₀, the drug concentration required to kill 50% of the cells as compared to the control cell survival was calculated from the dose-response curve.

**Statistics**

The chi-squared test with Yates’ correction and the Wilcoxon’s ranking test for unpaired data were used to two-tailed testing at a level of significance of 0.05.

**Results**

There were 28 B-lineage and ten T-ALL cases, and one ANLL case. All samples contained more than 80% blasts. The differences in blast percentages between leukaemic BM and PB samples were small, for the paired samples 93.1 ± 5.8 (mean ± s.d.) and 88.3 ± 7.8 respectively, for the unpaired samples 93.4 ± 6.0 and 92.9 ± 3.5 respectively. The normal PB samples contained 19% (median, range 4–38) monocytes after isolation at day 0, and 10% (0–21) at the end of the 4-days incubation period. The remaining cells were almost entirely lymphocytes. This relative decrease in monocytes was not caused by adherence of these cells to the walls of our polystyrene plates. The percentage of monocytes at day 0 did not correlate with sensitivity to any of the drugs (data not shown). The median T/B cell ratio as determined by the CD2⁺/CD19⁺ cell ratio, was 10.0 (range 3.5–45.5) before, and 18.0 (8.0–92.0) after the incubation period, indicating a selective decrease of B-lymphocytes. The median CD4⁺/CD8⁺ cell ratio was 1.3 (range 0.4–3.0) before, and 1.4

**Table 1**

| Drug                  | Concentration range (µg ml⁻¹) | Dilution step |
|-----------------------|------------------------------|---------------|
| Prednisolone (PRD)    | 0.08–250                     | 5             |
| Dexamethasone (DXM)   | 0.0003–0.8                   | 5             |
| 6-Mercaptopurine (6-MP)| 15.6–500                     | 2             |
| 6-Thioguanine (6-TG)  | 1.56–50                      | 2             |
| Cytosine Arabinoside (Ara-C) | 0.002–2.5                   | 4             |
| Vincristine (VCR)     | 0.05–50                      | 4             |
| Vindesine (VDS)       | 0.05–50                      | 4             |
| Daunorubicin (DNR)    | 0.002–2                      | 4             |
| Doxorubicin (Dox)     | 0.001–1                      | 4             |
| Teniposide (Teni)     | 0.003–8                      | 5             |
| Mafosfamide (Maf)     | 0.10–100                     | 4             |
| 4-Hydroperoxy-Ifosfamide (4-HI) | 0.10–100                  | 4             |
| Mustine (Must)        | 0.16–500                     | 5             |
| L-Asparaginase (L-Asp)| 0.003–0.1                    | 5             |
| Mitoxantrone (Mitox)  | 0.001–1                      | 4             |

*aPart of the samples was tested with a concentration range of 0.0006 to 2 µg ml⁻¹; b 1 IU ml⁻¹.

Figure 2 Dose-response curves for two representative drugs, VCR and DNR, calculated from individual curves (numbers in parentheses) of leukaemic and normal samples. Shown are the mean cell survivals (CS) ± 1 standard deviation. Vincristine: ■, Leukaemic samples (23); ▣, Normal samples (12). Daunorubicin: ■, Leukaemic samples (20); ▣, Normal samples (12).
(range 0.3–2.6) after the incubation. Normal lymphocytes reduced more MTT per living cell at day 4 than ALL cells: OD of 0.381/10^6 cells (mean, four samples) vs 0.210/10^6 cells (n = 15) respectively. Mean control cell survival at day 4 of normal lymphocytes (n = 4) was 78% (range 47–99%) vs 67% (23–127%) of ALL cells (n = 15). Neither significant proliferation nor transformation (to normal lymphoblasts) of normal lymphocytes was observed.

The mean control OD reading in case of normal samples was 0.192 (range 0.090–0.300), and for the ALL samples 0.167 (0.59–0.496). Both for normal lymphocytes and leukaemic cells dose-response curves were found for all drugs, except for MTX. We did not further evaluate the results obtained with MTX. Average dose-response curves were calculated, based on all individual curves, for the normal and leukaemic samples. Data for two representative drugs, VCR and DNR, are shown in Figure 2. For each drug the mean CS values of the leukaemic cells were lower than the CS values of the normal PB lymphocytes, i.e., the leukaemic cells were more sensitive. However, an overlap in the ranges of CS values existed (Figure 2). The CS values of the leukaemic cells varied to a greater extent than those of the normal PB lymphocytes. Leukaemic cells were significantly more sensitive to each drug evaluable, except to Maf, than normal PB lymphocytes (Table II). These differences retained a similar significance when only PB leukaemic cells were compared with normal PB lymphocytes, with exception of Maf (Table II). To Maf the PB leukaemic cells showed a significantly greater sensitivity than the normal cells, because the PB leukaemic cells tended (P close to 0.1) to be more sensitive to Maf than the BM leukaemic cells. Using the LC50 concentration lethal to 70% of the cells), PB leukaemic cells still showed a higher sensitivity to Maf, but the tendency diminished (P 0.25). Thus, normal PB lymphocytes were significantly less sensitive than leukaemic cells from BM and PB to

### Table II Drug sensitivity of normal peripheral blood lymphocytes and childhood acute lymphoblastic leukaemic (ALL) cells

| Drug            | LC50 values* median (range) | Normal samples (n = 11–13) | Leukaemic samples (n = 22–30)* | Normal vs BM + PB ALL samples | Normal vs PB ALL samples |
|-----------------|-----------------------------|-----------------------------|--------------------------------|-------------------------------|--------------------------|
| Prednisolone    |                             | 250 (1.58–>250)            | 1.84 (<0.08–>250)            | <0.05                         | <0.05                    |
|                 |                             | >0.8 (<0.003–>0.8)         | <0.01                         | <0.01                         |
| Daunorubicin    |                             | 410.7 (125–>500)           | 1.25 (<15.6–>500)            | <0.001                        | <0.01                    |
|                 |                             | >2.5 (<0.05–>50)           | <0.01                         | <0.01                         |
| Daunorubicin    |                             | 1.112 (0.63–>2)            | 0.992 (<0.002–>2.5)          | <0.01                         | <0.01                    |
|                 |                             | >1 (<0.08–>1)              | <0.01                         | <0.01                         |
| Doxorubicin     |                             | 1.493 (0.77–<0.58)        | 0.263 (<0.06–>8)             | <0.01                         | <0.01                    |
|                 |                             | >1.62 (3.2–>100)           | 0.16 (<0.003–>10)            | <0.01                         | <0.01                    |
| Doxorubicin     |                             | 1.26–>10                  | <0.01                         | <0.01                         |
| Mafosfamide     |                             | 0.839 (0.14–>1)           | 0.055 (<0.001–>1)            | <0.01                         | <0.01                    |
| L-Asparaginase  |                             | 0.36 (0.003–>10)          | 0.21 (<0.003–>10)            | <0.01                         | <0.01                    |
| Mitoxantrone    |                             | 0.067 (0.011–>1)          | 0.076 (<0.001–>0.7)          | <0.01                         | <0.01                    |

*Lethal concentration to 50% of the cells; 14-hydroperoxy-ifosfamide used in 13 samples; Paired samples: only PB samples included; Wilcoxon’s ranking test for unpaired data; ns: not significant (P > 0.05); 4IU ml^-1.

### Table III Drug sensitivity of childhood acute lymphoblastic leukaemic cells from bone marrow (BM) and peripheral blood (PB)

| Drug            | LC50 values* median (range) | BM samples (n = 17–24)* | PB samples (n = 11–18)* | P-value |
|-----------------|-----------------------------|-------------------------|-------------------------|---------|
| Prednisolone    | 23.3 (4.58–<250)            | 23.9 (4.58–<250)        | 3.3 (1.09–<250)         | 0.104   |
| Dexamethasone   | 0.001 (0.001–>0.8)          | 0.003 (0.001–>0.8)      | 0.27 (0.001–<0.8)       | 0.017   |
| 6-Mercaptopurine| 145.0 (125–>250)            | 125.0 (125–>250)        | 125.0 (125–>250)        | 0.017   |
| 6-Thioguanine   | 7.1 (3.5–>50)               | 6.8 (3.5–>50)           | 6.8 (3.5–>50)           | 0.017   |
| Cytosine arabinoside | 0.44 (0.51–<0.8) | 0.51 (0.51–<0.8) | 0.51 (0.51–<0.8) | 0.017   |
| Vincristine     | 2.4 (0.45–>50)              | 2.3 (0.45–>50)          | 2.3 (0.45–>50)          | 0.017   |
| Doxorubicin     | 0.08 (0.013–>0.6)           | 0.13 (0.013–>0.6)       | 0.13 (0.013–>0.6)       | 0.017   |
| Daunorubicin    | 0.50 (0.083–>1)              | 0.58 (0.083–>1)         | 0.58 (0.083–>1)         | 0.017   |
| Teniposide      | 0.26 (0.058–>8)              | 0.35 (0.058–>8)         | 0.35 (0.058–>8)         | 0.017   |
| Mafosfamide     | 8.8 (1.9–>100)              | 6.4 (1.9–>100)          | 6.4 (1.9–>100)          | 0.017   |
| 4-Hydroperoxy-ifosfamide | 10.0 (1.9–>29.2) | 5.1 (1.9–>29.2) | 5.1 (1.9–>29.2) | 0.017   |
| L-Asparaginase  | 0.36 (0.003–>10)            | 0.21 (0.003–>10)        | 0.21 (0.003–>10)        | 0.017   |
| Mitoxantrone    | 0.067 (0.011–>1)            | 0.076 (0.011–>1)        | 0.076 (0.011–>1)        | 0.017   |

*Lethal concentration to 50% of the cells; 14-hydroperoxy-ifosfamide used in 13 samples; Paired samples: only PB samples included; Wilcoxon’s ranking test for unpaired data; ns: not significant (P > 0.05); 4IU ml^-1.
We compared the range and median LC$_{50}$ values of each drug for all leukaemic BM samples and all leukaemic PB samples from 38 ALL patients. No significant differences were found between BM and PB leukaemic cells in sensitivity to any of the drugs (Table III). In 12 cases (11 ALL, 1 ANLL) drug sensitivity results from paired BM and PB samples were studied. Analysis of these paired data also showed no preferential sensitivity of BM or PB leukaemic cells to any of the drugs. Evaluating the individual data, 11 of the 12 patients showed no differences in drug sensitivity between their BM and PB leukaemic cells. One child with ALL showed a greater sensitivity of the BM cells. Although statistically significant, the actual differences in LC$_{50}$ values were small. There was a good correlation between the paired BM and PB LC$_{50}$ values in most individual cases and in the 106 paired BM and PB LC$_{50}$ comparisons together (Figure 3).

**Discussion**

Several studies have compared the drug sensitivity of non-malignant and leukaemic cells. Table IV summarises the results of the studies in which patient samples were investigated. This table shows that in most studies non-malignant cells were found to be less sensitive to the drugs used than leukaemic cells. Occasionally, a greater sensitivity of the non-malignant cells was found (Scholzel et al., 1986). For some drugs (e.g. DNR and Dox) the results are contradictory. This

| Reference          | Cells                        | Assay           | Drugs                  | Less sensitive (compared to normal cells) | More sensitive (compared to normal cells) |
|--------------------|------------------------------|-----------------|------------------------|------------------------------------------|------------------------------------------|
| Galli et al. (1980)| ALL, CLL, AML and CML vs normal BM and PB ly's | Viable cell count | Cortisol               | AML/CML                                   | ALL/CLL                                   |
| Spiro et al. (1981a,b) | CML-CFC vs normal BM and PB-CFC | Clonogenic      | Dox, DNR, L-Asp, Ara-C | CML                                       | CML (other drugs)                         |
| Speth et al. (1988) | ANLL BM vs normal BM progenitor | Clonogenic      | Dox                    | ANLL                                      |
| Singer et al. (1987) | AML-CFC (PB) vs normal GM-CFC | Clonogenic      | Maf, Mel, Ara-C, 4-HC, VP-16 | AML                                      |
| Schrek et al. (1967) | CLL (PB) vs normal PBL      | Viable cell count | L-Asp                  | CLL                                       |
| Schrek (1961, 1964) | CLL and LS vs normal PBL    | Viable cell count | Cortisol, PRD          | CLL/LS                                   |
| Scholzel et al. (1986) | AML-CFC vs normal BM CFC-E and -M | Clonogenic      | Mitox, DNR, 4-mdDNR, 4'doDox | AML                                      |
| Kline-Nel mans et al. (1984) | L-CFC vs normal CFC-GM and BFU-E | Clonogenic      | L-CFC                  | L-CFC                                    |
| Jayaram et al. (1986) | ANLL and ALL vs normal BM leukaocytes | Depression of [GTP] | Tiazofurin             | ANLL/ALL                                |
| Greenberg et al. (1976) | L-CFC vs normal granulocytic CFC | Clonogenic      | Ara-C, 6-TG            | L-CFC (6-TG)                             |
| Buick et al. (1979)  | AML-CFC vs normal granulopoietic and T-ly CFC | Colony | Dox, DNR                | L-CFC (AraC)                             |
| Asselin et al. (1989) | ALL BM vs normal BM | Viable cell count | L-Asp                  | CLL                                      |
| Weisenthal et al. (1987) | ALL and CLL vs normal PBL | DiSC            | VCR                    | ALL/CLL                                 |
| Tazte et al. (1983)  | (B-JCL-CFC vs normal T-PBL)  | Clonogenic      | HC, 5-FU, Mel, MTX, Dox, Blm, CA, CF, Ara-C | CLL (Blm) (other drugs)                      |
| Werthamer et al. (1971) | CML vs normal PB ly's     | RNA and protein precursor incorporation | Cortisol               | MTX not evaluable CLL                    |
| Verdonck et al. (1990) | AML-, ALL- and CMF-Clonogenic | Clonogenic      | alkyllysophospholipid   | AML/ALL/CML                              |
| Katano et al. (1989)  | ALL BM vs normal BM mononuclear | Bromodeoxy-uridine incorporation in S-phase cells | Ara-C                  | ALL                                      |
| Potter et al. (1980)  | AML BM vs normal BM$^{3}$ Thymidine incorporation | Clonogenic      | Ara-C                  | AML                                      |

AML: acute myeloid leukaemia; BFU-E: blood forming units-erythroid; Blm: bleomycin; Bs: busulfan; CA: chlorambucil; CFC: colony forming cells; CFC-E: CFC-erythroid; CFC-GEMM: CFC-granulocyte-erythrocyte-macrophage-megakaryocyte; CFC-GM: CFC-granulocytic-myeloid; CFC-M: CFC-myeloid; CLL: chronic lymphocytic leukaemia; CML: chronic myeloid leukaemia; CP: cisplatinum; 4-mdDNR: 4-demethoxy DNR, 4'doDox: 4'deoxyDox; 5-FU: 5-fluorouracil; GTP: guanyl triphosphate; HC: hydrocortisone; 4-HC: 4-hydroperoxycyclofosamide; HU: Hydroxy-ureum; L-CFC: leukaemic-CFC; LS: lymphosarcoma in leukaemic phase; ly: lymphocyte; Mel: melphalan; MTX: methotrexate. Other abbreviations: See Table I and text.
The cause(s) of the presented differential drug sensitivity of normal lymphocytes and leukaemic cells are largely unknown. However, these cells differ in several aspects, like immunophenotype and differentiation-stage. Normal PB lymphocytes are mainly of the T-lineage (which was even more accentuated after the 4-days incubation period of the MTT assay in the present study) and represent mature cells. Most childhood actue leukaemias are of the immature B-lineage phenotype, as was the case in this study. The T-lineage leukaemias show a less mature phenotype than normal T-cells. Recently we found that T-ALL cells were relatively resistant to various drugs compared to immature B-ALL cells (Pieters et al., in press). Therefore, the differences regarding immunophenotype between the tested leukaemic and normal lymphocytes could well contribute to the presented differences in drug sensitivity. Changes in immunophenotype of normal lymphocytes might occur in patients suffering a malignancy. However, we found that the removal of normal T-lymphocytes from ALL samples with less than 80% ALL cells resulted in increased drug sensitivity (unpublished data). This supports the conclusions of the present study. An extensive discussion of all other possible causes of the presented difference in drug sensitivity is beyond the scope of this report.

The analysis of the assay results obtained with (unpaired) BM and PB leukaemic cells from all 38 ALL patients did not reveal a preferential sensitivity of the PB or BM leukaemic cells to any of the drugs (Table III). Similarly, no preferential sensitivity of the (paired) BM or PB leukaemic cells from 12 leukaemic patients (one ANLL, 11 ALL) was found. In 11 out of 12 patients of whom we tested their (paired) BM and PB leukaemic cells, the sample source did not significantly influence drug sensitivity. In one case the leukaemic cells from the BM were significantly more sensitive than those from the PB, but the actual differences in LC50 values were very small and of no practical importance. The correlation for all 106 paired BM and PB LC50 comparisons was very good, with most pairs close to the ideal line $y = x$ (Figure 3). Our findings agree with those of Bird et al. (1986), who reported a significant association in sensitivity to a maximum of six drugs of leukaemic BM and PB cells from 12 patients. The same was found by Sargent and Taylor (1989) andSpiro et al. (1981a), in single cases.

We conclude that normal PB lymphocytes are more resistant than childhood ALL cells to a large number of drugs in vitro. Consequently, the number of normal lymphocytes contaminating an ALL sample to be tested should be low, when the MTT assay or a similar total cell kill assay is used. This is especially the case in view of the higher survival at day 4 and the higher MTT reduction per living cell of the normal lymphocytes compared to the untreated ALL cells. The MTT assay and the Differential Staining Cytotoxicity (DiSC) assay gave comparable results in samples with 80% (or more) leukaemic cells, the lowest percentage tested (Pieter et al., 1989). Therefore, in case of a sample with less than 80% leukaemic cells, the use of the DiSC assay – in which a distinction between non-malignant and leukaemic cells can be made – should be considered. Because this assay is laborious and subjective, we are investigating techniques to remove non-malignant cells from leukaemic samples.

Finally, because the drug sensitivity profiles of leukaemic cells from the BM are quite comparable to those from the PB, it is allowed to evaluate results obtained using samples from both sources together, which obviously is of practical importance.

The laboratory of the Dutch Childhood Leukemia Study Group (DCLSG) provided most of the patient samples. Board members of the DCLSG are J.R.M. Bökkerink, M.V.A. Bruin, P.J. Van Dijken, K. Hählen, W.A., Kamps, E.F. Van Leeuwen, F.A.E. Nebben, A. Postma, J.A. Rampeloo, I., Risseeuw-Appel, G.A.M. De Vaa, E. Th. Van't Veer-Korthof, A.J.P. Veerman, F.C. De Waal, M. Van Weel-Sipman and R.S. Weening.

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Figure 3 Comparison of in vitro drug sensitivity between (paired) BM and PB leukaemic cells from 12 patients. Each point represents a paired LC50 value ($n = 106$). The line shown is the line $y = x$.
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