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Equity of access to treatment on the Cancer Drugs Fund: A missed opportunity for cancer research?

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\textbf{ABSTRACT}

Using mixed-methods, we investigated the CDF in the South West of England (3193 cancer patients treated through the CDF, April 1st 2011–March 31st 2013) for evidence of: (1) equitable access across socioeconomic groups, age groups, sex, and Cancer Network; (2) time-to-treatment by socioeconomic group; and (3) the perception of the CDF as fair, using semi-structured interviews with oncology consultants.

There was no evidence of inequitable access to anti-cancer therapy for those in more deprived areas. For all cancer types, there was a lower proportion of women in the CDF cohort than in the Cancer Registry reference population (e.g., melanoma, CDF 36.8% female, reference population 48.7%; difference 11.9%, 95% CI 3.1–20.7%). There was a lower proportion of older patients in the CDF compared with the reference population (e.g., colorectal cancer, CDF 6.9% \(\geq 80\) years, reference population 30.1%; difference 23.2%, 95% CI 20.2–26.2%). Interviewed oncologists felt differences in performance status, not age, influenced referral to the CDF, with neither deprivation, nor gender contributing.

Our study suggests that the CDF has differential access by age and sex, but not by deprivation. The absence of high quality CDF data represents a missed opportunity to fully evaluate equity of access and the real-world costs and outcomes of novel anti-cancer drugs.

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1. Introduction

In 2011, the UK government introduced a £200 million Cancer Drugs Fund (CDF) to improve access to cancer drugs in England [1]. The CDF allowed access to: (a) drugs which were not recommended by the National Institute for Health and Care Excellence (NICE) because of poor or unproven cost-effectiveness; (b) drugs which had not yet been appraised by NICE; and (c) drugs used outside their marketing authorisation (off-label). In 2013, funding for the CDF was increased to £280 million annually and in 2014, a further budget increase (to £340 million) was coupled with the introduction of cost-effectiveness as a criteria for drug availability on the CDF. This was primarily due to a CDF overspend (£30.5 million in 2014) [2], but also reflects the rising number of high-cost cancer drugs, increasing cancer incidence [3], and the absence of a plan to disinvest from existing drugs to make way for new therapies. The opportunity cost of the CDF has been the subject of intense debate, for example, about whether the money could be better spent on other cancer treatment modalities and/or other diseases [4].

Inequity of access to anti-cancer therapy in the UK, prior to the CDF, has been demonstrated by: age [5,6]; deprivation [7–9]; place of residence [10]; hospital involvement with clinical trials [11], and hospital processes for facilitating best patient care (such as Multi-Disciplinary Team meetings) [12]. The intent of the CDF is to provide all patients with better access to “cancer drugs their doctors think will help them” [1]. However, there is no peer-reviewed evidence on whether the CDF has reduced or exacerbated inequalities in access to anti-cancer therapy. Using mixed-methods, we assessed the strengths and weaknesses of the CDF for research and investigated (1) whether access to the CDF during 2011–2013 was distributed equally across socioeconomic groups, age groups, sex, and Cancer Network; (2) whether time to treatment on the CDF varied by socioeconomic group; and (3) whether the CDF was perceived by oncologists as being fair.
2. Methods

2.1. CDF cohort

Anonymised patient-level CDF data for the period April 1st 2011–31st March 2013 for the south west (SW) region of England were obtained from NHS England South including age, sex, cancer type, cancer drug, general practitioner (GP) postcode, referring hospital trust, Cancer Network, CDF panel decision, treatment start, and end date and date of death. Cancer Networks (CN) were confederations of health organisations responsible for delivering the National Cancer Plan [13] in designated areas (now Strategic Clinical Networks (2013)) [14]. Data were not available after March 31st 2013 because regional CDF arrangements were transferred to a National Cohort List (a centrally agreed list of drugs available across England through the CDF). Out-of-region applications to the CDF (i.e., applications received in error and referred to another regional CDF) were excluded from the analysis, as were applications during the interim CDF period (October 1st 2010–March 31st 2011). Applications to the CDF which were not approved (3.0%) were not included in the analysis. Individuals who applied to the CDF more than once were identified by initials, GP postcode, diagnosis and age, and only the first application (93.8% of applications) was included in the analysis. Our primary analysis included SW patients resident in all six CNs (Avon Somerset and Wiltshire Cancer Services (ASWCS), Dorset, Peninsula, 3 Counties, Central South Coast, and Thames Valley) which were partially or wholly contained within the SW region. GP postcode data for all CDF participants (individual patient postcode data were not provided) were linked to lower super-output areas (LSOA) to obtain National Index of Multiple Deprivation (IMD 2010) quintiles [15]. Participants were grouped into nine diagnosis categories based on the cancer name recorded on the CDF application. International Classification of Diseases (ICD–10) diagnosis codes were very poorly recorded (49.0% missing or coded ‘N/A’) in the CDF. The diagnosis categories were: colorectal; prostate; breast; malignant melanoma; lung; gynaecological; upper gastro-intestinal; haematological; and other rare cancers. ‘Gynaecological cancer’ included uterine, ovarian and cervical; upper GI cancer included gastric, hepatic, pancreatic, and duodenal; and haematological cancer was made up of 84 different categories, including pre-cancerous conditions of myelofibrosis and amyloid. Other rare cancers were categorised based on being a member of the rare cancers list [16] and not being included in other named categories. Ethical approval was granted by the SW REC (REC reference 13/SW/0007 January 2013).

2.2. Cancer registry ‘reference’

We used cancer registry (CR) data to identify a comparative group of patients with advanced cancer in the SW region who were potentially eligible for CDF drugs (the ‘reference population’). The CR data, which includes information on cancer type, cancer stage, age, sex, and CN, were obtained from the public health England (PHE) Knowledge and Intelligence Team (SW). In our primary analysis of seven of the nine cancer types, CR patients were included in the reference population if they had the same cancer type, matched to the appropriate ICD-10 code, (Supplementary material) and were ‘advanced’ stage (IV). We selected only advanced stage tumors as this represents the subgroup of cancer patients most likely to be eligible for drugs prescribed on the CDF. In sensitivity analysis we expanded our inclusion criteria to include all stages. For malignant melanoma, where Tumour-Node-Metastases, based on Breslow staging, may be used more commonly clinically, and where stage IV cancers in the CR number less than those treated in the CDF, the reference population in the primary analysis included ‘all’ melanomas. For haematological cancers, where there is little stage 0–IV information in the CR, ‘all’ haematological cancers were included in the reference population in the primary analysis. CR patients’ postcodes were linked to IMD quintiles via LSOA.

2.3. Statistical analysis

2.3.1. Equity of access

Of 3530 CDF applications, 8 were out-of-region residents, 234 repeat applications for the same patient and 95 were not authorised by the CDF panel and were excluded from analysis, leaving 3193 (Fig. 1). Of these, 367 (11.5%) had missing or incomplete GP postcodes and could not be assigned an IMD designation. Other patient characteristics were missing in <2% of CDF applications.

Chi-Squared, Ordinal Chi-squared, and Fisher’s Exact tests were used to compare demographic characteristics of those treated on the CDF with the reference population.

2.3.2. Time-to-treatment

Time to receipt of treatment was calculated from the date of CDF panel authorisation to the date of treatment. Treatment start date was missing or incomplete for 1330 (41.7%) patients. Due to the large proportion of missing data, data were explored and found to be ‘missing at random’ for all observed variables apart from CN. A further 348 patients were excluded due to dates of authorisation occurring after treatment had started. Cancer types with fewer than 100 subjects were excluded from the regression analysis. The final model excluded missing data in IMD (n = 222) age (n = 22), and sex (n = 5) resulting in a final time-to-treatment analysis of 899 patients. Cox regression was used to calculate multivariable adjusted hazard ratios for time-to-treatment, where a hazard ratio >1 indicates more prompt treatment. Potential confounders were identified a priori and assessed for inclusion using likelihood ratio tests to develop the final model (adjusted for age, sex, cancer type, CN) for the impact of deprivation on time-to-treatment. All statistical analyses were performed with Stata 13.1 (StataCorp).

2.4. Sensitivity analysis

In the absence of a unique patient identifier linking the CR to the CDF, or complete diagnostic (ICD-10) coding in the CDF, two sensitivity analyses were conducted to assess assumptions used in selecting the ‘reference population’ in the CR. Firstly, we included ‘all stage’ cancers of the same cancer type in the reference population to test the assumption that ‘all’ stages better reflected the population who were eligible to apply for the CDF than advanced CR cancers in the primary analysis. Secondly, the study population was restricted to those treated in the three CNs whose entire population was eligible for the SW CDF (ASWCS, Dorset, Peninsula). This addresses the possibility that equity of access to the SW CDF was being distorted by including CNs where some residents get care through other regional CDFs.

2.5. Interview study

As part of a wider qualitative study, all colorectal and urological oncology consultants in four hospitals in the SW region were identified through hospital switchboards and websites and invited to take part in semi-structured interviews. Thirteen email and postal invitations were distributed and ten interviews were conducted between April 1st and December 31st 2013. Interview topic guides were used and included questions about the criteria that influenced the oncologists’ decision to refer a patient to the CDF, experiences of the CDF and its perceived impact on patients. Analysis used the technique of constant comparison to compare transcripts and elicit key themes [17]. The research was conducted iteratively, with
3. Results

In the 3193 unique patients (Table 1) approved for CDF treatment in the two year cohort period, there were 77 different cancer drugs prescribed at 31 hospitals. Table 2 displays interviewed participant characteristics (n = 10).

3.1. Equity of access

3.1.1. Age and sex

There were fewer than expected numbers of patients in the 80 years and over age category in the CDF compared with the reference population, most notably in colorectal cancer patients (6.9% in the CDF, 30.1% in the reference population, difference = 23.2% (95% CI 20.2–26.2)) (Table 3, Supplementary Table 1). In all cancer types studied, there was a lower proportion of women in the CDF than in the reference population. The difference was largest for melanoma (CDF 36.8% female, reference population 48.7%; difference 11.9% (95% CI 3.1–20.7%).

Oncology consultant participants universally felt that chronological age was not a ‘discriminator’ for referral to the CDF but that older patients may not be referred where their co-morbidities prevented it.

“I think the age issue is driven by general performance status…it’s a question of whether someone is fit enough for treatment...people who are elderly will have less access to the drugs fund and that’s a reflection that they have other medical problems...I don’t think we select against patients on the basis of age” [Dr. A, colorectal oncologist].

3.2. Socioeconomic status

The evidence of an association between socioeconomic status and inclusion in the CDF was inconsistent between cancer types. Prostate cancer and melanoma had greater proportions of individuals in more deprived areas (IMD quintiles 1–2) in the CDF, compared with the expected proportion based on the reference
The population of the CDF compared with the reference population for the CDF in the CR: Age, sex and socioeconomic status.

Table 1
Baseline characteristics of the CDF cohort.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0–59</th>
<th>800 (25.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–69</td>
<td>513 (18.8)</td>
<td>203 (31.5)</td>
</tr>
<tr>
<td>70–79</td>
<td>776 (28.5)</td>
<td>171 (26.2)</td>
</tr>
<tr>
<td>≥80</td>
<td>823 (30.2)</td>
<td>45 (6.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis category</th>
<th>Haematological (and amyloid)</th>
<th>Colorectal</th>
<th>Prostate</th>
<th>Breast</th>
<th>Other rare cancers</th>
<th>Upper GI</th>
<th>Skin</th>
<th>Gynaecological</th>
<th>Lung</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haem CDF (%)</td>
<td>808 (25.3%)</td>
<td>650 (20.4%)</td>
<td>529 (16.6%)</td>
<td>389 (12.2%)</td>
<td>350 (11.0%)</td>
<td>136 (4.3%)</td>
<td>129 (4.0%)</td>
<td>106 (3.3%)</td>
<td>87 (2.7%)</td>
<td>61 (1.9%)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>972 (30.4%)</td>
<td>693 (30.2%)</td>
<td>592 (16.8%)</td>
<td>389 (12.2%)</td>
<td>363 (11.3%)</td>
<td>136 (4.3%)</td>
<td>129 (4.0%)</td>
<td>106 (3.3%)</td>
<td>87 (2.7%)</td>
<td>61 (1.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>1890 (59.2%)</th>
<th>Female</th>
<th>1282 (40.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td></td>
<td>4 (&lt;1%)</td>
<td></td>
<td>367 (11.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMD quintile (2010)</th>
<th>1 (Most deprived)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (Least deprived)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDF (%)</td>
<td>266 (8.3%)</td>
<td>632 (19.8%)</td>
<td>758 (23.7%)</td>
<td>641 (20.1%)</td>
<td>529 (16.6%)</td>
<td>367 (11.5%)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>972 (30.4%)</td>
<td>693 (30.2%)</td>
<td>592 (16.8%)</td>
<td>389 (12.2%)</td>
<td>363 (11.3%)</td>
<td>21 (1%)</td>
</tr>
</tbody>
</table>

Population: e.g., prostate cancer 31.8% CDF, 25.2% reference population, quintile 1&2 ([difference = 6.6% (95% CI 1.7–11.5%)] (Table 3, Supplementary Table 1).

All but one interviewed oncologist dismissed the idea that socioeconomic status might influence referral patterns. One interviewed oncologist felt that a possible exception may be when a complex explanation of the risks and benefits of a treatment was required (in this context an off-label drug on the CDF). In this instance, deprivation may influence the likelihood of referral if an alternative treatment could be chosen that required less explanation.

“I suppose the only question about deprivation is would the patient understand side effects and when to get help, so that might sway you a little bit [not to refer to the CDF].” [Dr X, colorectal oncologist].

3.3. Cancer network

Use of the CDF by different CNs varied by cancer type (Table 4, Supplementary Table 2). Variation between CNs was most evident for colorectal and gynaecological cancers. For example, patients residing in ASWCS made up a higher proportion of the CDF colorectal cancer cohort (55.0%) than the colorectal reference population (34.7%), but the opposite trend was observed for the gynaecological cancer cohort (22.0%) and reference population (43.2%). There was no variation in referral to the CDF by CN for breast, upper gastrointestinal, melanoma, and other rare cancers.

Three oncologists described a sense that geographic variation had increased during the regional CDF but decreased following the introduction of the National Cohort List.

“. . .creating the regional Cancer Drugs Fund. . .reintroduce [d] the postcode prescribing that we were trying to get rid of by having NICE. . .it’s a huge waste of money. . .having it in four places around the country just to create inequality. . .it’s been made into a central panel which is better. . .but then why not just make it part of NICE.” [Dr C, colorectal oncologist].

Sensitivity analyses showed no difference in the direction of trends (Supplementary Tables 3 and 4).

3.4. Time-to-treatment

Time-to-treatment did not vary by IMD quintile or sex (Table 5). Patients in the Dorset CN had a faster time-to-treatment (hazard ratio) (HR) 1.25 (95% CI 1.04–1.50, P = 0.019, median 9.9 days) compared with ASWCS (reference group 1.0, median time 15.8 days).

4. Discussion

Our study suggests that receiving primary care from a deprived area has not been associated with worse access to the CDF. The majority of interviewed participants believed there would be no
association between CDF referral and patient deprivation. Prostate and melanoma cancer patients, who received their primary care in more deprived areas, were marginally more likely to be treated on the CDF. The willingness of clinicians to provide the most innovative treatment for those presenting with advanced disease (where advanced presentation is more likely in the more deprived) [18], combined with the tolerability of some newer cancer agents (e.g., Abiraterone) may explain this unexpected finding in the CDF. Prior to the CDF, increasing deprivation had been associated with reduced access to anti-cancer therapy in the literature [7–9].

Whether the preponderance of younger patients on the CDF is a consequence of better performance status (fitness for anti-cancer therapy), younger patients' preference for more aggressive therapy or clinician preconceptions and inequities of referral, cannot be determined without information on patients' performance status. Interviewed oncologists felt poor performance status, not older age was the key barrier for referral to the CDF. The literature corroborates older age as a barrier to anti-cancer therapy, even after adjustment for performance status [5,19].

The differential in CDF referral by gender is conceivably due to poorer performance status at presentation among females. The literature on equity of access to anti-cancer therapy by healthcare jurisdiction prior to the CDF is in keeping with the clinician participant's corroborated these hypotheses.

Table 5
Cancer network in the CDF and in the reference population.

<table>
<thead>
<tr>
<th>Cancer network</th>
<th>Haem (CDF) (%)</th>
<th>Haem (CR) (%)</th>
<th>CRC (CDF) (%)</th>
<th>CRC (CR) (%)</th>
<th>Prostate (CDF) (%)</th>
<th>Prostate (CR) (%)</th>
<th>Breast (CDF) (%)</th>
<th>Breast (CR) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASWCS</td>
<td>249 (37.5)</td>
<td>1015 (43.1)</td>
<td>286 (55.0)</td>
<td>557 (41.4)</td>
<td>184 (38.5)</td>
<td>376 (35.7)</td>
<td>158 (46.5)</td>
<td>189 (40.0)</td>
</tr>
<tr>
<td>Dorset</td>
<td>128 (19.3)</td>
<td>432 (18.3)</td>
<td>70 (13.5)</td>
<td>243 (18.1)</td>
<td>62 (13.0)</td>
<td>190 (18.1)</td>
<td>64 (18.8)</td>
<td>94 (19.9)</td>
</tr>
<tr>
<td>Peninsula</td>
<td>287 (43.2)</td>
<td>909 (38.6)</td>
<td>164 (31.5)</td>
<td>545 (40.5)</td>
<td>232 (48.5)</td>
<td>486 (46.2)</td>
<td>118 (34.7)</td>
<td>189 (40.0)</td>
</tr>
<tr>
<td>X² p value</td>
<td>0.031</td>
<td>&lt;0.001</td>
<td>0.044</td>
<td>0.172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Denotes where ‘all’ stage of cancers are presented in place of stage IV cancers.
b Avon Somerset and Wiltshire Cancer Network.

4.1. Strengths and limitations

Comparing the CDF population with a reference population gives conservative results because the numerator (CDF participants), is also included within the denominator (CR reference population), thereby attenuating differences between the two groups. Depreation in the CR data was estimated from the patient’s residential postcode whereas in the CDF, GP postcode was used as a proxy. As GP populations reside within local boundary areas, we do not believe this will have an important influence on our findings. Imperfect matching between CDF and reference populations for ‘advanced’ cancer stage may introduce selection bias if CDF patients have more advanced disease than reference populations.

4.2. Implications

Our analysis of equity of access to the CDF is restricted by the absence of key clinical variables (e.g., performance status) and incomplete data, (e.g., >40% in treatment start date) which would be required to more fully measure equity and assess survival. The paucity of these prospectively collected data, which also excluded quality of life, adverse event, and other core outcome data is indefensible, as recognised in the House of Commons Committee of Public Accounts (2015) [26]. If data quality cannot be improved, future research should rely on linkage with reliable data sources (e.g., CR, Hospital Episode Statistics) to overcome some limitations of existing data, and adjust for co-morbidity as a proxy for performance status. Given the huge amounts invested in the CDF, these data are a missed opportunity for research.

5. Conclusion

Our study found no increase in inequity of access to these agents by socioeconomic status. Age and sex differences in access may reflect unmeasured differences in patients’ performance status, patient preferences, or inequity resulting from clinician preconceptions about fitness for therapy and patient wishes. Data incompleteness and absent essential variables, such as performance status, in the CDF data has made drawing firm conclusions challenging. The CDF represents a missed opportunity for research in the equity of access and real-world costs and outcomes of anti-cancer therapies.

Conflict of interests

This manuscript has been developed without conflict of interests from pharmaceutical companies or political bias. Public health England (LH) is an executive agency, sponsored by the Department of Health and is not constrained by government policy.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcpo.2015.06.003

References