ENSAT registry-based randomized clinical trials for adrenocortical carcinoma

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Abstract (204 words)

Adrenocortical carcinoma (ACC) is an orphan disease lacking effective systemic treatment options. The low incidence of the disease and high cost of clinical trials are major obstacles in the search for improved treatment strategies. As a novel approach, registry-based clinical trials have been introduced in clinical research, so allowing for significant cost reduction, but without compromising scientific benefit. Herein, we describe how the European Network for the Study of Adrenal Tumours (ENSAT) could transform its current registry into one fit for a clinical trial infrastructure. The rationale to perform randomized registry-based trials in ACC is outlined including an analysis of relevant limitations and challenges. We summarize a survey on this concept among ENSAT members who expressed a strong interest of the concept and rated its scientific potential as high. Legal aspects, including ethical approval of registry-based randomization were identified as potential obstacles. Finally, we describe three potential randomized registry-based clinical trials in an adjuvant setting and for advanced disease with a high potential to be executed within the framework of an advanced ENSAT registry. Thus we therefore provide the basis for future registry-based trials for ACC patients. This could ultimately provide proof-of-principle of how to perform more effective randomized trials for an orphan disease.

Introduction

Adrenocortical carcinoma (ACC) is a rare disease for which diagnostic approaches and therapeutic strategies have only gradually changed over the past decades (1, 2). Accordingly, the overall survival for patients diagnosed with ACC remains in the range of 3–4 years (3, 4). Affected patients also experience severe morbidity due to endocrine disturbances as well as tumour growth (1, 5, 6). In a recent review, we identified topics including disease prevention and earlier detection, improved risk-stratification, controlling tumour growth and invasiveness as well as suppressing hormone production as unresolved problems that need to be addressed by research with the overarching aim to reduce ACC-related morbidity and mortality (1).

While clinical trials have the potential to explore strategies to approach these problems, the current research infrastructure fails in providing effective resources to perform such projects on rare diseases. In this context, registry-based clinical trials have emerged as a resource-efficient alternative solution to address clinical and translational research questions (7-10). In this review, we aim to describe how registry-based trials could be used to advance care of patients with ACC. Furthermore, we argue that the European Network for the Study of Adrenal Tumours (ENSAT) is well positioned to transform its current registry and advance its strong collaboration to implement registry-based clinical trials. Finally, we propose potential research projects with potential to be executed within this space.

Randomized clinical trials

A randomized controlled trial provides the experimental framework that aims to evaluate the effectiveness and safety of a medical intervention. By randomly assigning patients between experimental and control arms, it ensures the greatest reliability and validity of the results, by reducing impact from both known and unrecognized bias. Appropriately executed (11), it is considered as the gold standard for evaluating healthcare interventions. In contrast, those medical practices that are

based on evidence from non-randomized controlled data are prone to bias and misinterpretation. Clinical trials lacking a control arm and those using historical controls have repeatedly been shown to exaggerate the efficacy of treatments (12). Similarly, early clinical trials on small or diverse patient samples are prone to find higher response rates than those in subsequent randomized studies (13). Overall, these shortcomings have well been exemplified in a systematic review of >3000 randomized clinical studies demonstrating that a total of 396 formerly established medical practices had been identified as lacking clinical benefit (14).

While there are a few reported randomized controlled trials on ACC (Table 1), patient scarcity and high resource demand has limited the use of this method. As a consequence, among the 25 recommendations with evidence rating in the recent ACC guidelines by *the European Society for Endocrinology* and ENSAT, none were considered to have strong underlying evidence and only three were graded as having moderate evidence (5). Currently, there is only one randomized clinical trial active within the space of ACC: Mitotane With or Without Cisplatin and Etoposide After Surgery in Treating Participants With Stage I-III ACC With High Risk of Recurrence (ADIUVO-2, NCT03583710). This study has been designed to be executed within a clinical environment but has yet to be directly integrated into an established patient registry. This sets the stage for further optimization of the clinical trial method for the study of ACC in order to further improve clinical evidence and refine patient care.

Registry-based clinical trials

A randomized registry-based clinical trial is a prospective study using a clinical registry for patient identification, trial conduct and outcomes reporting. The registry-based randomized clinical trial maintains the strengths of a prospective clinical study, including high internal validity, stringent patient stratification, randomization to ensure unbiased study of interventions and analysing patient outcomes to determine the effect of the studied intervention (7, 9, 15). In variance to conventional trials, registry-

based studies provide the opportunity to lower costs and ensure more rapid patient inclusion (7, 9, 15). This method is particularly suitable for evaluation of interventions that are already established within the field, with documented data on adverse events and that does not require additional evaluations than those already performed within standard clinical practice.

A registry structure can be used to identify eligible patients, randomize between different interventions, provide follow-up data and evaluate outcomes. To remain resource-effective, addition of procedures beyond standard clinical practice should be avoided. Experience from cardiovascular research has demonstrated that registry-based clinical studies can be performed with more than 90% cost-saving compared to conventional trials (7, 9). On-going developments of this method include refinements of both biostatistical analysis and interpretation (16).

To our knowledge, there are no reported registry-based clinical trials and only a few on-going within the field of medical oncology or endocrinology. In a review by Foroughi and colleagues, on-going registry-based clinical trials were described (9) from which we select two relevant examples:

ALT-TRACC (17) is a phase II clinical trial randomizing patients with treatment naïve metastatic colorectal cancer between alternating oxaliplatin and irinotecan doublet schedules (experimental arm) versus continuous doublet chemotherapy (control arm). Primary objective is to evaluate the feasibility of conducting a multi-center, prospective, registry-based randomized clinical trial. The primary endpoint is recruitment rate. Secondary objectives focus on both efficacy and toxicity by collecting data from medical records and other data collection tools. The aim is to estimate progression free survival and radiological response rates. The study is based on the *Treatment of Recurrent and Advanced Colorectal Cancer* registry (9).

EX-TEM (18) is a phase III trial randomizing patients with newly diagnosed glioblastoma to six (control arm) versus twelve (experimental arm) cycles of post-radiation temozolomide chemotherapy. The primary objective is to study treatment efficacy and the primary endpoint is overall survival. Secondary endpoints include adverse events and the necessity for temozolomide dose modification determined by data recorded in the medical records. The study makes usage of *the Brain Registry Australia: Innovation and Translation* registry (9).

Current and previous randomized trials for ACC

An overview of randomized clinical studies on ACC is provided in Table 1. FIRM-ACT was the first randomized study performed on ACC and compared the efficacy of a chemotherapy combination (etoposide, cisplatin and doxorubicin, EDP) plus mitotane versus streptozocin plus mitotane in the advanced setting (19). It reported a hazard ratio of 0.55 (95% Confidence Interval (CI) 0.43-0.69) in favour for EDP plus mitotane for progression free survival. Survival was not significantly different, hazard ratio 0.79 (95% CI 0.61-1.02) in favour for EDP + mitotane. Quality of Life according the EORTC QLQ-C30 questionnaire revealed no changes at follow-up compared to baseline for the two treatment arms.

As recruitment within the FIRM-ACT protocol had been achieved, it was quickly followed by GALACCTIC, a randomized phase III trial of linsitinib (inhibitor of IGF-1R and the insulin receptor) versus placebo for locally advanced or metastatic ACC (20). No difference in overall survival between linsitinib and placebo was noted, HR 0.94 (95% CI 0.61-1.44). This study did, however, provide valuable information on the behaviour of untreated metastatic ACC progressive after mitotane therapy. In the control arm, median survival was 356 days (95% CI 249–556) while the disease control rate was 34.7% (95% CI 21.7–49.6) at 6 weeks and 8.2% at 12 weeks.

There are currently two on-going randomized trials on ACC, both in the adjuvant setting (Table 1), mitotane versus follow-up in low to intermediate risk ACC (ADIUVO

study) and mitotane versus mitotane plus cisplatin and etoposide (ADIUVO-2 study) in high risk ACC. These trials will be fundamental to evaluate current practices for adjuvant therapy that are currently supported by retrospective data (21).

The European Network for the Study of Adrenal Tumours

The European Network for the Study of Adrenal Tumours was formally established in 2002 through a merger of three already existing national networks on adrenal research: COMETE in France, GANIMED in Germany, and NISGAT in Italy with further teams joining in from the United Kingdom. In 2009, ENSAT became a membership-based society with statutes and by-laws. An increasing number of researchers and health workers have joined in the efforts of the ENSAT with currently 479 members from 35 different countries. The European Network for the Study of Adrenal Tumours has structured its operation under four different working groups by disease subtype: ACC, pheochromocytoma and paraganglioma, aldosterone-producing adenoma and non-aldosterone producing cortical adrenal adenomas. Through its patient registry, the largest body of clinical annotations and biospecimens from patients with adrenal tumours has been aggregated (22). Currently (April 2020) it includes data from 17,680 patients of 107 institutions, representing 33 predominantly European countries. A long list of disease specific clinical annotations has been collected. Current limitations of the ENSAT registry include its non-consecutive patient enrolment and lack of quality control.

Based on the information reviewed in previous sections, we hypothesized that registry-based trials would be a potential new tool to allow for more efficient studies on adrenal tumours. We hypothesized further that ENSAT would be ideally positioned to implement this technology as it already forms a strong network with large patient populations and operates a prospective registry. Finally, ACC was identified as the most suitable patient population among adrenal tumours to be evaluated in a pilot project due to large unmet needs in combination with up-to-date

clinical practice guidelines and potentially relevant study endpoint already available in the registry (5, 23).

The ENSAT ACC registry

Currently, the ACC database includes data from 3,835 patients from 63 institutions (April 2020). It is structured under the following sections; diagnostic procedures (34 variables), tumour staging (16 variables), biomaterial (20 variables), chemoembolization (four variables), chemotherapy (seven variables), follow-up (18 variables), metabolomics (two variables), mitotane (nine variables), pathology (20 variables), radiofrequency (five variables), radiotherapy (eight variables) and surgery (six variables). In total, these comprehensive data can be used to study endpoints relevant for patients with ACC; overall survival, recurrence free survival, progression free survival (accordingly to local analysis, but no specific protocol for radiological evaluation is requested, yet) and early discontinuation of medical therapy. Furthermore, appropriate factors for disease characterization can be used as inclusion / exclusion criteria as well as being incorporated into a future randomization module.

Assessing the potential for registry-based clinical trials within ENSAT

Two online surveys as well as discussions at scientific meetings had been conducted to determine the potential of registry-based clinical trials to be performed within the ENSAT community (Supplementary materials and methods). In a first survey (Supplementary table 1) responses had been collected from eighty-six members, including 66 full members and 20 associate members. The respondents represented 22 different countries; Italy (*n*=22), Germany (*n*=10), France (*n*=8), Greece (n=7), United Kingdom (*n*=7), Netherlands (*n*=6) and Spain (*n*=4) being the most frequent. The high interest for registry-based clinical trials in ACC was reflected not only in the active participation in online surveys and real life meetings, but was also expressed

directly in the surveys through the rated scientific potential, mean score 4.5 (maximum 5), and the anticipation to collaborate and contribute, with a mean rating of 4.3 (maximum 5).

General topics for ENSAT registry-based trials were proposed with positive/negative response options available (Figure 1A); evaluation of drugs or other medical interventions (90% positive), evaluation of prognostic or predictive biomarkers for therapeutic stratification (89% positive), prospective collection of clinical data and/or bio samples (71% positive), and comparison of different follow-up strategies (69% positive). Study participants were also asked, which ACC patient population should primarily be addressed (positive/negative response options available); neo-adjuvant setting (75% positive), adjuvant setting (87% positive) and advanced disease (61% positive). Next, survey participants were asked if they would foresee legal or any other administrative challenges related to registry-based clinical trials, which was answered with yes in 56% of cases with eight free text comments provided. Among these responses, reluctance from ethical review boards to provide ethical permissions were specifically mentioned. Another example demonstrating the strong interest in registry-based clinical trials could be noted in the active discussion of particular scientific projects: There were a total of 48 different research projects being proposed. The ENSAT ACC working group scientific board prioritized these projects based on scientific quality and feasibility for further evaluation.

In the subsequent survey (Supplementary table 2) there were 62 respondents, 50 full members and 12 associate members. These represented 19 different countries with Italy (*n*=19), France (*n*=6), Germany (*n*=6), Greece (*n*=5) and the United Kingdom (*n*=5) as the most frequent. A total of 87% of responders phrased the expectation that a registry-based clinical trial would be accepted by the local ethical committee, with eight additional comments in free text. In the next question, 43% assumed that randomization of study sites to different interventions ("cluster randomization") would be more likely to be acceptable to ethical review boards compared to randomization

of individual patients. Furthermore, concrete ideas for problems to be addressed within an ENSAT registry-based platform were collected.

Proposal for registry-based studies on ACC based on the ENSAT platform

Of the 48 different research projects being proposed by the ENSAT ACC working group, the scientific board and its members had previously selected and prioritized the following projects that gained particularly high scoring based on scientific value and feasibility (Figure 1B):

Adjuvant setting - Comparison of different durations of mitotane treatment for effectiveness and toxicity. Adjuvant treatment with mitotane is recommended in patients without macroscopic residual tumour after surgery who have a perceived high risk of recurrence (5, 21, 24). However, the optimal duration of mitotane treatment, to balance efficacy and adverse effects of the compound is currently unknown. Therefore, a randomized controlled study between a duration of e.g. 2 vs. 5 years of mitotane treatment would be informative.

Advanced ACC I - Comparison of different first-line chemotherapy protocols for effectiveness and toxicity. The most validated first-line treatment option for unresectable and advanced ACC is the combination of etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) (19). Treatment with EDP-M comes with a risk of adverse events. Based on small trials (25, 26) and individual experience (5) it has been hypothesized that omitting doxorubicin from the treatment protocol would increase tolerability without a clinically relevant loss of efficacy. This hypothesis could be evaluated through a randomized controlled study between EDP-M (standard arm) versus etoposide, cisplatin and mitotane (experimental arm).

Advanced ACC II - Comparison of anti-tumour efficacy of mitotane at different concentrations. It is believed that mitotane toxicity and efficacy is strongly correlated to plasma levels of the compound (27-29). It has been hypothesized that

by lowering the therapeutic concentration target for mitotane in advanced ACC, patients would experience less treatment related toxicity. This could potentially result in improved quality of life without clinically significant loss in efficacy. For this purpose, a randomized controlled study between standard therapy aiming at a mitotane blood level > 14 mg/L (standard arm) versus a mitotane regime aiming at lower concentration (e.g. > 10 mg/L; experimental arm) would lead to clinically important information.

Potential objectives to be investigated in these three proposals include the evaluation of recruitment feasibility, quality of data capture, patient benefit in terms of overall survival and quality of life as well as drug tolerability. Furthermore, we propose that quality of life could be measured through patient self-reporting through a web-based application (currently not available in the ENSAT registry). In addition, safety could be described from the documentations made in the patient records. We also argue that both cluster and patient randomization could be used to address these three research questions. The studies could also be designed as superiority and/or non-superiority trials, all depending on what primary endpoint is finally selected.

In addition to studying different interventions, we envision the possibility to execute prospective longitudinal observation studies to collect information and biomaterial on predictive markers of treatment response as well as prognostic factors. The underlying rationale comes from the rapid advances in our understanding of the biology of ACC (1, 30-35), which translates into a need for efficient test beds to evaluate new biomarkers for different clinical purposes.

Challenges

Examples in clinical cardiovascular research has provided a clear proof of concept of how a strong network can be enhanced to perform registry-based clinical trials through technical advances of the current infrastructure but only minor changes in

clinical and research practice (7). One potential factor limiting the dissemination of registry-based trials could be legal and administrative restrictions. In our surveys, a high proportion of participants (87%) anticipated acceptance of a registry-based trial by their local ethical review boards. However, as the registry-based randomized trial is a concept currently lacking a clear definition it is expected to be treated with the same level of scrutiny as conventional clinical trials. This will impose rules and regulations not applicable to registry based randomized trials. As such, the current legislative environment needs to be adopted to fit randomized registry-based clinical trials in order to ensure a lower complexity that will otherwise increase costs.

While the foundation for a future infrastructure for registry-based trails exist within ENSAT, additional method development will be required including a randomization module as well as the possibility for source data verification (Figure 2). There is also a need for data monitoring to ensure high validity of the data within the registry. Furthermore, our work also raised the potential to implement clinical decision support, active suggestion of potential research studies and integration with patient self-reporting into the ENSAT registry. While such infrastructure upgrades are all technically feasible, additional resources will be necessary for its implementation. And as this research direction is pursued in other medical settings, ENSAT could potentially co-operate with other relevant registries for method development and to share experiences.

Summary

The ENSAT ACC community has expressed a strong interest and support of in registry-based trials as a new infrastructure with potential to significantly advance care for patients with this rare disease. This review summarises the scientific foundation for this research direction and outlines potential questions to be addressed within such a new infrastructure and provides a roadmap for future pilot projects.

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