SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT

An international registry of the safety and efficacy in cancer patients with concurrent use of direct oral anticoagulants and targeted cancer therapies

Subcommittee

Malignancy & Haemostasis

Person responsible (Chair / Principal Investigator):

Chair: Marc Carrier

Principal investigator: Tzu-Fei Wang

Description Abstract

Targeted cancer therapies (such as imatinib, ibrutinib, sorafenib, crizotinib, and more) have been developed and utilized with increasing frequency in various cancer types. Direct oral anticoagulants (DOAC) are also increasingly used for treatment of venous thromboembolism (VTE) in cancer patients, given its availability in oral formulation and convenience. Recently, randomized controlled trials such as the Hokusai VTE Cancer study showed that edoxaban (a DOAC) was non-inferior to the standard therapy low-molecular-weight-heparin (LMWH) in the composite outcome of recurrent VTE and major hemorrhage for patients with cancer associated thrombosis[1]. While the risk of VTE recurrence may reduce with DOAC, the risks of major or clinical relevant non-major bleeding are shown to increase with DOAC as compared to LMWH for patients with cancer related thrombosis[1]. The Select-D study showed similar outcomes when rivaroxaban (another DOAC) was compared to LMWH[2]. These two studies did show the efficacy and safety of using DOAC for the treatment of at least selected cases of cancer related thrombosis. Many cancer patients also have atrial fibrillation that requires anticoagulation. DOACs are increasingly used for this situation as well.

While DOAC is thought to have less drug interactions compared to vitamin K antagonists, they are substrates of P-glycoprotein (P-gp) and/or CPY3A4, so drug interactions could be a concern with other medications metabolized by P-gp and/or CPY3A4. Many targeted cancer therapies are P-gp or CYP3A4 inducers or inhibitors. Unlike a vitamin K antagonist, laboratory testing to monitor DOAC level or therapeutic effects is not routinely available. Therefore, the effects of potential drug interactions with anticoagulation are largely unknown. In addition, some targeted cancer therapies such as ibrutinib could increase the risk of bleeding, and vitamin K antagonists are contraindicated in patients on ibrutinib, however, there are a paucity of data regarding the concurrent use of ibrutinib with DOAC. Some DOACs (such as edoxaban) have dose reduction recommendation during the time of concurrent use of P-gp/CAP3A4 inhibitors while others do not.

We aim to develop an international registry to evaluate the outcomes of patients on concurrent targeted cancer therapies and DOACs, in hope to provide more evidence for clinicians who may face the situation of concurrent use of both drugs. The objective of the study is to develop an interactional registry to evaluate the safety and efficacy of concurrent use of DAOCs and targeted cancer therapies. The primary outcome includes major bleeding defined by the ISTH criteria[3] within 6 months of concurrent therapy.

Secondary outcomes include VTE recurrence, arterial thrombotic events, clinically relevant non-major bleeding, and all-cause death within 6 months.

Design and methodology (Data expected to collect, sample size and statistical analysis):

This is a prospective, observational, international registry as a hypothesis-generating study.

We plan to recruit physicians who are members of ISTH to participate in the study by making registry announcements at annual meetings of the Standardization and Scientific Committees of the ISTH as well as by e-mail communications. We will ask physicians to enter de-identified information relating to patient and cancer specific variables into the online registry in a secure web page. We plan to include patients who are followed for at least 6 months, or until death if it happened prior to 6 months. As this is an observational registry and the duration of anticoagulation and cancer treatment are left to individual clinicians, patients do not have to have concurrent use for the full 6 months. The case report form will request the following de-identified patient information:

1. Patient and cancer baseline clinical characteristics
   - Gender
   - Age at the time of concurrent use
2. Characteristics of cancer treatment
   - Date of cancer diagnosis (at least year)
   - Type of cancer
   - Stage of cancer
   - Presence of brain metastasis
   - Type and dose of targeted cancer therapy
3. VTE characteristics (can omit for patients with atrial fibrillation only)
   - Date of diagnosis of VTE
   - Type and location of VTE
   - Other risk factors (such as surgery, hormone therapy)
4. Management of VTE
   - Anticoagulation type, dose, duration
   - Other management other than anticoagulation (i.e. IVC filter, serial ultrasound etc)
   - Duration of concurrent use of anticoagulation and targeted cancer therapy
5. Outcomes (within 6 months follow up)
   - Recurrent VTE (location, type, date, treatment)
   - Ischemic cerebral vascular events (location, type, date, treatment)
   - Major bleeding (location, type, date, treatment)
   - Clinically relevant non-major bleeding (location, type, date, treatment)
   - Cancer status (stable, improved, progression)
   - Mortality

Statistical analyses will be descriptive and non-comparative. We aim for a sample size of 100 for patients on DOAC for VTE and 100 for patients on DOAC for atrial fibrillation. Sample size is determined for convenience. Descriptive statistics (mean, standard deviation, median, and range) will be calculated for continuous variables while count and percentage distribution will be calculated for categorical variables.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Inclusion criteria

- Adult patients of at least 18 years old.
- Patients with active malignancy (histologically confirmed), defined as malignancy diagnosed or treated within the past 6 months or metastatic/recurrent malignancy (excluding in-situ skin cancer).
- Patients who have been taking one of the listed targeted cancer therapies (see list below) and any kind of DOACs concurrently.
- Patients with a minimum of 6 months of follow up from the initiation of concurrent use.
- The targeted cancer therapy drugs of interest are listed in the below table. This is not an exhausted list of targeted cancer therapy, but these drugs are particularly selected for their known metabolism through P-gp and/or CYP3A4 and are potentially at high risk of interaction with DOACs.

Category	**Medications**
BTK inhibitors	Ibrutinib Acalbrutinib
PI3Kinase inhibitor	Idelalisib
BCR-ABL inhibitors	Imatinib Dasatinib Nilotinib Bosutinib Ponatinib
VEGF inhibitors	Sunitinib Sorafenib Regorafenib Vandetanib Pazopanib Axitinib Cabozantinib Lenvatinib Axitinib
EGFR, ALK inhibitors (lung cancer)	Erlotinib Crizotinib Osimertinib Alectinib Ceritinib Afatinib
HER2 inhibitors (breast cancer)	Lapatinib
BRAF inhibitor (melanoma)	Dabrafenib Vemurafenib
mTOR inhibitor	Everolimus (both CYP3A4 and P-gp inhibitors)

Expected timeline:

Project stage/set up -- 6 months
Launch – 2-3 months
Duration – 2-3 years for recruitment
Finalization/analysis – 3 months
Reporting – 3 months

Expected outcomes (ie. publications):

Once the initial enrollment goal is reached, we plan to publish the results as an original article in a peer-review journal. Depending on the speed of recruitment and the outcome of the study, considerations may be made to expand the study to include a bigger population of patients.

Publication type (SSC Communication, Guidance document or original article):

Original article in a peer-review journal

Description of project set/up and management, needed infrastructure and resources (summary):

We plan to use the ISTH REDCap platform to generate case report forms and for data collection on a secure webpage where all investigators can input de-identified data. Support for REDCap set-up and project creation are highly appreciated and needed. Support from the SSC and ISTH to promote the registry and encourage participation from members will also be sought. If funding is available, we plan to give investigator/site $100 per patient enrolled, to cover staff time for patient enrollment and data entry. It is estimated that $20,000 would be needed for the planned 200 patient enrollment.

Possible references:

1. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia DA, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang T-F, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med.* 2018;378(7):615-624.
2. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs R, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36(20):2017-2023.
3. Schulman S, Kearon C, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-694.