Cancer Treatment and Research Communications 27 (2021) 100309

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Research Related Tumour Biopsies in Early-Phase Trials with Simultaneous Molecular Characterisation – a Single Unit Experience

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ARTICLE INFO

Keywords:
Phase 1 cancer trials
Research biopsy
Sequencing
Drug development
Research ethics
Informed consent

ABSTRACT

Early-phase cancer clinical trials are becoming increasingly accessible for patients with advanced cancer who have exhausted standard treatment options and later phase trial options. Many of these trials mandate research tissue biopsies. Research biopsies have been perceived as ethically fraught due to the perception of potential coercion of vulnerable human subjects. We performed an audit of two years of practice to assess the safety of ultrasound (US)-guided research biopsies, and to look at the yield of a simultaneous tumour next-generation sequencing (NGS) and immunohistochemistry (IHC) molecular characterisation programme. We show that in our institution, US-guided research biopsies were safe, produced adequate tumour content and in a selected subset who underwent in-house NGS sequencing, showed a high rate of actionable mutations with 30% having a Tier 1 variant. Nevertheless, these research biopsies may only provide direct benefit for a minority of patients and we conclude with a reflection on the importance of obtaining truly informed consent.

1. Introduction

The scientific argument for protocol mandated research biopsies as part of the Pharmacological Audit Trail in the era of biomarker-driven personalised medicine is no longer in question [1]. The ethical argument is more controversial. Patients considering early phase clinical trials may be considered "fragile" due to their limited prognosis [2] and may be affected by therapeutic misconception [3]. Although biopsies are considered "safe" they carry procedural risk such as pain and bleeding. Undergoing the biopsy facilitates patient access to trial but there is low likelihood of net clinical benefit from early phase clinical trials that focuses on dose finding and determination of safety profile. We are therefore asking participants to accept additional risk receiving little in return, which goes against a fundamental human clinical research principle that potential harms are balanced by potential benefits. In this context, mandatory research biopsies can be viewed as coercive or exploitative. Ultimately, with informed consent, a valid motivation would be altruism and the desire to benefit future patients. Consequently, some commentators have characterised research biopsies as "taking without giving in return" [4]. ASCO has released a comprehensive framework to improve the ethics of research biopsies aiming to maximise scientific utility, minimise risk and increase oversight [5].

When taking research biopsies, it is possible to take extra tissue cores, under the appropriate consent, to perform additional testing. Such tumour molecular characterisation (MC) programmes, run in parallel to early phase trial mandated analyses, can serve several purposes; furthering knowledge of frequency of molecular drivers and providing tissue for translational researchers to advance scientific knowledge and drug development. However, MC programmes may also provide an opportunity to "give back" to patients, as the knowledge of key molecular drivers may aid access to drugs with higher likelihood of clinical benefit within later phase clinical trials or with licensed drugs. The likelihood of providing such benefit to patients has not been established.

The Royal Marsden Drug Development Unit is one of the largest early phase cancer clinical trials unit in Europe with 40 – 50 active clinical trials running at any one time. We aimed to audit US-guided research biopsies to interrogate safety of biopsies and our programme of simultaneous MC.

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https://doi.org/10.1016/j.ctarc.2021.100309

Available online 11 January 2021

2. Materials and Methods

We performed a retrospective analysis of US-guided biopsies performed in the Drug Development Unit. Approval for this audit and for the tumour molecular characterization study was granted by the local clinical audit committee and local research and ethics committee (CCR3171). Electronic patient records were interrogated for complications during biopsy. Statistical analyses were performed using Fisher's exact test for the comparison of adverse event rates between two independent groups with GraphPad Prism (USA). Determination of Tier of molecular variant in ESMO Scale of Clinical Actionability of Molecular Targets (ESCAT) [6] was made by authors on basis of review of variant in COSMIC database [7] and knowledge of current investigative and standard of care options for each tumour type.

The US guided biopsies were performed by a single Radiologist (NT) with 10 years experience in US-guided biopsies. The decision on performing the biopsy was made after review of all relevant imaging and a pre-procedure US examination by the radiologist to assess and discuss feasibility and risks with the patient.

Samples for the tumour MC, are processed and analysed at the Cancer Biomarker Laboratory at the Institute of Cancer Research. Tumour content of the sample is assessed by a pathologist. After DNA extraction, targeted next-generation sequencing (NGS) is performed using a customised GeneRead DNAseq Panel (Qiagen, USA) covering 113 genes and run on MiSeq sequencer (Illumina, USA). Mismatch repair (MLH1, MSH2, MSH6, PMS2), PTEN and ATM protein expression is determined by means of immunohistochemical (IHC) assessment, as previously validated [8,9] . Samples with more than 25% tumour content are deemed optimal for analyses.

3. Results

151 US-guided biopsies were performed between January 2017 and December 2018. The biopsies were taken as part of 39 different research studies and included 42 sets of two or three study-specific serial biopsies. Median age of the patients at the time of the biopsy was 60, 55% were male (Table 1). The most common cancer-type biopsied was colorectal, prostate and breast (Table 1). A fewer number of deep biopsies were carried out than superficial biopsies (38.4%, n=58 versus 61.6%, n=93). 113 biopsies were performed using a 16-gauge needle and 37 with an 18-gauge (one biopsy had no record of needle gauge used).

Of the 151 biopsies audited, 8.6% had mild or moderate adverse events, including pain (n=10) and hypotension (n=3) (Table 1). There were no serious or life-threatening adverse events. Deep biopsies had a higher complication rate than superficial ones (13.8% vs 5.4%, $p = 0.08$). Biopsies with fewer than 3 cores taken had similar adverse event rates compared to ones with 3 or more cores (11.1% vs 10.5%, $p > 0.99$). 22.5% of the biopsies were performed in patients on anticoagulation therapy (anti-platelet, n = 4; low-molecular weight heparin, n = 22; novel oral anticoagulant, n = 6; combination anticoagulation therapy n = 2), which was held according to our institution's guidelines. No procedure-related bleeding was reported. One patient reported grade 1 anxiety with no specific fear (e.g. risk of tumour seeding) identified.

63 samples were processed for on-site lab for in house testing, and 56 (89%) were suitable for molecular analysis. Of the 7 samples which were inadequate for analysis, five were from deep biopsies and five had fewer than 3 cores taken. NGS and/or IHC was performed on 42 selected patients, based on potential utility and yield. Of these, 64% (27) had actionable molecular characteristics identified, which can be stratified by evidence-based actionability using the ESCAT (Table 2); 30% having tier 1 variants (Table 1). Tier 1 variants included a colorectal cancer patient with *BRAF* mutation (tier 1), PTEN (Phosphatase and tensin homolog) loss (tier 2) and ATM (Ataxia-Telangiectasia Mutated) loss (tier 3); and a triple-negative metastatic breast cancer patient with PTEN loss (tier 3), who was allocated to a trial involving a PI3K (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase) inhibitor.

Table 1

Abbreviations: ARID1A: AT-rich interactive domain 1A (SWI-like); ATM: Ataxia-Telangiectasia Mutated; ATR: ataxia telangiectasia and Rad3-related protein; BRCA: BReast CAncer gene; CHK2: Checkpoint kinase 2; EGFR: epidermal growth factor receptor; EZH2: Enhancer Of Zeste 2 Polycomb Repressive Complex 2 Subunit); FANC: Fanconi anemia complementation group; GIST: gastrointestinal stromal tumour; MMR: mis-match repair; NRAS: neuroblastoma ras viral oncogene homolog; PALB2: partner and localizer of BRCA2; PI3KCA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PTEN: Phosphatase and tensin homolog; SMARCA4: SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4.

Patient and biopsy characteristics	
Male: Female	83 (55%); 68 (45%)
Age, years, median (range)	60 (29-79)
Tumour type	
Colorectal	35 (23.2%)
Prostate	27 (17.9%)
Breast	23 (15.2%)
Mesothelioma	11 (7.3%)
Melanoma	8 (5.3%)
Ovarian	7 (4.6%)
Cervical	7 (4.6%)
Lung	6 (4.0%)
Other	27 (17.9%)
Biopsy site	
Nodal	70 (46.4%)
Liver	35 (23.2%)
Peritoneal	16 (10.6%)
Chest wall	10 (6.6%)
Abdominal wall	7 (4.6%)
Other	13 (8.6%)
Other biopsy characteristics	
Deep: superficial	58 (38.4%); 93 (61.6%)
Sets of serial biopsies	42
Patients on anticoagulation therapy	33 (21.9%)
Cores median (range)**	2 (1-3)

Tumour biopsy adverse events

Adverse event	Grade 1 (mild)	Grade 2 (moderate)
Pain	7 (4.6%)	3 (2.0%)
Anxiety	1 (0.7%)	-
Fever	1 (0.7%)	-
Presyncope	-	1 (0.7%)
Hypotension	1 (0.7%)	2 (1.3%)
Bloating	1 (0.7%)	-

Actionable variants found

Tumour type	Tier 1	Tier 2	Tier 3	Tier 4	Tier 5
Melanoma					
Melanoma	*BRAF*			*NRAS; FANCL*	
Melanoma				*NRAS*	
Melanoma			*BRCA2, MET*	*FANCM, NRAS, PALB2,*	
Colorectal				*ATR; PTEN; EGFR*	
Colorectal					
Colorectal					
Colorectal					
Colorectal			*MET*		
Colorectal	*BRAF*		PTEN loss*	ATM loss*	
Colorectal				*KRAS, CTNNB1*	
Colorectal					

(*continued on next page*)

Table 1 (*continued*)

				KRAS, CTNNB1	
Colorectal	*BRAF*				*PIK3CA*
Prostate			*BRAF*		
Prostate	*BRCA2*			*SMARCA4*	
Prostate					
Prostate	MMR deficiency*				
Prostate		*PTEN*			
Pancreas				*KRAS, EGFR,*	
Breast	*PIK3CA*				
Breast	*PIK3CA*			*ARID1A, CHEK2*	
Breast				*KRAS*	
Breast			PTEN loss*		
Breast				*FANCL*	
Breast				*ATM*, ATM loss*	
Ovarian					
Ovarian				*FANCL*	
Ovarian	*BRCA1*			*FANCA, ATRX, FANCI, FANCL,*	
Ovarian					
Ovarian			*MET*		
Mesothelioma					
Mesothelioma					
Mesothelioma					
Mesothelioma					
GIST					
Sarcomatoid/ undifferentiated carcinoma of chest wall					
Peritoneal					
Lung			*BRCA1*		
Oesophageal				*SMARCA4,*	
Small intestine				*FANCI, KRAS*	
Sarcoma					
Cervical			*BRCA1*	*EZH2, FANCE*	
Highest tier ESMO ESCAT variant found	**7**	**1**	**8**	**11**	**0**

* Protein expression loss by immunohistochemistry
** Data on biopsy cores available for 65 biopsies

4. Discussion

Our audit of 151 biopsies performed by a single radiologist confirms that US-guided research biopsies can be safe (low complication rate) and effective (high rate of tumour content suitable for analysis). These results are comparable to those reported by two other large early phase cancer trials units [10,11]. Multiple core biopsies did not increase complication rates, indicating that a MC programme can be safely run in parallel with clinical trial-associated biopsies. The parallel MC programme had value in providing relevant data that may directly impact patient care. MC results could open up biomarker-based clinical trial participation, as well as provide guidance to options outside the trial setting. These potential benefits are tempered by limitations – actionable aberrations may have been previously identified or there may not be a targeted trial or treatment option available. We conclude therefore, that tumour testing has a small potential to give potentially actionable MC results to patients.

An important question is asked by Helft and Daugherty [4] - if patients understood that research-related biopsies would provide no benefit to their own health or care, would they still find the practice acceptable? Whilst acknowledging the relatively small sample size of our audit, the results suggest that the practice causes only mild to moderate adverse effects for a minority. These data do not rule out the possibility of serious biopsy-related complications. While research participants should be made aware that research biopsies play a vital role in understanding drug effects and driving forward drug development, they should also understand that direct benefit from the research biopsy is highly unlikely. Hence, we must focus on communicating this information as clearly as possible to patients prior to study enrolment and research biopsy procedures and ensure they do not harbour any therapeutic misconceptions, in order to obtain truly informed consent.

Finally, given that the altruism of patients, whether explicit or otherwise, plays a large part in trial participation, it is incumbent on the research community to ensure biopsies provide scientific yield and benefit to future patients. We note that it was recently shown that in a retrospective audit of 866 biopsies across cancer clinical trials performed between 2005 - 2010, the majority (61%) did not report trial specific results from research biopsies [12]. Similarly, in an audit of cancer clinical trials performed between 2000 – 2015 which included endpoints involving biopsies or tissues, only 50.8% of trials reported on these results [13]. Strikingly, trials which met their primary endpoint had a higher rate of biopsy reporting than those that did not (72% vs 45%). The sequencing data presented here is collated across multiple early phase trials of investigational agents and represent a limited set of analyses, but do show the potential scientific utility from these research biopsies. We strongly support ongoing efforts for cancer clinical trials to publicise the results of the research biopsies to ensure that while we are not always able to “give back” directly to the patients on our clinical trials we make every effort to “give back” to future patients in the form of scientific data obtained during the pharmacological audit trail for novel agents, successful or otherwise.

5. Ethics approval and consent to participate

Approval for this audit and for the tumour molecular characterization study was granted by the local clinical audit committee and local research and ethics committee (CCR3171).

Table 2
Description of tiers of molecular variants in the ESMO Scale of Clinical Actionability of Molecular Targets (ESCAT) adapted from (6).

ESCAT Tier	Description
1	Target ready for routine use. Alteration-drug match is associated with improved outcome in clinical trials.
2	Investigational target. Alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown.
3	Hypothetical target. Alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration.
4	Hypothetical target. Preclinical evidence of actionability.
5	Target for combination development. Alteration-drug match is associated with objective response, but without clinically meaningful benefit.

6. Consent for publication

N/A

7. Data availability

The datasets used in this study are available from the corresponding author on reasonable request.

8. Funding information

This study represents independent research supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The authors also acknowledge funding from Cancer Research UK and the Experimental Cancer Centre Initiative.

Authors' contributions

AB: Conceived and designed the work that led to the submission, acquired data, and interpreted results, and was a primary author of the manuscript.

AP: Conceived and designed the work that led to the submission, acquired data, and interpreted results, and was a primary author of the manuscript.

RR: Acquired data

RS: Acquired data

CT: Acquired data

FL: Acquired data

CB: Acquired data

CB: Acquired data

MC: Acquired data

AF: Acquired data

RP: Acquired data

IF: Acquired data

SM: Acquired data

BG: Acquired data

SC: Acquired data

UB: Interpreted results

JSDB: Conceived and designed the work that led to the submission

JL: Conceived and designed the work that led to the submission

NT: Conceived and designed the work that led to the submission

AM: Conceived and designed the work that led to the submission, acquired data, and interpreted results, and was a primary author of the manuscript.

All contributing authors drafted or revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A Biondo: AB is now an employee of Astex Pharmaceuticals; A Pal: None declared; R Riisnaes: None declared; R Shinde: None declared; C Tiu: None declared; F Lockie: None declared; C Baker: None declared; M Crespo: None declared; A Ferreira: None declared; R Pereira: None declared; I Figueiredo: None declared; S Miranda: None declared; B Gurel: None declared; S Carreira: None declared; U Banerji: Has received honoraria from Astellas, Novartis, Karus Therapuetics, Pheonix Solutions, Eli Lilly, Astex, Vernalis, Boehringer Ingelheim Is a recipient of an NIHR Research Professorship Award and has received CRUK funding: Cancer Research UK Scientific Executive Board, Cancer Research UK Centre Award. Cancer Research UK Drug Discovery Committee – Programme Award. All unrelated to this work J de Bono: JDB has served on advisory boards and received fees from many companies including Astra Zeneca, Astellas, Bayer, Bioxcel Therapeutics, Boehringer Ingelheim, Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Janssen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Vertex Pharmaceuticals. He is an employee of The ICR, which have received funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi, Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Sierra Oncology, Taiho, Pfizer, Vertex, and which has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income). He was named as an inventor, with no financial interest, for patent 8,822,438. He has been the CI/PI of many industry sponsored clinical trials. JDB is a National Institute for Health Research (NIHR) Senior Investigator. J Lopez: Research grant funding from Roche, Basilea, and Genmab unrelated to this work; N Tunariu: None declared; A Minchom: Has served on advisory boards and received fees from Merck, FARON, Novartis, Bayer, Janssen All unrelated to this work

Acknowledgements

N/A

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