Deliverable 4 – Health Analytics Project Submission

# Introduction

Thrombocythaemia represent in various myeloproliferative disorders, including chronic myeloid leukaemia, agnogenic myeloid metaplasia, and essential thrombocythaemia (ET) (Sanchez & Ewton, 2006), which is characterized by platelet production increase, and elevated platelet counts (Spencer & Brogden, 1994). Thrombocythaemia is usually seen in elderly patients, and could be dangerous, as the increased number of platelets might cause dangerous complications such as systemic thrombosis (Xiong et al., 2017). Thus, there is an essential need for drug development to limit the patient’s platelet count in normal range, in order to minimize the risk of the potential cardiovascular adverse effects.

Anagrelide is an orally active quinazolin, which is known for causing thrombocytopenia, and has thus been evaluated for treating thrombocythaemia (Spencer & Brogden, 1994). Anagrelide is approved by FDA in 1997 in order to treat essential thrombocythemia, under then commercial name of AGRYLIN by Roberts Pharmaceutical. In the associated clinical trial, among a total of 551 patients, the most frequently reported adverse reactions were headache, palpitations, diarrhea, and abdominal pain (Solberg Jr et al., 1997). Patient thrombosis data was not included in this clinical trial.

Hydroxyurea is a time-tested older drug, which has been widely used to treat sickle cell disease in 1980s (although FDA has not approved its usage until 1998) (Okam, Shaykevich, Ebert, Zaslavsky, & Ayanian, 2014). Compared with newer drugs, hydroxyurea is also cost-effective. The cost for hydroxyurea oral capsule 500 mg is around $78 for a supply of 100 capsules, while the cost for Anagrelide oral capsule 0.5 mg is around $273 for a supply of 100 capsules (Drugs.com, 2019).

In 2012, a clinical trial in 2012 compared 122 patients treated with Anagrelide and 137 treated with Hydroxyurea suggest that both groups show similar risk of all kinds of thrombosis, including major/minor arterial/venous thrombosis, and concluded that “Anagrelide as a selective platelet-lowering agent is not inferior compared with hydroxyurea in the prevention of thrombotic complications.” (Gisslinger et al., 2013) However, a more recent research article published in 2019 checked the Anagrelide clinical trials back in the 1990s, and noticed that the thrombosis-free survival data for ET patients diagnosed before the 1997 FDA approval date is significantly better compared with that after the 1997 FDA approval date (Tefferi et al., 2019). In more recent literature review, transfusion experts suggest directly that the main indication for treatment in ET is to prevent thrombosis, and that “none of the newer drugs have been shown to be superior to the time-tested older drugs (e.g., hydroxyurea).” (Tefferi, Vannucchi, & Barbui, 2018). These works indicate that it is beneficial to compare Anagrelide with Hydroxyurea on the risk of thrombosis, using a broader data generated in actual clinical practice.

One of the driving force for the development of Anagrelide is that Hydroxyurea has been reported for being related with cancer risk. For example, Nand et. al. reported that hydroxyurea has J–U.V% risk of causing leukemic transformation ([ref] Nand, Stock, Godwin, & Fisher, JVVC). Hanft et. al. further suggested that in vivo hydroxyurea exposure could cause acquired DNA mutations ([ref] Hanft et al., L<<<). Thus, whether such suggestions against hydroxyurea is reasonable, and whether the alternatives thereof, such as Anagrelide, could perform better in cancer risk, will need to be investigated.

Angiotensin-converting enzyme (ACE) inhibitors are factors that prevent an enzyme from producing angiotensin II which subsequentially narrows down vessels. Since angiotensin II releases substances that raise blood pressure, ACE inhibitors also have the effect of lowering blood pressure (“Angiotensin-converting enzyme (ACE) inhibitors - Mayo Clinic,” n.d.). Examples of ACE inhibitors include Accupril (Quinapril), Aceon (Perindopril), Altace (Ramipril), Benazepril (Lotensin), Capoten (Captopril), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril), Mavik (Trandolapril) and Moexipril (Univasc) (“Types of ACE Inhibitors for Heart Disease Treatment,” n.d.).

Note:

The original question was:

In patients undergoing treatment for thrombocythemia, does those that have been treated with Anagrelide has a higher risk of thrombosis, compared with a more conventional alternative, Hydroxyurea?

# Patient Counts

* [hxia40] patients taking Anagrelide

<http://gt-health-analytics-1.us-east-1.elasticbeanstalk.com/#/cohortdefinition/446>

* [hxia40] patients taking Hydroxyurea

<http://gt-health-analytics-1.us-east-1.elasticbeanstalk.com/#/cohortdefinition/449>

* [hxia40] cancer patients exposed to either drug

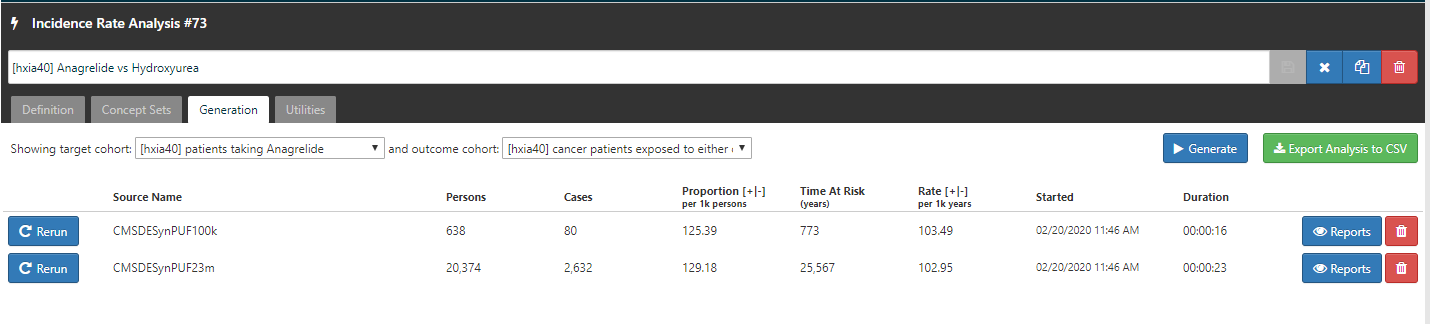
<http://gt-health-analytics-1.us-east-1.elasticbeanstalk.com/#/cohortdefinition/452>

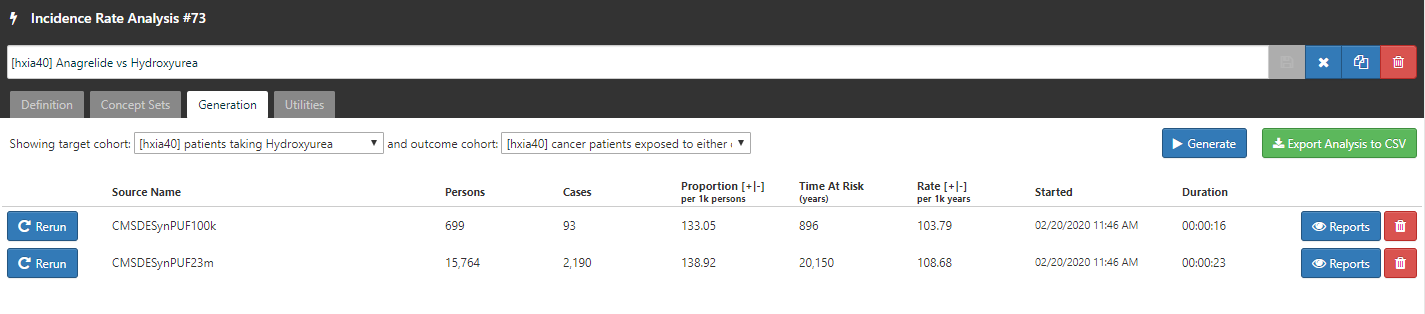
Patient counts in both datasets:

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort | Patients taking Anagrelide | Patients taking Hydroxyurea | Cancer patients exposed to either drug |
| CMSDESynPUF100k | 638 | 699 | 172 |
| CMSDESynPUF23m | 20,392 | 15,774 | 4,801 |

# Incidence Rates

Among patients taking Anagrelide, 125.39/1,000 patients in the 100k dataset and 129.18/1000 patients in the 23m dataset were diagnosed with cancer. The incidence rates per 1k years are 103.49 and 102.95. Among patients taking Hydroxyurea, 133.05/1000 in the 100k dataset and 138.92/1000 patients in the 23m dataset were diagnosed with cancer. The incidence rates per thousand years are 103.79 and 108.68. Results are shown as below:





<http://gt-health-analytics-1.us-east-1.elasticbeanstalk.com/#/iranalysis/73>

# Cohort Characterization

<http://gt-health-analytics-1.us-east-1.elasticbeanstalk.com/#/cc/characterizations/65/design>