From: Rivera, Donna (NIH/NCI) [F]
To: "Barbara Galligan"; Benjamin Chan
Cc: Meghan A Soulsby; Barbara M. Galligan (bgalligan@ucdavis.edu)
Subject: RE: Hand off discussion
Date: Wednesday, June 29, 2016 11:35:05 AM

Hi all,

The incidence by age is quite variable. In AML, incidence is higher in adults, however it is a common childhood cancer. See attached.

Donna

From: Barbara Galligan [mailto:bmgalligan@gmail.com]
Sent: Wednesday, June 29, 2016 1:09 PM
To: Benjamin Chan <chanb@ohsu.edu>
Cc: Meghan A Soulsby <masoulsby@ucdavis.edu>; Barbara M. Galligan (bgalligan@ucdavis.edu) <bgalligan@ucdavis.edu>; Rivera, Donna (NIH/NCI) [F] <donna.rivera@nih.gov>
Subject: Re: Hand off discussion

Hi Ben,

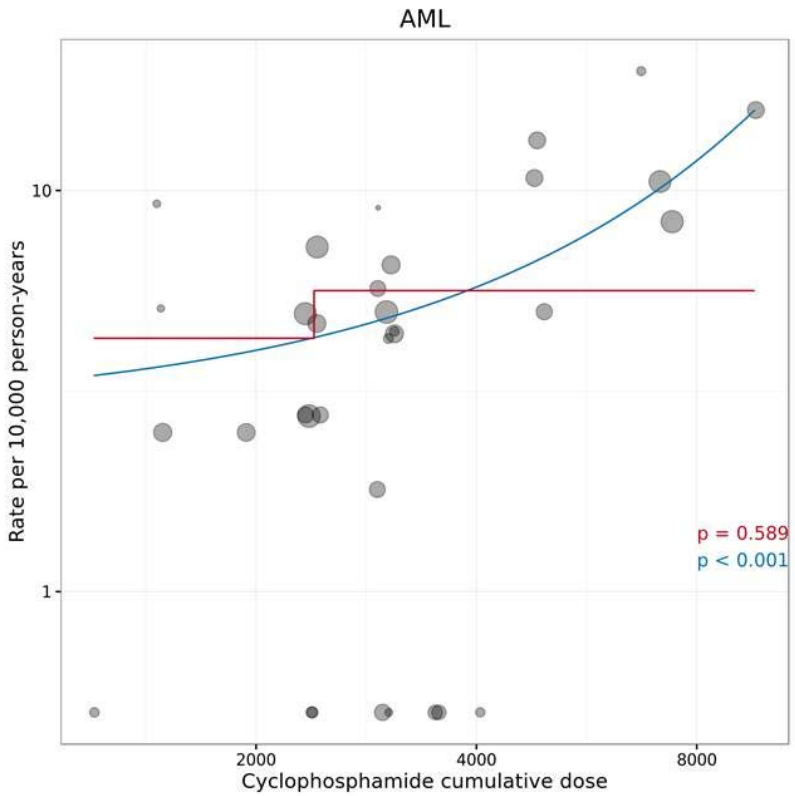
The "all ages" could be a problem. We would want the data for adult population (age > 18). I don't know off the top of my head if childhood rates are higher than adults.

It's OK that it's "all sexes, all ages" because we are looking for baseline incidence in adults.

Barbara

On Wed, Jun 29, 2016 at 7:30 AM, Benjamin Chan <chanb@ohsu.edu> wrote:

> Barbara, Meghan,
>
> I reran the meta-regression models for AML alone. The predicted incidence rates from the model are still a magnitude order higher than the SEER incidence rates Donna provided. Note: my incidence rates are per 10,000 person-years. SEER's is per 100,000 p-y. I did notice that the roughly 4 per 100,000 number from SEER is "All Ages All Races Both Sexes". Could this explain our higher incidence rate?



drug	x	xHighDose	malType	predLin	confLowerLin	confUpperLin	predBin	confLowerBin	confUpperBin	scale
Cyclophosphamide	1200	FALSE	AML	3.46	2.37	5.05	4.28	1.22	15.02	10000
Cyclophosphamide	1500	FALSE	AML	3.65	2.55	5.22	4.28	1.22	15.02	10000
Cyclophosphamide	2000	FALSE	AML	4.00	2.89	5.52	4.28	1.22	15.02	10000
Cyclophosphamide	2400	TRUE	AML	4.30	3.19	5.78	5.63	2.31	13.71	10000
Cyclophosphamide	3000	TRUE	AML	4.79	3.68	6.23	5.63	2.31	13.71	10000

Cyclophosphamide	3600	TRUE	AML	5.34	4.22	6.77	5.63	2.31	13.71	10000
Cyclophosphamide	4000	TRUE	AML	5.74	4.59	7.19	5.63	2.31	13.71	10000
Cyclophosphamide	4800	TRUE	AML	6.64	5.35	8.25	5.63	2.31	13.71	10000
Cyclophosphamide	6640	TRUE	AML	9.27	7.02	12.25	5.63	2.31	13.71	10000
Cyclophosphamide	7200	TRUE	AML	10.26	7.51	14.03	5.63	2.31	13.71	10000
Cyclophosphamide	9600	TRUE	AML	15.86	9.71	25.90	5.63	2.31	13.71	10000

From: Benjamin Chan
Sent: Wednesday, June 29, 2016 12:26 AM
To: 'Meghan A Soulsby'
Subject: RE: Hand off discussion

Meghan, I reran the non-breast solid meta-regressions. Not much difference from before. Barbara's take on the analysis still holds. Click the PNG links from below. Correcting the cyclophosphamide dose data for Colleoni didn't change the analysis; they didn't report any malignancies (NA, not 0).

AFTER: https://github.com/benjamin-chan/SecMalAfterBreastCaACT/blob/1.3.0/README.mdhttps://github.com/benjamin-chan/SecMalAfterBreastCaACT/blob/1.3.0/README.md
BEFORE: https://github.com/benjamin-chan/SecMalAfterBreastCaACT/blob/1.2.1/README.mdhttps://github.com/benjamin-chan/SecMalAfterBreastCaACT/blob/1.2.1/README.md

One thing I think I can do before Thursday's call is "break-out our data by AML". The SEER data Donna provided had incidence for AML only. And our AML + MDS incidence seemed really high.

From: Benjamin Chan
Sent: Tuesday, June 28, 2016 11:33 PM
To: 'Meghan A Soulsby'
Subject: RE: Hand off discussion

Meghan, I saw your note about Colleoni (2009). I'm going to put in 600 for the cyclophosphamide dose for the EC regimen (same as the AC-CMF regimen). There wasn't one being read in on from the spreadsheet. I think it might be a merged cells issue. So cumulative dose is 600 * 3 = 1800. Let me know if you disagree. Otherwise, no reply needed.

From: Benjamin Chan
Sent: Tuesday, June 28, 2016 10:53 AM
To: 'Meghan A Soulsby'
Subject: RE: Hand off discussion

Hi Meghan, I'll get to rerunning the analysis tonight. Getting slammed this week and guessing the revisions won't change the direction of the manuscript. Need to digest what Barbara wrote too.

From: Meghan A Soulsby [mailto:masoulsby@ucdavis.edu]
Sent: Monday, June 27, 2016 1:41 PM
To: Benjamin Chan
Subject: RE: Hand off discussion

Hi Ben,

Attached is the revised spreadsheet. A few changes to the solids but nothing drastic. I've also posted this to box, as well as the manuscript appendix table.

Thanks,
Meghan

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From: Meghan A Soulsby
Sent: Monday, June 27, 2016 11:28 AM
To: Ben Chan (chanb@ohsu.edu)
Subject: RE: Hand off discussion

Hi Ben,

I am nearly finished triple checking the non-breast solid incidence data and there are a couple of slight changes – will have that to you today

Meghan

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From: Barbara M. Galligan
Sent: Monday, June 27, 2016 11:26 AM
To: Joy Melnikow; Meghan A Soulsby; Benjamin Chan
Subject: Hand off discussion

Hi Team

It's been an exciting week with a lot of interesting work. I'd like to highlight some future directions and plan my hand-off.

As I mentioned last month, I finish at UCD this week. Tomorrow (6/28) is my last day at UC Davis. I also will be out of contact July 1 - mid-Setember. I can be on the conference call 6/30, but that's probably not the best forum to hand off the entire project in detail.

My thoughts so far:

Regarding the project:

In the past two weeks we have updated our data for risk of secondary / therapy-related AML/MDS . We showed statistically significant dose-dependent increases in AML/MDS with cyclophosphamide and taxanes.

We also obtained SEER data for AML risk. Our combined risk AML/MDS is much higher than SEER incidence data on AML. This may be because we combined MDS/AML, so we are asking for more SEER data from Donna to better evaluate combined MDS/AML

Given the information we have, the SEER data, and past research, we have more areas of work that need to be addressed. I'm concerned about the following:

1) We expect an increased risk of SM with alkylating agents, especially with cumulative increases in cyclophosphamide, but our reported risk is coming in much higher than SEER data. We need to

- review SEER data for MDS
- break-out our data by AML and MDS and see if it's more comparable to the SEER results
- break-out the results by patient age (< 65 >)

2) We would expect an increased risk in AML/MDS following anthracycline use. Should see this 2-3 years after therapy. We are not seeing this increase in our data. We need to

- look for an explanation of this discrepancy from commonly understood risk of anthracycline

3) We typically would not expect an increase in risk with taxane use. Our research shows increased use with the taxanes. We need to

- explain discrepancy in risk of taxanes from prior research

4) There are clear risks associated with radiation therapy. The most recent data (Registry cohort out of Swedish Cancer Center) only found increased risk in young patients treated with radiation or radiation plus chemotherapy, not in chemotherapy alone . The older studies also confirmed the importance of radiation therapy. We need to:

- stratify our results by radiation received yes/no
- stratify our results by age (65 y/o)

To summarize –
I think digesting this meta-analysis by cumulative dosing of single agents of chemotherapy was a helpful way to organize the information. Now that we see those results in the context of the entire field of research I'm concerned that our results are diluted down and over-simplified, partly because not all the studies in our analysis provide all the information we are looking for. Given the amount of effort put in to date, we should try to address:

- separating out MDS and AML results
- our data compared with SEER incidence

- why our rates with alkylating agents are so high
- why we do not see increased risk with anthracyclines
- why the unexpected risk with taxanes
- what is the impact of radiation
- stratifying results by age (< 65 >)

Regarding the hand-off:

Please let me know the best way for me to communicate with the team to make the transition smooth.

Of note - there are two Jr Faculty here at UCD who research secondary AML. I e-mailed them to see if they would be interested in talking with us about this project. There is a lot of complex and conflicting data in this field, so having an AML expert advise and guide the next writer would be invaluable. It's possible that we could find something new and robust with our meta-analysis, but we need to explain it in context of the prior results as well.

I am attaching a revised version of the initial draft of work. It has the new data and a lot of the issues I brought up above written in to the document with references.

Can't wait to see all this good work come to fruition! Megan and Ben have my gmail address - bmgalligan@gmail.com and cell 510-637-9498.

Barbara