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Adjuvant tyrosine kinase inhibitor therapy improves outcome for children and adolescents with acute lymphoblastic leukaemia who have an ABL-class fusion

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Abstract

Patients with an ABL-class fusion have a high risk of relapse on standard chemotherapy but are sensitive to tyrosine kinase inhibitors (TKI). In UKALL2011, we screened patients with post-induction MRD ≥1% and positive patients (12%) received adjuvant TKI. As the intervention started during UKALL2011, not all eligible patients were screened prospectively. Retrospective screening of eligible patients allowed the outcome of equivalent ABL-class patients who did and did not receive a TKI in first remission to be compared. ABL-class patients who received a TKI in first remission had a reduced risk of relapse/refractory disease: 0% vs. 63% at four years (P = 0.009).

Keywords: paediatric acute lymphoblastic leukaemia, ABL-class fusion, tyrosine kinase inhibitor, targeted therapy, prognostic factors.
Patients with acute lymphoblastic leukaemia (ALL) who have a BCR-ABL1-like or Philadelphia chromosome(Ph)-like gene expression profile have a poor outcome.1,2 ABL-class gene fusions are a network of chimaeric gene fusions whose functional consequence results in constitutive activation of the ABL pathway; mimicking BCR-ABL1 fusion.2 A subset of patients with BCR-ABL1-like ALL harbour an ABL-class fusion defined as a fusion between ABL1, ABL2, PDGFRB/A or CSF1R and a variable partner gene. Patients harbouring ABL-class fusions have high levels of minimal residual disease (MRD) at the end of induction (EOI) and a high risk of relapse.3,4 There is experimental and pre-clinical evidence that ABL-class fusions are sensitive to treatment with tyrosine kinase inhibitors (TKI).5 In addition, case reports and case series demonstrate good clinical responses to treatment with a TKI.5,6 However, these fusions are rare and only one study has compared the outcome of ABL-class fusion patients treated with and without adjuvant TKI therapy.7

Patients with refractory disease on the UKALL2003 trial harboured a high frequency of ABL-class fusions (10%), and specifically EBF1-PDGFGRB patients had high levels of EOI MRD and a high rate of relapse.3,8 Hence, in the UKALL2011 trial, we screened patients who responded slowly to induction therapy for the presence of ABL-class fusions and, where positive, supplemented their therapy with imatinib. Here, we describe the total cohort and compare the outcome of those patients who received adjuvant TKI therapy in first remission with those patients who did not receive TKI in first remission, because they were diagnosed before the intervention was established.

Methods

Patients were enrolled and consented onto the UKALL2011 trial (ISRCTN number 64515327) and were diagnosed with ALL using standard morphological and immunophenotypic criteria. MRD was evaluated by PCR analysis of Ig/TCR rearrangements.9 B-cell precursor and T-cell patients were eligible for ABL-class fusion screening if they had a MRD level ≥1%, induction failure or M2/M3 marrow at the EOI and did not harbour another class-defining chromosomal abnormality. ABL-class screening was performed using commercially available FISH probes for BCR-ABL1, ABL1, ABL2 or PDGFRB/CSF1R, either centrally by the Leukaemia Research Cytogenetics Group (LRCG) or at regional NHS genetic laboratories. FIP1L1-PDGFRA fusion was identified by SNP array analysis (Illumina 850k SNP array) and AGGF1-PDGFRB by RNA fusion panel (Illumina TruSight) standard survival endpoints and statistical analysis were performed.9
Results and discussion

Among 191 patients who had a slow response to induction therapy, 43 patients were not tested due to their background cytogenetics: high hyperdiploidy \( (n = 28), \) ETV6-RUNXI \( (n = 8), \) KMT2A rearrangement \( (n = 5), \) t(1;19)(q23;p13) \( (n = 1) \) and iAMP21 \( (n = 1). \) A further 22 cases could not be screened due to lack of material. Among 126 patients tested, 21 \((17\%)\) harboured an ABL-class fusion. The frequency of ABL-class fusions among all B-cell precursor and T-cell ALL patients with a slow response to induction therapy was 16/122 \((13\%)\) and 5/47 \((11\%)\), respectively; in line with previous reports linking ABL-class fusions with high MRD.\(^7,^8\)

The 21 ABL-class fusion patients had a median age of nine years, comprised 15 males and six females and had a median white cell count at diagnosis, of \(35 \times 10^9/\text{l}\) (Table I). By definition, all patients had a high EOI MRD, but the mean level of 32\% was considerably higher than the entry level of 32\%. The partner gene was FIP1L1- PDGFRA in nine cases in the TKI group compared to 2/8 \((25\%)\) in the control group \((P = 0.2).\) As the intervention started, received standard post-induction therapy without a TKI (control group). There were no differences between the TKI and control groups with regard to age, sex, white cell count or EOI MRD (Table I). In particular, the mean EOI MRD was 39\% and 24\% in the TKI and control groups, respectively, \((P = 0.001);\) in keeping with previous observations.\(^3,^6\) The partner gene was determined in six patients (Table I). All EBF1-PDGFRB patients had BCP-ALL, whereas the other fusions were split between BCP-ALL and T-ALL. NUP214-ABL1 fusion in T-ALL is well documented, and rare cases of FIP1L1-PDGFR, ETV6-ABL2 and other PDGFRB fusions have been reported.\(^10–^12\)

Thirteen cases identified prospectively were treated with imatinib in first remission (TKI group). The remaining eight cases, identified retrospectively and diagnosed before the intervention started, received standard post-induction therapy without a TKI (control group). There were no differences between the TKI and control groups with regard to age, sex, white cell count or EOI MRD (Table I). In particular, the mean EOI MRD was 39\% and 24\% in the TKI and control groups, respectively, \((P = 0.3).\) Notably, 8/13 \((62\%)\) cases in the TKI group had EBF1-PDGFRB compared to 2/8 \((25\%)\) in the control group \((P = 0.2).\) As the intervention was initiated after the start of the trial, 9/13 patients in the TKI group were diagnosed after 2016, compared to 0/8 in the control group.

Although the TKI patients followed the UKALL2011 protocol, they were treated off-trial, as supplementing therapy with imatinib was not part of the protocol therapy. Patients started on imatinib in first remission with a median start time of 46 days from initial diagnosis \((range~22–116).\) Patient 10 started TKI before EOI \((day~22)\) because FIP1L1-PDGFR fusion was detected serendipitously by SNP array during routine genetic analysis. Patient 13 was not tested until week 14, but started TKI within six days of detection of the fusion. Initially, all patients in the TKI group received imatinib at a daily dose of 300–400 mg/m\(^2,\) with two patients switching to dasatinib (Table I). None of the patients received TKI as a single agent and post-induction chemotherapy was administered at the discretion of the treating clinician (Table I).

Among eight patients in the control group, six remained on trial receiving regimen C, while two patients were taken off trial and received regimen C plus additional chemotherapy (Table I). Nine of 13 \((69\%)\) patients in the TKI group had a bone marrow transplant in first remission, compared with 3/8 \((38\%)\) in the control group \((P = 0.2).\)

During the follow-up period \((median~3–9\ years),\) 0/13 patients in the TKI group suffered a leukaemia-related event, whereas among 6/8 patients in the control group relapsed or died of primary refractory disease (Fig 1). The four-year relapse/refractory rate for the TKI and control groups was 0\% and 62.5\% \((95\%~CI~33–91\%);\) respectively, \((log~rank\ P = 0.009).\) The equivalent EFS and OS rates were 83\% \((94–96\%)\) vs. 37.5\% \((9–67\%);\) \(P = 0.07\) and 83.9\% \((49–96\%);\) vs. 75\% \((31–93\%);\) \(P = 0.4),\) respectively. Three of the five patients in the control group who relapsed were treated with TKI post-relapse but two patients subsequently died of respiratory/multi-organ failure. Two patients in the TKI group died due to transplant complications. Overall, 2/13 \((15\%)\) patients in the TKI group died compared with 4/8 \((50\%)\) in the control group. Eight of 20 \((40\%)\) patients suffered one or more grade 3/4 toxicities which, although higher, is comparable to patients receiving similar high-dose chemotherapy on UKALL2003.\(^13\) Only two toxicities, one in the TKI group and one post-relapse in the control group, were likely to be associated with the TKI treatment (Table I).

Ad hoc case reports of patients with refractory disease and an ABL-class fusion responding to TKI treatment initially highlighted the potential benefit of precision medicine for these patients.\(^2,^14,^15\) Two studies have recently examined the efficacy of frontline TKI therapy in small cohorts.\(^6,^7\) The French study showed that ABL-class patients receiving adjuvant TKI therapy had a better than expected outcome compared with historical cohorts.\(^6\) However, their study comprised children and adults, delivered a mix of TKI drugs and did not have a contemporary cohort for comparison. In contrast, the AIEOP-BFM study compared ABL-class fusion patients registered on a trial according to whether they receive a TKI in conjunction with chemotherapy.\(^7\) They did not observe a survival advantage for patients receiving TKI therapy but their groups were not comparable. The screening and intervention policy they employed was based on institutional preference resulting in the TKI-treated cohort being more likely to be assigned to the high-risk treatment group, compared with the non-TKI cohort. In addition, the start time of TKI therapy ranged from post-induction to post-consolidation and, in one instance, to post-transplant. Evidence from BCR-ABL1 positive ALL shows that early administration of TKI therapy is beneficial.\(^16\)

The scarcity of these patients and the strong biological rationale for treating them with targeted therapy makes a randomised clinical trial very unlikely. Hence, evidence for the efficacy of TKI therapy in this subtype of ALL is likely to...
## Table I. Demographic, clinical, treatment and outcome details of 21 patients with ALL and an ABL-class fusion treated with or without a tyrosine kinase inhibitor in first remission

| Patient Group | Sex | Age at diagnosis | Immunophenotype | ABL-class fusion | Induction therapy (%) | Time started TKI | TKI dose and schedule | MRD @ EOI (%) | Time started TKI | TKI dose and schedule | MRD @ Week 9 (day) | MRD @ Week 14 (day) | Off-therapy (if yes, when) | Post-induction therapy | Transplant | Grade 3/4 Toxicity | If yes, related to TKI? With details | Relapse (yes/no) | Dead (yes/no) | Survival (months) |
|---------------|-----|-----------------|-----------------|-----------------|----------------------|------------------|----------------------|---------------|------------------|----------------------|-----------------------|-----------------------|------------------------|------------------------|------------|-----------------|----------------------------------|-----------------|--------------|------------------|
| Early TKI     | Female 5 | 16-40 B-cell precursor EBFI1-PDGFRB | B | 50% | day 32 | Imatinib (300 mg/day) until SCT (49 m). | 6% | 0%29 | Induction Regimen B plus NOPHO High-risk blocks | Yes | Yes | No | No | Yes, post-transplant encephalopathy | 12 9 |
| Early TKI     | Female 8 | 39-00 B-cell precursor EBFI1-PDGFRB | B | 30% | day 38 | Imatinib (300 mg/day) for 27 m. | 0%4 | 0% (day 118) | Induction Regimen C | No | Yes | No | No | No | 57 3 |
| Early TKI     | Male 12 | 34-00 T cell NUP214- ABL1 | B | 30% | day 75 | Imatinib (330 mg/day) for 27 m and then dasatinib (70 mg/day) for 3.9 m. | 20% | 2% (day 125) | Induction Regimen C, Nelarabine, FLAD, FLA, Bortezomib | Yes | Yes | No | No | No | 47 3 |
| Early TKI     | Male 17 | 4-30 B-cell precursor EBFI1-PDGFRB | B | 50% | day 52 | Imatinib (600 mg/day) for 3 weeks. | 50% | 0%05 | Induction Regimen C, FLA-Ida, FLA | Yes | No | - | No | No | 49 9 |
| Early TKI     | Male 18 | 36-90 B-cell precursor ZC3HAV1- ABL2 | B | 20% | day 49 | Imatinib (400 mg/day) for 4 weeks, dasatinib (140 mg/ day) for 4 weeks, then post-SCT imatinib (100- >600 mg/day) 3.5 years and ongoing. | 0% | 0% | Induction Regimen C, FLA-Ida, Nelarabineb | Yes | Yes | Yes, Stevens-Johnson Syndrome while on dasatinib (grade 4) | No | No | No | 46 8 |
| Early TKI     | Male 9 | 26-00 B-cell precursor EBFI1-PDGFRB | A | 90% | day 37 | Imatinib (300 mg/day) for 3 years and ongoing. | 0.0100% | 0.002 | Induction Regimen C | No | No | - | No | No | 43 7 |
| Early TKI     | Male 9 | 2-00 B-cell precursor EBFI1-PDGFRB | A | 50% | day 42 | Imatinib (400 mg/day) until week 16 and then switched to dasatinib (80 mg/day). | 0% | 0% | Induction Regimen C plus NOPHO High-risk blocks | Yes | Unknown | - | No | Yes, infection post-SCT | 18 8 |
| Early TKI     | Female 9 | 34-00 T cell ETV6- ABL2 | B | 1% | day 78 | Imatinib (400 mg/day) for 33 m and ongoing. | 5% | 0%6 | Consoliation Regimen C, NECTAR | No | No | - | No | No | 33 6 |
| Early TKI     | Male 17 | 28-00 B-cell precursor EBFI1-PDGFRB | B | 9% | day 40 | Imatinib (400 mg/day) for 3.4 m until SCT. Restarted (200 mg/day) 9 m post-SCT for 1 year and ongoing. | 0% | 0% | Consoliation Regimen C | No | No | - | No | No | 31m5 3 |
| Early TKI     | Male 15 | 32-00 T cell PIP/JL1-PDGFRB | B | 4% | day 22 | Imatinib (500 mg/day) for 7.1 m until SCT, restarted at same dose 7 m post-SCT for 1 year. | 2% | 0% | Induction Regimen C plus NOPHO High-risk blocks | Yes | No | - | No | No | 35 9 |

Short Report

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### Table I. (Continued)

| Patient Group | Sex | Age at diagnosis | WCC | Immuneophenotype | ABL-class fusion | MRD Induction @ IOI (%) | Time started TKI | TKI dose and schedule | MRD @ Week 9 (day) | MRD @ Week 14 (day) | Off-trial therapy | Post-induction therapy | Transplant | Grade 3/4 Toxicity | If yes, related to TKI? | With details | Relapse (yes/no) | Dead (yes/no) | Survival (months) |
|---------------|-----|------------------|-----|------------------|------------------|------------------------|------------------|------------------------|-------------------|-------------------|-----------------|------------------------|------------|----------------|----------------|----------------|----------------|----------------|------------------|
| 11 Early TKI  | Male| 5                | 2900 | B-cell precursor | BCR-ABL1         | 90%                    | Week 5           | Imatinib for 5 m until SCT (6 m). | 60% (day 9)      | 0.4% (day 108)   | Induction        | Regimen C, NPHO, High-risk blocks | Yes         | No             | -              | No             | No            | No             | 21.7             |
| 12 Early TKI  | Male| 5                | 12700| B-cell precursor | ABL1            | 10%                    | day 43           | Imatinib (300 mg/day) until SCT (73 m). | 0.2% (day 13)   | 0.07% (day 108) | Induction        | Regimen C, Blinatumomab CAR-T          | Yes         | Yes            | No             | No             | No            | No             | 20.3             |
| 13 Early TKI  | Male| 10               | 3600 | B-cell precursor | BCR-ABL1         | 70.00%                 | day 136*         | Imatinib (320 mg/day) for 4 weeks until CAR-T. | 70% (day 108)   | 23% (day 108)   | Consolidation    | Regimen C, Blinatumomab CAR-T          | No          | No             | -              | No             | No            | No             | 13.4             |
| 14 Control    | Male| 8                | 3180 | B-cell precursor | BCR-ABL1         | 50%                    | Post-relapse     | Imatinib | n/d             | 0.07%            | On-trial Regimen C | Yes             | Yes            | No             | Isolated BM (6 m) | Respiratory failure post-transplant | 70.3       |
| 15 Control    | Female| 1           | 3500 | B-cell precursor | PDGFRB/CSF1R rearrangement | 20% | Not received | n/a | 0.5%          | 0%               | On-trial Regimen C | No             | No             | -              | No             | No            | 72.5             |
| 16 Control    | Female| 18            | 9200 | B-cell precursor | BCR-ABL1         | 50%                    | Post-relapse     | Imatinib (400 mg) for 19 m until SCT and then same dose post-SCT for 2 m and ongoing. | n/d             | 0.60%            | On-trial Regimen C | Yes             | Yes            | No             | Marrow & CNS (41 m) | No             | 74.9             |
| 17 Control    | Male| 2               | 46900| T-cell          | PDGFRB/CSF1R rearrangement | 10% | Not received | n/a | 20%            | 10%              | Induction Regimen C, Nolabnine, AsK | Yes             | No             | -              | Marrow (62 m) | Yes, relapse | 6.5             |
| 18 Control    | Female| 12          | 2280 | B-cell precursor | RANBP2-AVL1      | 20%                    | Post-relapse     | Dasatinib (100 mg/day) for 2.2 m until death. | 4%              | 0%               | On-trial Regimen C | Yes             | Yes            | Yes, nausea and headaches | Marrow & CNS (47 m) | Multi-organ failure post-transplant | 50.9       |
| 19 Control    | Male| 3               | 3200 | B-cell precursor | PDGFRB/CSF1R rearrangement | 5% | Not received | n/a | 0.01%          | 0.01%             | On-trial Regimen C | No             | No             | -              | Isolated eye relapse (24 h) | No             | 57.6             |
| 20 Control    | Male| 14              | 430  | T-cell          | PDGFRB/CSF1R rearrangement | 7% | Not received | n/a | 0.009%        | 0.009%            | On-trial Regimen C | No             | No             | -              | No             | No            | 67.6             |
| 21 Control    | Male| 23              | 6240 | B-cell precursor | ABL2             | 30%                    | Not received | n/a | 50%            | 20%              | Induction Regimen C, FLAG-IDA | No             | No             | -              | Never remitted | Yes           | 3.5             |

*Late start was due to delay in detection but TKI started within six days of detecting fusion.
†MRD measured by flow cytometry.
Fig 1. (A) Swimmer plot illustrating the outcome of patients with an ABL-class fusion treated with and without adjuvant imatinib therapy in first remission; (B) Kaplan–Meier graph showing the relapse/refractory rate among ABL-class fusion patients treated with and without adjuvant imatinib therapy in first remission. Time to relapse was measured from diagnosis to relapse, censoring at time of death in remission. In this graph, patient 21, who did not achieve a complete, was counted as having an event on day 35; (C) Kaplan–Meier graph showing the event-free survival of patients in the TKI and control groups. [Colour figure can be viewed at wileyonline library.com]
be limited to retrospective studies such as this one and the other two discussed above.6,7 Even though our study was not a randomised clinical trial for TKI therapy, it has a number of advantages compared with previous studies. Most importantly, because our two treatment cohorts were due to a protocol change, they were comparable in terms of key risk factors and can be thought of as randomly chosen. However, it should be noted that all patients received additional and different high-dose chemotherapy and many patients were transplanted. Even though TKI therapy was administered according to the physicians’ choice, the patients received similar doses of imatinib and, crucially, started TKI early during treatment, mostly within a few weeks after induction. Our cohort was restricted to those patients with EOI MRD ≥1% but it is well established that the majority of ABL-class patients have a slow response to initial therapy.3,6,7

In conclusion, ABL-class fusions are frequent among BCP and T-ALL patients who respond slowly to induction therapy. We have demonstrated a reduced risk of relapse for ABL-class fusion patients with EOI MRD ≥1% treated with adjuvant TKI without a significant increased risk of severe toxicity. The ALLTogether 01 trial (EUDRACT number: 2018-001795-38) will screen patients at diagnosis for ABL-class fusions and add imatinib from day 15 (day 28 if aged ≥16 years) to a standard chemotherapy backbone to investigate whether early TKI reduces EOI MRD and improves outcome for all patients with an ABL-class fusion.

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Authorship contributions

Conception and Design: Anthony V Moorman, Christine J Harrison, John Moppett, Sujith Samarasinghe, Ajay Vora. Collection and assembly of laboratory and trial data: Claire Schwab, Emily Winterman, Jerry Hancock, Pam Kears, Amy A Kirkwood. Data analysis and interpretation: Anthony V Moorman, Claire Schwab, Ajay Vora. Financial and administrative support: Anthony V Moorman, Nick Goulden, Christine J Harrison, Pam Kears, John Moppett, Sujith Samarasinghe, Ajay Vora. Provision of patients and outcome data: Neha Bhatnagar, Anna Castleton, Michelle Cummins, Brenda Gibson, Donna Lancaster, Madhi Mabrouk, Andrew McMillan, Jayashree Motwani, Alice Norton, Aengus O’Marcaigh, Katharine Patrick, Armana Qureshi, Deborah Richardson, Simone Stockley, Gordon Taylor, Frederik van Delft, Ajay Vora. Manuscript writing: Anthony V Moorman. Final approval of manuscript: All authors.

Disclosure of Conflict of Interest

None.

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