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General Information

Key Personnel (in addition to PI): **First Name:** jose miguel
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Degree: PhD, MPH, MBA, MSc
Primary Affiliation: Universidad Pompeu Fabra, Barcelona.

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00653952 - A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX® versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

A Meta-analysis of current treatments ' efficacy for Relapsed Ovarian Cancer

Narrative Summary:
This study will evaluate the prognosis (independent) variables which might be relevant to predict survival outcomes in women with Relapsed Ovarian Cancer -following a first line chemotherapy treatment-. Exploratory independent variables are: Age, Health Status, Tumor Metastases , Residual Tumor Size after first cytoreductive surgery, intervention name (active treatment after relapse), Race, Time since last disease progression, and Cancer Antigen-125 level elevation.
Following interventions will be included:
Paclitaxel (+/- Carboplatin)
Gemcitabine (+/- Carboplatin)
Topotecan
Pegylated Liposomal Doxorubicin (+/- Carboplatin, +/- Trabectedin)
Bevacizumab (+/- Gemcitabine/Carboplatin)

Scientific Abstract:
Background:
Ovarian cancer is the leading cause of gynecologic cancer mortality, responsible for an estimated 266000 new cases in 2013. Most patients will initially respond well to treatment, but unfortunately, approximately three quarters of all women treated will develop recurrent disease and will no longer be considered curable. Treatment after recurrence focuses on prolonging life and improving quality of life (Qol), but it heavily depends on the time since first relapse.
Objective:
To compare different treatment strategies (with or without platinum) for the relapsed, advance setting; including the newly added olaparib and bevacizumab, by using meta-analysis techniques (mixed treatment comparisons)
Study Design:
Meta-analysis of RCTs, Phase III trials, for Relapsed Ovarian Cancer Treatment, since 1994 up to now; to compare survival endpoints using the Cochrane Library Methodology. Comparative, non-interventional.
Participants:
Women with Relapsed Ovarian Cancer, in any condition and age, with at least one previous relapse to chemotherapy.
Main Outcomes and statistical Plan
Hazard Ratios and Odd Ratios of Overall Survival, Progression Free Survival, Time to Next Therapy, Treatment Related Serious Adverse Effects, Next Therapy choice. Also, a multivariate regression analysis using Individual Patient Level data; to stratify PFS and OS by
ECOG
Age
PFI (Platinum Free Interval) lenght
Treatment Choice (discrete variable)
Previous Cytoreductive Surgery (Secondary)
Time to First Subsequent Therapy
Third Line treatment

Brief Project Background and Statement of Project Significance:
The type and intensity of chemotherapy used routinely for women with advanced ovarian cancer has varied because of uncertainty
about the effectiveness of the different regimens. The objective of this review was to compare single therapies versus combinations of drugs:
platinum versus non-platinum based, and newer (maintenance or targeted therapies), by means of multi-variate analysis, in women with advanced, relapsed ovarian cancer.

To our knowledge, this will be the first study to analyze the true effects on Survival Endpoints in terms of a number of covariates , this will allow to predict the future success odds of incoming treatment strategies , and, ultimately, finding out optimal treatment strategies for patients-.

Specific Aims of the Project:
The study will evaluate predictive factors, by means of a multi-variate analysis, of the following dependent clinical endpoints:
Overall Survival
Progression Free Survival
Overall Response Rate
The main hyphotesis is to test whether any treatment (intervention) is found clinically superior to the others (at 95% statistical level significance), or, otherwise, there are other factors greatly impacting survival and/or progression rather than treatment strategies.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Preliminary research to be used as part of a grant proposal
Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
RCTs will be extracted from MEDLINE, Scopus, EMBASE, Cochrane Register of Trials, and Cancer Research registers of trials. We will also search for the proceedings of meetings and drug companies.
As long as the methodology involves Multi-regresion Analysis, access to Individual Patient Data is absolutely needed, and therefore, requested.
Inclusion Criteria: Women with Relapsed (confirmed diagnosis) Ovarian, Epithelian Cancer, with/out previous cytoreduction (primary and/or secondary) surgery.
Exclusion Criteria: None
Selection criteria
Randomised trials of:
(1) single non-platinum versus non-platinum combination chemotherapy
(2) single non-platinum versus platinum combination chemotherapy
(3) non-platinum regimen versus the same regimen plus cisplatin
(4) single platinum versus platinum combination chemotherapy
(5) maintenance based therapies (triplets) versus traditional schema (the above 1-4 named strata)

Main Outcome Measure and how it will be categorized/defined for your study:
Hazard Ratios (Credible Interval, assigned by Fixed and/or Random effects models weight) of OS, PFS, TFST (Time to First Subsequent Treatment)
Odds Ratio of Overall Response Rate and Treatment Related Serious Adverse Effects (measured along all follow-up times, or at least, within 60 months of observations).
Fixed effects model approach shall be used preferably, but it will depend on the found variability across trials (tested by Cochrane Q-Test and I2).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Age, Health Status, Platinum Free Intgerval Lenght, previous debulking surgeries (primary)), previous taxane based treatments, ascites presence, cancer-antigen 125 elevation, treatment arm (numeric), overall response rate to latest treatment (categorical), time from diagnosis (days), presence of metastases (y/n) to outside of ovary and fallopian tube.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
none.

Statistical Analysis Plan:
With the IPD from selected trials, we will stratify by:
Platinum Free Interval lenght (<6 and >6 months)
Age (<60 and >=60 years)
CA-125 elevation (2 * ULN, yes/no)
Previous Taxane (y/n)
Overall Response Rate (Progression vs. Non-progression)
Treatment arm
and other 2-3 variables

Then, we will run a multivariable analysis, taking Overall Survival and Progression Free Survival as dependent variables; whilst seeing, if at 95% level significance, any of the above variables are truly predictor of the outcomes -making a bootstrap approach-. Software to be employed is "R".

Then, we will test against a validation set, made of different trials, in which we might not be able to get the IPD, to check the prediction versus the real values.
Finally, an adjusted H.R. (using a matched adjusted comparisons and/or propensity scores) is to be found between the treatments included in the project.

Project Timeline:
Starting Date: ASAP
Publication Date: December 2016

Dissemination Plan:
ISPOR abstract: June 2016 (submission of previous findings)
Cochrane Library of Systematic Reviews: December 2016
The NEJM, 2017, full papers submission with key data and supplementary appendixes.