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Comparison between Single Saturating Dose Ligand Binding Assay and Enzyme Immunoassay for Low-salt Extractable Oestrogen and Progesterone Receptors in Breast Cancer: a Multicentre Study

Massimo Gion, Ruggero Dittadi, Antonette E. Leon, Giuliano Bruscagnin, Dario Pelizzola, Gloria Giovannini, Melchiorre Giganti, Gianni Messeri, Massimo Quercioli, Emanuela Flamini, Angela Riccobon, Cecilia Bozzetti, Magda Benecchi, Mario De Lena, Angelo Paradiso, Giuseppina Ruggeri, Patrizia Luisi and Adriano Piffanelli

An excellent correlation between ligand binding assay (LBA) and enzyme immunoassay (EIA) for both oestrogen (ER) and progesterone (PR) receptors has been reported. Nevertheless, considering that the clinical value of any discrepancy between LBA and EIA probably varies with the receptor level, we undertook a collaborative study in which a single saturating dose (SSD) LBA and EIA were compared in different ER and PR dose ranges. The values of ER measured by EIA were higher in tumours with low or intermediate receptor content, causing a misclassification of ER status in 9% of cases (ER+: 77.5%, EIA, 68.8% SSD). In the case of ER, EIA values tended to be higher than SSD in all centres. For PR, EIA and SSD were generally more comparable (PR+: 66.0% EIA, 72.0% SSD, discordance rate 6%), with EIA showing, however, different trends in different centres. PR concentration was not significantly different in ER SSD−/EIA+ and in ER SSD+/EIA+ cases, suggesting that EIA detects at least in part integer ER. We conclude that although EIA may be a reliable methodological alternative to SSD, the two methods are not interchangeable until effective cut-off levels for clinical decisions are assessed for EIA.
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INTRODUCTION

THE DETERMINATION of oestrogen (ER) and progesterone (PR) receptors is an essential tool for the routine characterisation of breast cancer. The usefulness of ER and PR for both prognostic evaluation and the prediction of effectiveness of endocrine therapy has been pointed out frequently. ER and PR are currently measured routinely in high-speed cytosol of breast cancer samples by ligand binding assay (LBA). Considering the clinical importance of steroid receptor determination, the LBA method has been standardised [1] and effective quality control programmes have been activated [2–5] in order to reduce the variability related to methodological bias. In spite of great efforts, quality control programmes demonstrated that both intralaboratory precision and accuracy reached a plateau level which was not satisfactory. The performance characteristics of LBA are not easily improved, probably because of drawbacks intrinsic in the LBA methods itself [6–8], such as the high lability of the steroid binding ability of the receptor, difficulty in the actual standardisation of the method due to possible unrecognised variations in the assay procedures (e.g. preparation and storage of buffers, degradation of the radiolabelled steroid, control of working temperature and different degrees of receptor saturation by endogenous steroids. A further source of error may be related to incorrect handling and storage of the tissue from sample collection to the assay, which may degrade the receptor binding capability. The availability of monoclonal antibodies to both the oestrogen [9] and the progesterone receptor proteins [10] led to the development of commercially available enzyme immunoassays (EIA) which should overcome the main drawbacks of LBA since (1) the immunological characteristics of the receptor protein are probably more stable than its steroid-binding ability (ref. 11 and M.G.); (2) the immunologically detectable receptor is functional as far as the induction of PR synthesis is concerned, as was shown by S. Thorpe [11] and demonstrated in the present study; (3) a full standardisation

Correspondence to M. Gion.
Requests for reprints to Comitato Italiano per il Controllo di Qualità del Laboratorio in Oncologia, Casella Postale n. 39-44034 Copparo, Ferrara, Italy.
M. Gion, R. Dittadi, A.E. Leon and G. Bruscagnin are at the Centro Regionale Indicatori Biochimici di Tumore, Divisione di Radioterapia, Ospedale Civile, Venezia; D. Pelizzola, G. Giovannini, M. Giganti and A. Piffanelli are at the Cattedra di Medicina Nucleare (Istituto Radiologia) Università di Ferrara, Ferrara; G. Messeri and M. Quercioli are at the Laboratorio di Endocrinologia, Ospedale di Careggi, Firenze; E. Flamini and A. Riccobon are at the Servizio di Oncologia, Ospedale Morgagni, Forlì; C. Bozzetti and M. Benecchi are at the Centro Oncologico, Parma; M. De Lena and A. Paradiso are at the Istituto Oncologico, Bari; and G. Ruggeri and P. Luisi are at the Istituto di Chimica dell'Università, Brescia, Italy.
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of EIA methods is feasible [12]; and (4) the immunological detection of the receptor protein should not be affected by the grade of saturation of the receptor. Even though very recent EIA results from the EORTC Receptor Study Group demonstrated external precision and accuracy coefficients comparable to LBA data (EORTC Receptor Study Group, Crete, April 1990), several authors confirmed the good performance characteristics of the EIA method [13–16]. The probable ineffectiveness of the grade of receptor saturation on receptor quantification has also been reported [17, 18]. Moreover, even if receptor concentration and positivity rates were slightly higher using the EIA method, an excellent correlation between LBA and EIA has been shown in several published studies [14–26].

However, the evaluation of the correlation between data obtained with LBA and EIA in the overall receptor concentration range is not completely adequate for clinical purposes. The clinical importance of any difference of the measured receptor concentration is indeed closely related to the actual receptor concentration, being probably lower in receptor rich tumours, but certainly higher in receptor poor tumours.

In a previous study, Thorpe demonstrated that the slopes of the correlation curves between EIA and LBA were different in different dose ranges of ER [11]. Therefore, in the present study, receptor levels obtained by a single saturating dose (SSD of LBA and EIA were compared separately in different groups of cases grouped according to their receptor concentration, in order to identify any possible clinical weight of methodological differences.

MATERIALS AND METHODS

To date, 696 patients with untreated primary breast cancer have entered the study. All the participating centres followed a standardised protocol for tissue collection and storage, cytosol preparation and steroid receptor determination [1, 27]. Tissue samples were collected fresh from the operating room and immediately chilled on crushed ice. Fat and necrotic tissue was dissected away and the tumours were minced and frozen in liquid nitrogen. Tissue samples were stored in liquid nitrogen until assayed. Labelled steroids (oestradiol, ORG 2058) and unlabelled ORG 2058 were purchased from Amersham International (Cardiff, UK). Other chemicals were purchased from Sigma.

Cytosol preparation

Tissue samples were powdered using a microdismembrator (Braun, Melsungen, Germany; single-ball; diameter, 9 mm; amplitude, 12 mm; time, 45 s × 2). The powdered tissue was homogenised with 8–10 volumes of cold 10 mmol/l phosphate buffer (pH 7.4, containing 1.5 mmol/l EDTA, 1 mmol/l dithiothreitol, 20 mmol/l sodium molybdate, glycerol 10% v/v, 3 mmol/l NaN_3) by aspiration in a Pasteur pipette. Low-salt extract (cytosol) was prepared by centrifugation at 100 000 *g* for 1 h at 4°C.

Radioligand binding assay

ER and PR were measured in the low-salt extract using the dextran-coated charcoal (DCC) method recommended by the EORTC, which has been described in detail elsewhere [27]. Both the Scatchard plot and SSD techniques were used. Results determined by SSD were used for EIA/SSD comparisons, considering that Scatchard plot and SSD give results closely correlated [28] and that the SSD is technically comparable with EIA since SSD procedure is simple and can be used even when only small tissue samples are available. For SSD, three replicate aliquots of cytosol were incubated for 18–20 h at 4°C with a final concentration of 4 nmol/l [2, 4, 6, 7-^{3}H] oestradiol for ER and 16α-ethyl-21-hydroxy-19-nor-[6, 7-^{3}H] pregnen-4ene-3,20-dione (ORG 2058) for PR determination, with and without a 100-fold excess concentration of diethylstilbestrol and ORG 2058, respectively, to correct for non-specific binding. Unbound steroids were removed by dextran-coated charcoal (charcoal activated 0.5% w/v, dextran 70 0.05% w/v).

Enzyme immunoassay

Both ER and PR were determined by the Abbott enzyme immunoassay kits according to the manufacturer's instructions, with the exception of the use of phosphate buffer which had been previously shown not to affect the results obtained by the enzyme immunoassay [15, 18, 26]. Briefly, aliquots of cytosol, and control standard were incubated in duplicate with polystyrene beads coated with one monoclonal antibody (D547 for ER, KC146 for PR) for 18(±1)h at 4°C. After the incubation, the beads were washed twice with distilled water and a second antibody conjugated with peroxidase (H222 for ER, JZB39 for PR) was incubated with the receptor-bead complex for 1 h (at 37°C for ER or at 4°C for PR). Beads were washed twice with distilled water and transferred to polyethylene tubes. A solution of o-phenylendiamine diluted in citrate-phosphate buffer containing 0.02% hydrogen peroxide was added to each tube and after a 30 min incubation at room temperature the reaction was stopped by sulphuric acid 1 mol/l and the adsorbance read at 492 nm.

Protein assay

The total protein in the cytosol (c.p.) was measured by the Bradford method (Coomassie Brilliant Blue, Biorad) using human serum albumin as a standard (Kabi–Vitrum, Sweden).

Statistical evaluation

Data were analysed with the Fisher exact test, Mann–Whitney *U* test, Wilcoxon signed-rank test and regression analysis using both data and logarithms of data; correlation coefficients were estimated from least-squares best fit. The difference in slope was analysed by the Behrens–Fisher test. Results of SSD were treated as the independent variable. Menopausal status was classified as follows: premenopausal = patients with regular menstrual cycles, and perimenopausal and postmenopausal = those whose last regular menses occurred less than and more

Table 1. Characteristics of patient series

		Menopausal status			Age	
Centre	Cases	Pre	Peri	Post	Median	Range
Overall	696	167	26	454	57	28–96
1	163	25	9	108	60	37–88
2	62	8	–*	52	62	40–92
3	100	30	15	52	54	33–89
4	165	52	–*	113	58	29–88
5	39	12	3	22	55	42–96
6	23	–†	–†	–†	–	–
7	144	40	–*	104	55	28–79

* Perimenopausal patients were included in premenopausal group.
† Age and menopausal status not specified.

Table 2. Low-salt extractable ER. Correlation between SSD and EIA

Centre	Overall	Premenopausal	Postmenopausal
Overall			
n	619	149	394
r	0.885*	0.899*	0.886*
Slope	1.26	1.36	1.25
Intercept	30.4	19.3	33.0
1			
n	153	22	101
r	0.909*	0.798*	0.904*
Slope	1.36	2.07	1.34
Intercept	28.0	2.5	35.7
2			
n	62	8	52
r	0.919*	0.888‡	0.912*
Slope	1.19	1.05	1.19
Intercept	8.2	3.3	11.4
3			
n	100	30	52
r	0.865*	0.920*	0.911*
Slope	1.34	1.19	1.57
Intercept	20.0	19.2	18.8
4			
n	155	51	103
r	0.916*	0.892*	0.920*
Slope	1.18	1.32	1.16
Intercept	34.0	24.2	34.3
5			
n	39	13	22
r	0.844*	0.937*	0.825*
Slope	2.09	2.2	2.06
Intercept	23.6	12.2	39.6
6			
n	23	–	–
r	0.709†		
Slope	1.35		
Intercept	96.0		
7			
n	89	25	64
r	0.586*	0.927*	0.526*
Slope	1.16	2.56	0.984
Intercept	29.9	3.9	34.9

* $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.01$.

than 2 years before, respectively. When studying differences related to menopausal status, perimenopausal patients were excluded from the evaluation, since the receptorial pattern in perimenopausal patients was shown to be different from that of both premenopausal and postmenopausal patients [8].

RESULTS

Table 1 reports the number of cases, age and menopausal status of the patient series evaluated in each centre. Menopausal distribution patterns of patients from different centres were significantly different. Therefore, the comparison between SSD and EIA was carried out after stratification of patients according to menopausal status.

Results of different centres

Table 2 reports the results of regression analysis of ER levels measured with SSD and EIA. Both the overall patient series and the results of each centre were evaluated separately. The correlation between SSD and EIA was highly significant between both logarithms (data not shown) and concentrations, the results obtained with EIA method being, however, higher than those of SSD determination in each centre, as the slope value shows. Slope values were significantly higher in premenopausal than in postmenopausal patients in the overall series ($P < 0.01$). In agreement with the latter data, the EIA/SSD ratio was significantly higher in premenopausal (median 1.94) than in postmenopausal (median 1.52, $P = 0.009$).

Correlation between SSD and EIA was also highly significant in the case of PR using both concentrations (Table 3) and logarithms of concentration (data not shown). Nevertheless, in two centres EIA measured PR levels lower than SSD, and in two others the behaviour of EIA was opposite; while in one centre EIA and SSD gave similar results. No differences were found between premenopausal and postmenopausal patients in the overall patient series.

Analysis of SSD-EIA relationships in different receptor concentration range

The correlation between SSD and EIA was evaluated by subdividing patients in groups according to the receptor level

Table 3. Low-salt extractable PR: correlation between SSD and EIA

Centre	Overall	Premenopausal	Postmenopausal
Overall			
n	311	76	214
r	0.777*	0.819*	0.755*
Slope	1.05	0.99	1.02
Intercept	25.6	33.3	24.1
1			
n	76	14	47
r	0.898*	0.943*	0.891*
Slope	1.84	1.5	2.02
Intercept	12.6	33.3	10.4
2			
n	62	8	52
r	0.950*	0.961*	0.949*
Slope	0.88	0.83	0.88
Intercept	−7.6	−19.7	−4.6
4			
n	37	15	22
r	0.966*	0.945*	0.985*
Slope	1.18	1.11	1.25
Intercept	−4.1	0.39	−7.9
5			
n	39	13	22
r	0.662*	0.907*	0.514†
Slope	0.413	0.58	0.109
Intercept	24.3	30.4	18.1
7			
n	97	26	71
r	0.585*	0.484†	0.665*
Slope	1.08	1.08	1.21
Intercept	43.3	56.9	37.3

* $P < 0.0001$, † $P < 0.05$.

Table 4. Low-salt extractable ER: correlation between SSD and EIA in different ER concentration ranges (overall evaluable patients)

SSD concentration range	ER concentrations					Logarithms of ER concentrations				
	n	*r*	*P*	Intercept	Slope	*n*	*r*	*P*	Intercept	Slope
< 5	130	0.031	0.724	–	–	130	−0.015	0.868	–	–
≥ 5	489	0.868	< 0.0001	41.4	1.22	489	0.890	< 0.0001	0.348	0.929
< 10	193	0.286	0.0001	5.8	1.27	193	0.292	< 0.0001	0.605	0.379
≥ 10	426	0.855	< 0.0001	50.6	1.19	426	0.866	< 0.0001	0.535	0.840
< 20	247	0.597	< 0.0001	3.4	2.19	247	0.544	< 0.0001	0.514	0.666
≥ 20	372	0.840	< 0.0001	59.2	1.16	372	0.836	< 0.0001	0.628	0.796
< 50	357	0.731	< 0.0001	2.8	2.37	357	0.759	< 0.0001	0.423	0.871
≥ 50	262	0.798	< 0.0001	76.2	1.11	262	0.771	< 0.0001	0.644	0.788

found by the SSD method. Table 4 shows the results of regression analysis for ER. In the 130 tumours which did not express ER according to the SSD method (ER below 5 fmol/mg c.p.), no significant correlations were found between SSD and EIA and ER values found by EIA were higher than 5 fmol/mg c.p. in 51/130 cases (39.2%) and higher than 10 fmol/mg c.p. in 25/130 cases (19.2%) (Fig. 1). In the other patient subgroups reported in Table 4 the correlation was always significant, but the regression analysis showed that the measured receptor level was higher by EIA.

Significantly higher ($P < 0.0001$) ER concentrations were found with EIA in the overall patient series, as well as in the groups of patients subdivided according to several SSD dose range (Table 5). The overall positivity rate, using 10 fmol/mg c.p. as the negative/positive cut-off value, was significantly higher ($P < 0.0001$) with EIA (480/619, 77.5%) than with SSD (426/619, 68.8%). Table 6 reports the ratio between SSD−EIA+ ER and the overall SSD−ER cases categorised using several cut-off points and subdivided according to menopausal status. The number of SSD−EIA+ ER cases was higher in premenopausal than in postmenopausal patients with all the evaluated cut-off points; differences between premenopausal and postmenopausal patients were statistically significant ($P < 0.05$) using 10 and 20 fmol/mg c.p. as cut-off values.

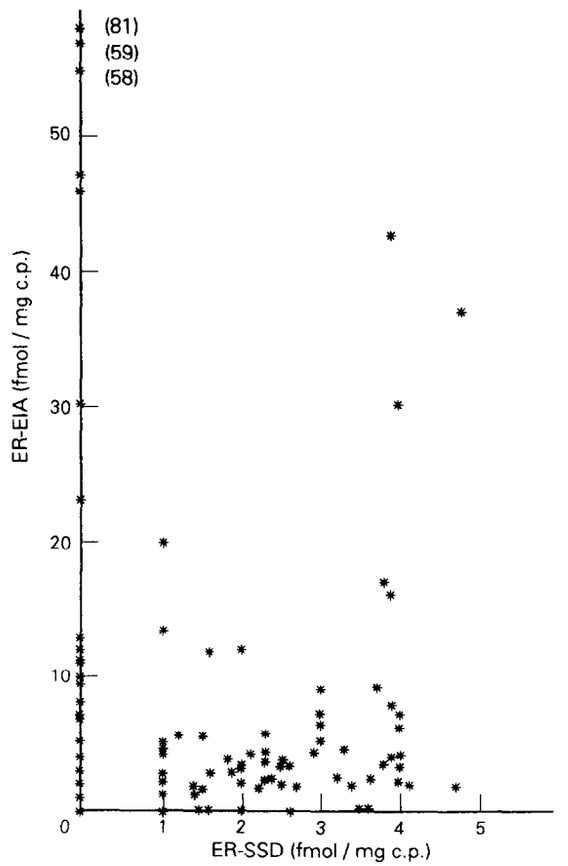

Fig. 1. Correlation between SSD and EIA in 130 cases with SSD level lower than 5 fmol/mg c.p.

Table 5. ER concentration with SSD and EIA

	Mean (S.E.)	Median (25–75 percentile)
Overall (*n* = 619)		
SSD	88 (5.1)	34 (6.7–114)
EIA	141 (7.3)	69 (12–210)
< 5 (*n* = 130)		
SSD	1.5 (0.1)	1.1 (0–2.6)
EIA	7.5 (1.1)	3.6 (1.7–8.2)
≥ 5 (*n* = 489)		
SSD	110 (6.1)	58 (21–144)
EIA	177 (8.5)	108 (42–250)
< 10 (*n* = 193)		
SSD	3.3 (0.2)	2.5 (0–5.8)
EIA	10.1 (1.0)	5 (2.0–11.6)
≥ 10 (*n* = 426)		
SSD	126 (6.6)	72 (32–168)
EIA	200 (9.2)	140 (60–277)
< 50 (*n* = 357)		
SSD	13.9 (0.7)	8.5 (2.3–23)
EIA	35.8 (2.4)	18.1 (4.4–56)
≥ 50 (*n* = 262)		
SSD	188 (8.8)	130 (88–239)
EIA	284 (12.2)	234 (150–375)

Evaluation in the overall patient series and in groups of patients subdivided according to receptor level.

Table 6. ER SSD−EIA+/overall SSD-: relationship to menopausal status

Cut-off point (by SSD)	Overall	Patients	
		Premenopausal	Postmenopausal
5	51/130 (39.2%)	17/31 (54.8%)	29/82 (35.3%)
10	60/193 (31.1%)	23/48 (47.9%)	30/119 (25.2%)
20	69/247 (27.9%)	26/68 (38.2%)	34/142 (23.9%)
50	100/357 (28.0%)	35/109 (32.1%)	52/193 (26.9%)

In the case of PR, no significant correlation was found between EIA and SSD in cases in which PR was less than 5 fmol/mg c.p. and less than 10 fmol/mg c.p with SSD. The correlation was significant ($P < 0.0001$) in both positive and negative cases using 20 or 50 fmol/mg c.p. as a cut-off value. In the case of PR we did not find a constant trend in the differences between the two methods (slope values ranging from 0.95 to 1.04). The overall concordance rate between EIA and SSD was fairly good (cut-off 10 fmol/mg c.p.: 66.0% EIA, 72.0% SSD; cut-off 20 fmol/mg c.p.: 55.6% EIA, 54.3% SSD). Accordingly, no statistically significant ($P > 0.05$) different PR concentrations were found between SSD and EIA in the overall patient series, nor in cases grouped according to receptor content (data not shown).

ER-PR receptor status: concordance rate between SSD and EIA

The assessment of receptor status by assaying low-salt extractable ER and PR either by SSD or EIA gave results which lead to a different clinical evaluation in 31.6% of cases using 10 fmol/mg c.p. as the positive/negative cut-off value for both receptors (Table 7). Discordance was mainly due to the rate of cases SSD−EIA+ for ER. The discordance rate was not significantly modified (24.8% overall discordant clinical evaluation) using 20 fmol/mg c.p. as a positive/negative cut-off value for PR.

Table 7. Low-salt extractable ER/PR receptor status: concordance rate between SSD and EIA

SSD	EIA			
	ER+PR+	ER+PR−	ER−PR+	ER−PR−
ER+PR+				
n	108	16	2	2
%	46.2	6.8	0.9	0.9
ER+PR−				
n	5	19	−	−
%	2.1	8.1	−	−
ER−PR+				
n	20	5	3	14
%	8.5	2.1	1.3	6.0
ER−PR−				
n	2	4	4	30
%	0.9	1.7	1.7	12.8

Negative/positive cut-off: ER, 10 fmol/mg c.p.; PR, 10 fmol/mg c.p.
Evaluated cases = 234, overall concordance rate = 68.4.

PR levels in SSD/EIA discordant cases

PR concentrations and positivity rates were evaluated in relation to ER status assessed by both SSD and EIA. PR concentration showed a trend that was not significant ($P > 0.05$) toward lower values in SSD−EIA+ ER (median 21.1, interquartile 10.8–101 fmol/mg c.p.) than in SSD+EIA+ ER cases (median 49.0, interquartile 15.1–173 fmol/mg c.p.); PR was, however, significantly higher ($P < 0.0001$) in SSD−EIA+ ER than in SSD−EIA− ER cases (median 6.0, interquartile 0–12.6 fmol/mg c.p.). PR levels in the 4 SSD+EIA− ER cases (10.5, 13.3, 14.4 and 21) were close to those found in SSD−EIA− ER tumours. The receptor protein recognised by EIA, but not by SSD alone, seems to indicate the integrity of the receptor mechanism of action, at least as far as the regulation of the progesterone receptor synthesis is concerned.

DISCUSSION

The commercially available EIA methods for the determination of ER and PR provide the following advantages over the currently used LBA methods: (1) the EIA methods are fully standardised and possibly more reproducible [13–16]; (2) they probably measure receptors both free and saturated by endogenous steroids; and (3) they can be performed using small amounts of tissue and the immunological detection of the receptor is less sensitive to several factors (such as heat and ionic strength) that may affect its binding capability. Although neither LBA nor EIA measure the absolute receptor content, LBA is conventionally considered as the reference method in comparative studies so far performed.

In the case of ER, clinical studies showed an excellent correlation between LBA and EIA. The slope values of the regression analysis showed that ER concentrations measured by EIA were slightly higher than those found with LBA using the Scatchard plot. The discrepancy was more evident when LBA was carried out using the SSD [14, 19, 20]; this could have been expected considering that the SSD gives lower ER results than the Scatchard method which measure the receptor's concentration at theoretically infinite ligand dose. In the case of PR, available clinical studies are less extensive and still conflicting.

In the present multicentric study, we chose to compare EIA with the SSD method rather than with the Scatchard analysis because the SSD assay is comparable to EIA from the technical point of view. Scatchard analysis is cumbersome and cannot be performed when only small tissue samples are available, as frequently occurs in clinical practice. Data obtained by Scatchard and SSD are comparable, although SSD tends to underestimate the receptor content [28]. This behaviour may be critical in the low receptor dose range and could at least in part justify the discrepancies between the present investigation and other studies in which EIA and LBA gave similar results when using the Scatchard analysis. Nevertheless, the results of the present investigation confirm the highly significant correlation between EIA and LBA for both ER and PR. The slope values of the regression curve were comparable with those reported by other studies in which the SSD had been used [14, 19, 20].

In the case of PR no clearcut conclusions can be drawn with analysis from different centres showing different patterns. This could be due at least in part to the fact that PR LBA assay is less

reproducible than ER LBA, as has been demonstrated by interlaboratory quality assurance programmes [2, 4–8].

Another possible interpretation could be related to a possible batch to batch variability of the PR EIA kit, as has been suggested by Raam *et al.*, who showed significant differences of EIA/LBA concordance rate among different kits [29].

In the case of ER the differences between EIA and SSD were similar in all centres, with EIA values higher than SSD. This pattern was seen in both premenopausal and postmenopausal patients. However, both slope values, the EIA/SSD ratio and the number of SSD−EIA+ ER cases were higher in premenopausal than in postmenopausal patients. These findings are in agreement with those of Mobbs [18], but conflict in part with those of other groups. Goussard *et al.* did not find differences between EIA and SSD in 56 postmenopausal patients [20]. Leclercq *et al.* reported no differences in the slope values between premenopausal and postmenopausal cases [21]. The statistical analysis used in the latter investigation was, however, different and not comparable with the method used in the present study.

When evaluating SSD/EIA correlation in different dose ranges the tendency of EIA to measure higher ER concentration than SSD was always demonstrated. This, in part, conflicts with the results of Thorpe who found higher ER levels with EIA than with LBA in the low–intermediate ER dose range, but demonstrated an opposite trend (higher ER levels with LBA than with EIA) in the high ER level range [11]. Considering the arbitrarity of the choice of positive/negative cut-off point, several cut-off levels were used to categorise tissue samples.

The rate of SSD−EIA+ cases was high with all the cut-off points evaluated. SSD−EIA+ rate was higher in premenopausal than in postmenopausal cases. The reason why EIA measures higher ER levels than SSD is still under debate. The possibility that EIA methods measure inactive fragments of the receptor protein, which was suggested by Pousette *et al.* [22], has been more recently disputed by Senekjian *et al.* [30]. A second possible interpretation is that ER saturated by endogenous oestrogens is detectable by EIA but not by LBA. This interpretation is supported by several findings: lower EIA/LBA ratios were found in postmenopausal than in premenopausal patients in whom higher oestrogen levels are present; a reduction of the number of LBA−EIA+ cases was obtained using an exchange technique for LBA [17]; and PR levels and positivity rates in SSD−EIA+ ER cases were similar to those found in SSD+EIA+ ER cases (the function of the immunologically detected ER is, at least in part, conserved), as was shown in the present study. These findings are in agreement with those of Thorpe, who found that EIA+LBA− tumour expressed PR and/or nuclear ER in 10 out of 12 cases [11]. In contrast, the findings of several groups which demonstrated that ER levels assayed by LBAs are not significantly affected by endogenous oestrogens weigh against the latter interpretation [31–33].

Whatever the reason, ER concentration and positivity rates, using several +/− cut-off points, tend to be higher when using EIA methods. Considering that the rate of ER+ cases not responsive to endocrine manipulations is more or less 30% using LBA methods, the use of EIA methods could further increase this figure, increasing as well the difficulty in the choice of patients to submit for endocrine therapy. Similar problems will probably be found when assessing the prognostic role of ER measured by EIA.

The substitution of SSD with EIA should therefore not be recommended for routine use until prospective clinical studies in which ER and PR are assayed with both SSD and EIA assess the most reliable cut-off points for hormone responsivity and prognosis.

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Mechlorethamine, Vinblastine, Procarbazine and Prednisolone (MVPP) for Advanced Hodgkin's Disease

Margaret J. Harding, Laura J. McNulty, Jim Paul, Fred Lee, Alec Brown and Michael Soukop

Between January 1972 and October 1985, 60 patients with advanced Hodgkin's disease were treated with mechlorethamine/vinblastine/procarbazine/prednisolone (MVPP). The complete remission (CR) rate was 50%; the introduction of computed tomography in 1980 reduced the proportion of CR from 62% to 30% ($P = 0.017$) as a consequence of residual mediastinal abnormality of uncertain significance. With a median follow-up of 9 years, actuarial 5 and 10-year overall survival was 70% and 57%, respectively, with 79% and 65% free from Hodgkin's disease. Only age and pathological subtype influenced survival sufficiently to be of prognostic significance, though the effect of serum albumin, ECOG performance status and B symptoms on Hodgkin's disease mortality may have been clinically important.
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INTRODUCTION

THE ADVENT of combination chemotherapy in the 1960s radically altered the prognosis of patients with advanced Hodgkin's disease [1]. Previously single agents had yielded at best a 5% 5-year survival [2], whereas the mechlorethamine/vincristine/procarbazine/prednisone (MOPP) regimen pioneered by de Vita has resulted in 10-year overall and disease-free survivals of 50% and 60%, respectively [3].

A British modification of the MOPP combination substituted vinblastine for vincristine to reduce the neurotoxicity [4]. The resulting MOPP regimen was adopted by several UK centres as standard treatment for Hodgkin's disease. We here report the mature data with MVPP from Glasgow Royal Infirmary.

PATIENTS AND METHODS

Between January 1972 and October 1985, 53 consecutive patients with advanced or bulky Hodgkin's disease and 7 with