Case	Gestational age (weeks)*	Reason for screen	Duration of rupture of membranes (h)	Vaginal swab	Chest radiograph	C-reactive protein (mg/L)†	Platelet count ($\times10^9$/L)‡	White blood cell count§ (absolute neutrophil count [$\times10^9$/L]¶)
1	28	Premature, severe respiratory distress syndrome	39	Positive	Respiratory distress syndrome	96	208	16·5 (2·1)
2	31	Premature, respiratory distress, prolonged rupture of membranes	56	Positive	Normal	124	137	13·6 (4·8)
3	32	Premature, prolonged rupture of membranes	69	Positive	Respiratory distress syndrome	50	72	6·2 (0·4)
4	37	Respiratory distress	32	Positive	Pneumonia	<4	205	4·2 (1·5)
5	40	Respiratory distress	10	Positive	Pneumonia	26	257	23·1 (8·3)
6	40	Respiratory distress, prolonged rupture of membranes	72	Positive	Pneumonia	198	135	6·3 (0·1)
7	40	Respiratory distress	15	Negative	Normal	80	141	3·9 (3·0)
8	41	Respiratory distress, poor condition at birth	7	Negative	Normal	112	149	18·5 (7·1)
9	41	Meconium aspiration, persistent pulmonary hypertension	11	Positive	Pneumonia	131	213	12·8 (1·9)

Deep-ear swab was positive for group B streptococci for all infants. Median values *37 weeks, †96 mg/L, ‡141×10⁹/L, §6·3×10⁹/L, ¶1·9×10⁹/L.

Table 2: **Babies with probable group B streptococcal infection**

of respiratory signs (table 2). This pattern could simply be related to duration of group B streptococcal infection before presentation of the baby with symptoms and measurement of C-reactive protein. The differences could also be associated with cytokine promoter polymorphisms of C-reactive protein-inducing cytokines, such as interleukin 6. A disproportionate number of babies with infection were black, of African or Caribbean ethnic origin: seven infected babies were born to 1940 white mothers, a rate of 3·6 per 1000, and six to 682 black mothers, a rate of 8·8 per 1000 livebirths.

We might have inadvertently included babies whose features of clinical sepsis were caused by organisms other than group B streptococcus, which are unidentifiable with conventional culture techniques. However, probable EOGBS sepsis was more likely underestimated than overestimated, since we strictly excluded stillbirths and cases treated for infection in the maternity unit but from whom a deep-ear swab had not been obtained.

The results of this prospective study confirm our previous finding[5] that relying on blood or cerebrospinal cultures alone to assess the incidence of EOGBS sepsis results in underestimation of the true burden of this disease in neonates. Our data suggest that UK regional variations in prevalence[2] could be related in part to the ethnic origin of the population.

The outcome of UK health economic analyses needs to be known before prevention policies for EOGBS are available in this country, and cases of probable sepsis should be included in such an analysis. We suggest that in the meantime there should be active surveillance of both definite and probable EOGBS infection in every maternity unit, to plan and implement appropriate local prevention guidelines.

Contributors

All authors contributed to data collection and drafting of this letter. A Bedford Russell, P Heath, A Breathnach, M Torry , and K d'Ageyepeff designed the protocol, and A Bedford Russell coordinated the study. M Torry, K d'Ageyepeff, S Luck, and A Pitt collected date, and P Heath did the statistical analysis. S Luck, A Bedford Russell, P Heath, A Breathnach, M Torry, K d'Ageyepeff, and A Pitt wrote and edited the report.

Conflict of interest statement

P Heath is a member of the Public Health Laboratory Service group B streptococcal working group.

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Gynaecomastia in men with chronic myeloid leukaemia after imatinib

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cKit and platelet-derived growth-factor receptor (PDGFR) are receptor tyrosine kinases expressed in the testis, are involved in testosterone production, and are inhibited by imatinib. We measured hormone concentrations in 38 men receiving imatinib for chronic myeloid leukaemia at baseline and during treatment. Mean follow-up was 23·6 months (SD 7·5). We noted seven cases of gynaecomastia (18%, 95% CI 6–30%). A comparison of hormone concentrations in 21 patients before and during treatment showed that patients who developed gynaecomastia had a reduction in free testosterone concentrations of 29·53 pmol/L (95% CI 11·63–47·43), while patients who did not had a decrease of 6·36 pmol/L (–1·02 to 13·74). In most men with chronic myeloid leukaemia studied here, imatinib was associated with a reduction in the production of testicular hormones and in some, with the development of gynaecomastia.

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Imatinib is a signal transduction inhibitor; it inhibits the oncogenic tyrosine kinase BCR-ABL, cKit, and

platelet-derived growth factor receptor (PDGFR), both members of the receptor tyrosine kinase subclass 3 family.[1] Imatinib is effective against BCR-ABL leukaemias, especially those in patients with chronic myeloid leukaemia in the late chronic phase,[2] and the drug has been approved for treatment of this disease.

The toxicological profile of imatinib is still under investigation. Common and usually mild side-effects include oedema, muscle cramps, skin rash, and conjunctival inflammation.[2] Several cases of gynaecomastia in patients with chronic myeloid leukaemia treated with imatinib prompted us to investigate the hormonal profile in these patients.

We assessed hormone concentrations in 38 consecutive male patients with chronic myeloid leukaemia who were enrolled in trials of imatinib. Median age was 50 years (range 28–84 years). 28 patients were in chronic phase (resistant to interferon alfa), eight were in accelerated phase, and two in blast crisis. Imatinib dosage was 400 mg daily in 16 patients and 600–800 mg in 22. Treatment duration ranged from 6 to 31 months (median 25·5 months). Original study protocols were approved by the local ethics committee.

We assayed follicle-stimulating hormone (FSH), luteinising hormone, β human chorionic gonadotropin (βHCG), 17-β-oestradiol, progesterone, and dehydroepiandrosterone sulphate (DHEAS) using chemiluminescence and 17-hydroxyprogesterone, free testosterone, androstenedione, prolactin, and testosterone were assayed with radioimmunoassay.

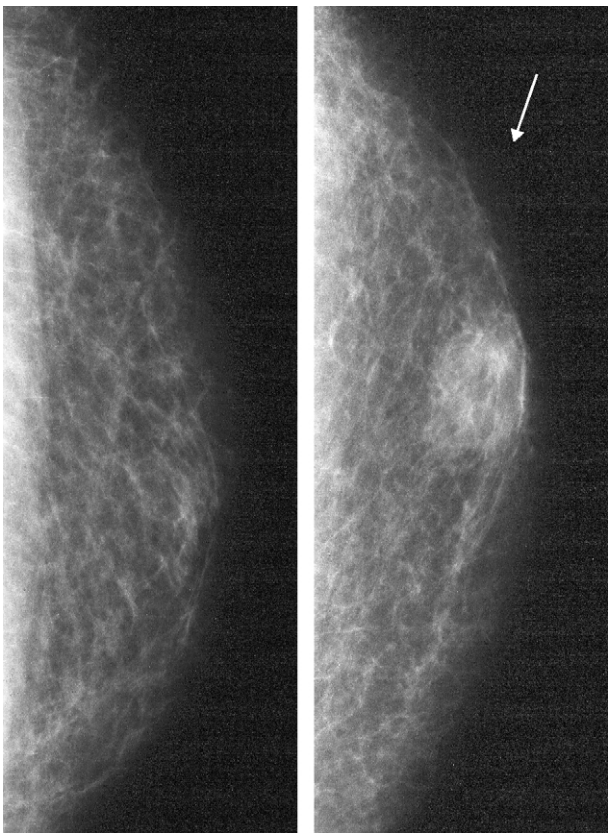
We examined patients for gynaecomastia at scheduled visits (ie, every week in the first month of follow-up; monthly for months 2–12; and then every 3 months, or when clinically indicated). We graded gynaecomastia as grade 1 (2–4 cm enlargement from the nipple) or grade 2 (>4 cm enlargement, or monolateral).

We used Mann-Whitney *U* test, Fisher's test, and multivariate log linear models for statistical analysis. In 38 patients, we noted seven cases of gynaecomastia (one grade 1 and six grade 2) (18%, 95% CI 6–30%). Gynaecomastia, which is often preceded by discomfort and pain in the nipple area, developed after 5–13 months of treatment. The figure shows an example of unilateral gynaecomastia.

There was no difference in the mean age of patients who had gynaecomastia and those without the disorder (57 years [SD 16·7] *vs* 50 years [13·6], respectively; p=0·2). During follow-up, about a quarter of patients reported a decrease in sexual activity, which was in some cases associated with gynaecomastia. Because we did not record sexual function before treatment, the effect of imatinib on sexual function cannot be conclusively investigated and will require further prospective studies.

During treatment (month 5–16), 35 patients (92%) had abnormally low serum concentrations of testosterone and 28 (73%) had low free testosterone. 19 (49%) had high progesterone, and 16 (42%) had raised serum 17-hydroxyprogesterone.

We retrospectively compared pretreatment hormone concentrations with those during treatment (obtained at months 6–14) in 21 patients for whom pretreatment samples were available (table). We considered free testosterone concentrations for the following reasons: (1) a decrease in this hormone can cause gynaecomastia; and (2) concentrations of free testosterone are not affected by those of sex hormone binding globulin in serum. The mean reduction in free testosterone during treatment was 29·53 pmol/L (95% CI 11·63–47·73) in patients who developed gynaecomastia and 6·36 pmol/L (–1·02 to 13·74) in patients who did not (p=0·018). Analysis of samples taken in months 15–25 showed the same pattern of hormone concentrations. None of the patients was taking drugs that might have caused gynaecomastia.



Mammography of patient 5

The image was taken at month 14 of treatment, 2 months after clinical detection of unilateral gynaecomastia. Arrow shows fibroglandular enlargement in the right mammary gland.

We did a prospective analysis in six patients at months 1, 2, 3, and 6 of treatment. Data for concentrations of testosterone, free testosterone, progesterone, 17-hydroxyprogesterone confirm the overall trend noted in other patients, and show that the hormonal changes became evident 60–90 days after the start of treatment with imatinib.

The presence of gynaecomastia was associated with hormonal abnormalities (combined low testosterone and high progesterone values; p=0·0045). Results of a multivariate loglinear model also showed a significant correlation between treatment dose (400 mg *vs* >600–800 mg) and hormonal abnormalities (p=0·0340), suggesting that treatment is a factor in the development of gynaecomastia, possibly through hormonal mechanisms.

Our results can be explained by the different ability of normal cells to compensate for the pathways affected by imatinib, in accordance with their genetic background and other variables, such as co-morbid conditions. Patients in this study had fairly advanced disease, we did not include people who were treated at diagnosis, and we did not investigate the effects of imatinib on fertility. What are the mechanisms for the effects of imatinib on frequency of gynaecomastia? The disorder is probably caused by a reduction of testosterone

	Age	Imatinib dose (mg/day)	Detection of gynaecomastia (months of treatment)	Testosterone (nmol/L)*		Free testosterone (pmol/L)†		Progesterone (nmol/L)‡		17-hydroxyprogesterone (nmol/L)§	
				Before treatment	During treatment	Before treatment	During treatment	Before treatment	During treatment	Before treatment	During treatment
Gynaecomastia											
1	60	600–800	13	15·75	2·88	30·64	11·69	7·06	10·49	4·48	NA
2	41	600–800	5	15·75	10·1	58·99	28·8	2·16	4·77	5·17	20·06
3	39	600–800	12	11·03	7·74	54·69	13·19	2·89	6·04	10·29	22·85
4	45	600–800	8	7·53	6·38	41·99	16·31	0·64	3·5	3·99	19·94
5	71	600–800	12	11·76	7·01	59·68	25·33	1·14	3·82	4·3	15·01
6	60	600–800	13	15·48	10·24	96·81	37·48	2·64	3·82	4·12	24·42
7	84	400	11	1·21	2·29	4·62	7·98	2·73	2·26	1·15	19·06
No gynaecomastia											
12	72	400	..	7·36	3·71	23·25	22·56	1·24	2·58	NA	NA
23	56	400	..	7·98	5·86	32·34	40·95	2·13	1·27	5·99	15·04
24	64	400	..	14·02	14·4	54·31	74·26	2·32	2·73	6·45	12·5
25	59	400	..	11·9	10·24	42·75	31·23	1·43	4·13	4·09	15·95
27	51	400	..	9·99	6·84	43·9	36·44	1·69	3·75	3·84	16·46
28	32	400	..	9·06	9·61	37·34	38·52	1·97	2·61	7·75	8·59
29	36	400	..	9·85	4·37	51·98	38·52	0·86	1·81	2·24	14·22
30	50	600–800	..	11·24	14·19	48·23	49·27	1·84	2·1	4·18	15·43
31	67	600–800	..	12·53	9·89	68·53	36·09	2·13	2·32	4·09	12·95
32	42	400	..	8·19	10·24	31·2	27·07	1·72	0·92	4·33	6·05
33	57	400	..	12·39	9·72	55·17	37·48	2·26	2·8	7·81	11·11
34	45	600–800	..	13·39	10·48	32·62	28·8	0·64	3·66	NA	NA
35	68	600–800	..	15·89	9·96	61·42	38·52	1·65	2·67	4·42	13·68
36	34	600–800	..	9·02	7·7	28·49	30·19	2·42	2·48	4·72	7·63

NA=not assessed. *Normal value 10–31 nmol/L. †Normal value 29–190 pmol/L. ‡Normal value 0·318–3·180 nmol/L. §Normal value 1·5–10·6 nmol/L.

Patients' hormone concentrations before and during treatment with imatinib

and free testosterone. The rise of progesterone and 17-hydroxyprogesterone are not of clinical relevance, but they might contribute to the understanding of gynaecomastia in our patients, and could represent the accumulation of testosterone precursors as a consequence of impairment of key enzymes in the steroidogenic cascade (ie, 17,20 Lyase (Cyp17) or 17 ketosteroid reductase). cKIT and PDGF receptors, as well as their respective ligands, are expressed in the testis where, through complex interactions between germ cells, Sertoli cells, and Leydig cells, they stimulate testosterone secretion by Leydig cells, in a pathway complementary to that for luteinising hormone.[3,4] In fact, an effect of stem-cell factor on the cellular concentrations of two enzymes that have a role in sexual hormones biosynthesis (Cyp17 and 3′-β-hydroxysteroid dehydrogenase) and a trophic effect of PDGF on Leydig cells have been shown.[4,5]

Gynaecomastia can develop after long term imatinib use and is probably because of the reduction of testosterone production through the block of PDGFR and cKit in the testis. These data will contribute to a better understanding of the mechanism of action of imatinib and of its safety profile. Future ABL inhibitors with higher specificity will further improve the treatment profile of this class of drugs and will hopefully provide an even better treatment for patients with chronic myeloid leukaemia.

Contributors

L Tornaghi did patient follow-up and data collection and analysis. N Cambiaghi did hormonal assays. P Rossi, F Cavagnini, and F Pecori-Giraldi acted as endocrinological consultants. C Gambacorti-Passerini coordinated the study and E Pogliani and G Corneo helped in the study coordination. L Mariani gave statistical advice. L Gnessi was instrumental in the analysis, presentation, and discussion of these data.

Conflict of interest statement

C Gambacorti-Passerini, E Pogliani, and G Corneo are coinvestigators in three trials of imatinib that are sponsored by Novartis.

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