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TOXICITY OF INTRA-CSF BIOLOGIC AGENTS IN PATIENTS WITH NEOPLASTIC MENINGITIS

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ABSTRACT

Introduction

Neoplastic meningitis (NM) is a profoundly morbid, almost inevitably fatal, and increasingly common complication of cancer. Despite multimodal therapy, prognosis is dismal with a median survival of 2-3 months. Disease resistance has usually been blamed for this poor outcome, but therapeutic nihilism and a paucity of treatments considered suitable for intra-CSF administration may play a more important role. Biologic agents represent one of the most active therapies for extra-CNS malignancies, but often have limited access to the CSF when administered systematically, and have not been widely used for intra-CSF administration. We describe the safety and efficacy of tumor-specific, intra-CSF biologic therapy in a large group of patients with neoplastic meningitis.

Methods

We interrogated the database of an international neoplastic meningitis registry (NeMeRe) to identify all patients with neoplastic meningitis who received at least one dose of an intrathecal biologic agent as part of their neoplastic meningitis-directed therapy. Patient demographics, treatments, toxicity, and outcome data were extracted and analyzed.

Results

We identified 110 patients who received an intrathecal biologic agent as part of a histology and molecular profile-adjusted intraventricular chemotherapy treatment approach. These agents included rituximab (45 patients with lymphoma, 193 cycles), trastuzumab (40 patients, 207 cycles in patients with malignant primary brain tumors, 13 patients and 138 cycles in patients with breast cancer), panitumumab (2 patients with lung cancer, 3 cycles), and alpha-interferon (7 patients with melanoma, 22 cycles). Grade III toxicity occurred in 8.8% of rituximab, 4.6% of trastuzumab, and 0% of panitumumab and alpha-interferon-containing cycles. There was no grade IV or V toxicity. Median survival in patients with lymphomatous meningitis (348 days), solid tumor NM from primary brain tumors (219 days), HER-2+ breast cancer (315 days), and melanoma (307 days) was encouraging. No difference in survival was seen between patients with or without treatment-related toxicity in any histologic group.

Conclusions

This large patient series suggests that rituximab, trastuzumab, panitumumab, and alpha-interferon may be safely administered into the CSF, and, as part of a multi-agent intra-CSF treatment regimen, does not appear to compromise survival. More widespread use of these agents, and prospective evaluation in appropriate patient populations is warranted.

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INTRODUCTION

Neoplastic meningitis (NM) is an almost always rapidly debilitating and inexorably fatal complication of both extraneural cancers and primary brain tumors. This complication afflicts at least 3-5% of all cancer patients, although incidences vary according to tumor type, and both underdiagnosis and underreporting are widespread[1]. Prognosis is dismal, with a median survival for all patients in randomized controlled trials of 2-3 months, and little variation according to underlying tumor histology[1].

Standard treatment for NM includes radiation to sites with bulky leptomeningeal disease and to sites producing disabling symptoms, as well as optimum systemic therapy for disease outside of the nervous system, but the mainstay of treatment consists of intrathecal chemotherapy delivered through a ventricular reservoir. While many agents have been investigated for intrathecal administration, and eleven are available for routine use [2-5], in practice nearly all patients receive single-agent therapy with one of several drugs: methotrexate, cytarabine, or liposomal cytarabine. Although biologic agents including trastuzumab, rituximab, panitumumab, and alpha-interferon play an important role in the treatment of extraneural malignancies, intrathecal administration of these agents has been described only in case reports, a few small case series, and one formal phase I trial [6-20], and concerns regarding toxicity have prevented their widespread use. We have routinely incorporated these four biologic agents into multi-agent intrathecal chemotherapy regimens for patients with neoplastic meningitis for the last seven years. We now report on our experience, focusing on toxicity and also presenting preliminary response data.

PATIENTS AND METHODS

Since June 1st, 2010, all patients seen under the auspices of the neuro-oncology service at Penn State Hershey Medical Center have been enrolled, and their data recorded, in an international neoplastic meningitis registry (NeMeRe), currently with 12 participating sites in the United States, Canada, and Europe. Data is extracted from patients' electronic medical records, and is entered into a HIPAA-compliant REDCap (Research Electronic Data Capture) database. REDCap is a secure, web-based application designed to support data capture for research studies[22]. All registry participants have obtained institutional IRB approval both for data entry and for the use of de-identified data to support research studies. For this investigation, we identified from the database all patients $\geq$ 18 years of age who had received intrathecal trastuzumab, rituximab, panitumumab, or alpha-interferon as part of their NM-directed therapy between June 1st, 2010 and November 20th, 2016. Patient demographics, treatments, toxicity, and response data were extracted. Any recorded adverse event following the administration of the intraventricular biologic agent was counted as a treatment-related toxicity. Demographic information is presented as means and standard deviations for interval data; medians and percentiles for ordinal data; and proportions for nominal data. Comparisons between groups were calculated using t-tests and Fisher exact tests as appropriate. Survival data is presented using Kaplan-Meier curves, and differences in survival between groups were analyzed using Wilcoxon and log rank tests. A p-value ≤ 0.05 was considered statistically significant. All calculations were made using R[23] and the "survminer" survival analysis package[54]

RESULTS

One hundred and ten patients were identified in the registry who had received at least one dose of intrathecal trastuzumab, rituximab, panitumumab, or a-IFN, either as a single agent or in combination with other intrathecal drugs. All agents were administered intraventricularly through an Ommaya reservoir.

Table 1.

Demographic Characteristics of Study Patients					
Treatment	Rituximab	Trastuzumab	Alpha-Interferon	Panitumumab	Total
Patient #	45	57	7	2	110
Age (mean, SD)	63.8, 13.4	55.1, 13.4	55.1, 14.6	69.5, 2.03	58.8, 13.0
Male/ Female	25/20	25/32	3/4	1/1	54/57
KPS (mean, SD)	68.6, 12.0	73.3, 11.7	74.3, 7.87	65, 35.4	70.7, 12.7
Cycle #	193	350	22	3	568
Toxicity Cycle #	17	16	0	0	33

Note. This table outlines the demographic information of patients by treatment, including incidence of toxicity. Due to one patient receiving at least one treatment cycle of both rituximab and trastuzumab, the total in the patient row adds to 111, though only 110 are present in the study. Additionally, in this table, KPS refers to Karnofsky Performance Scale, which is a non-linear approximation of overall patient health from 100 (perfect health) to 0 (death).

A total of 568 cycles of some intraventricular biologic agent were administered. There were no grade IV or grade V toxicities. Grade III toxicity occurred in 33 cycles (5.8%) and in 17 individual patients. Of these, 16 episodes of grade III toxicity occurred in patients receiving trastuzumab (4.6% of all trastuzumab-containing cycles), and 17 in patients treated with rituximab (8.8% of all rituximab-containing cycles). In 15 of the 33 observed episodes of grade III toxicity (45.5%), the biologic agent was co-administered with a second chemotherapy agent. No episodes of grade III or greater toxicity were seen in patients receiving intraventricular a-IFN or panitumumab.

Table 2.

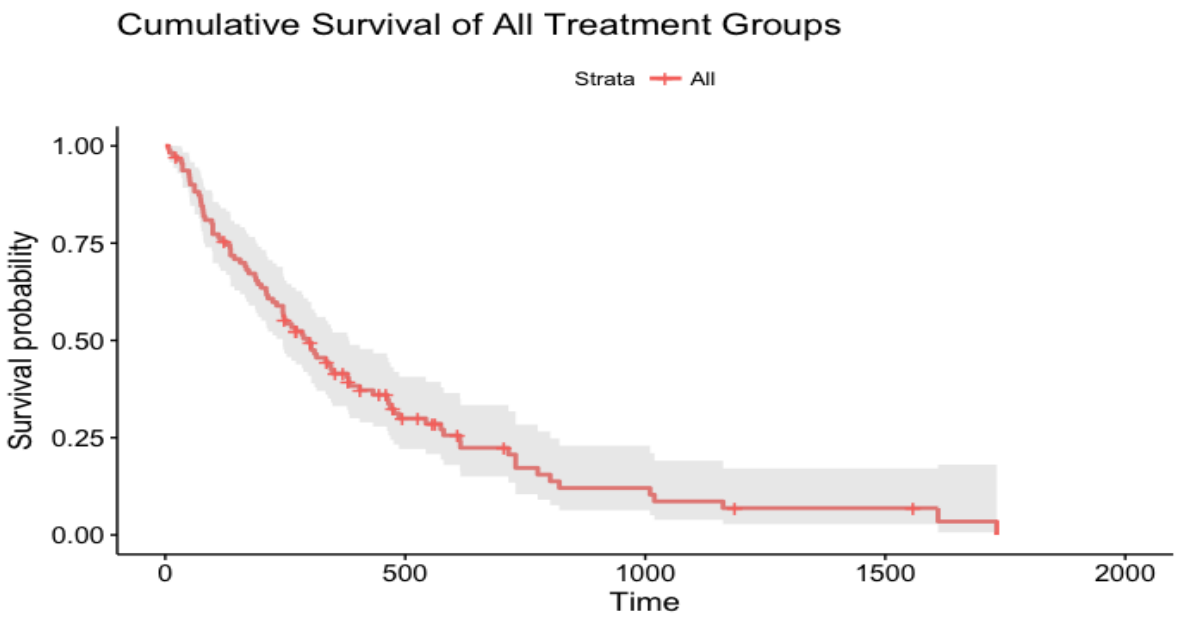
Types of Grade III Toxicity		
Drug	Rituximab	Trastuzumab
Bacterial meningitis	1	0
Chemical meningitis/ arachnoiditis	2	3
Headache	3	5
Fever	2	0
Encephalopathy/ confusion	4	2
Myelosuppression	1	0
Memory loss or dementia	0	2
Gait impairment	0	2
Nausea	2	2
Other	2	0

Note. This table outlines toxicities by treatment cycle.

Median survival for all 110 patients in this cohort was 297 days [95% CI: 200-382]. There was no statistically significant difference in overall survival between patients who experienced at least one episode of grade III toxicity and those who experienced no grade III toxicity (median

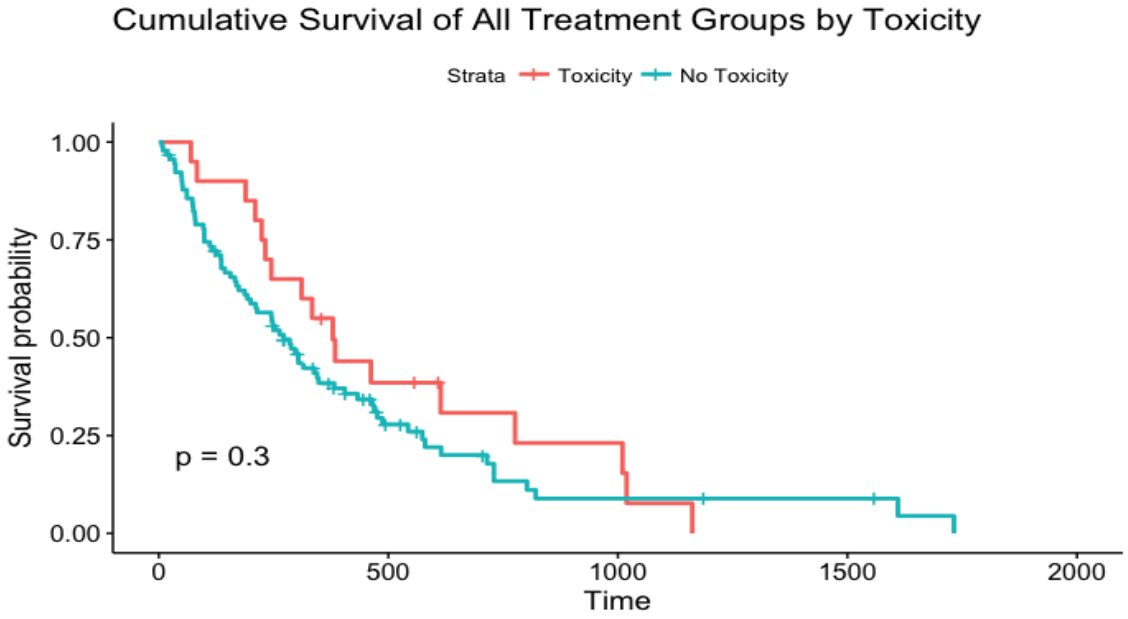
survival 379 vs. 272 days, log rank p = .3). The same pattern was observed when survival was calculated by tumor histology.

Figure 1.



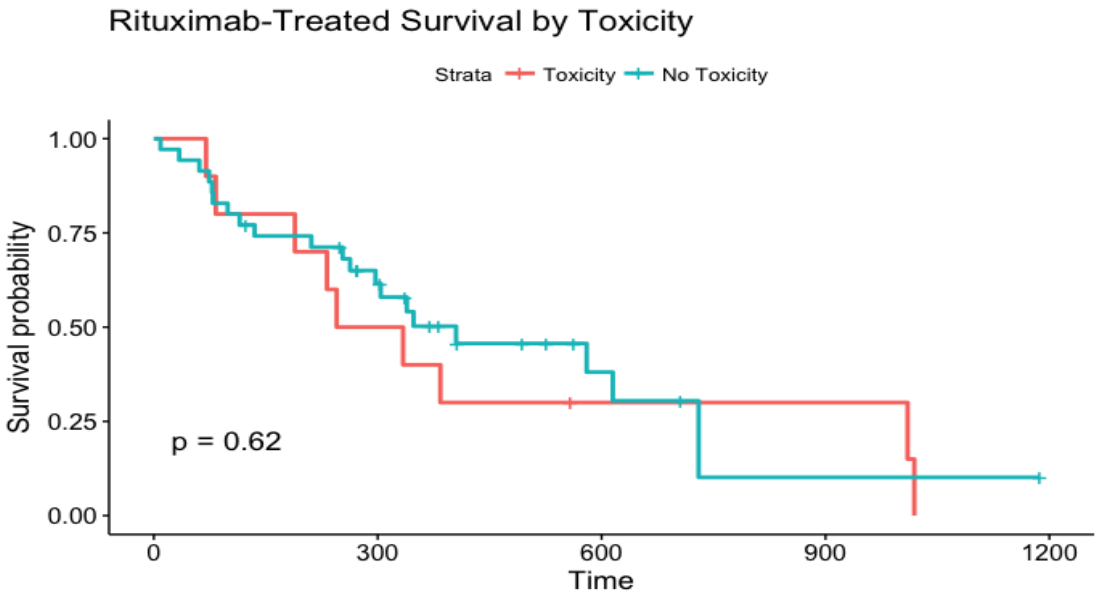
Note. This Kaplan-Meier survival curve outlines patient survival over all treatment groups and tumor histologies. The 95% confidence interval is outlined in grey. Censored data points are represented by crosses on the main graph line.

Figure 2.



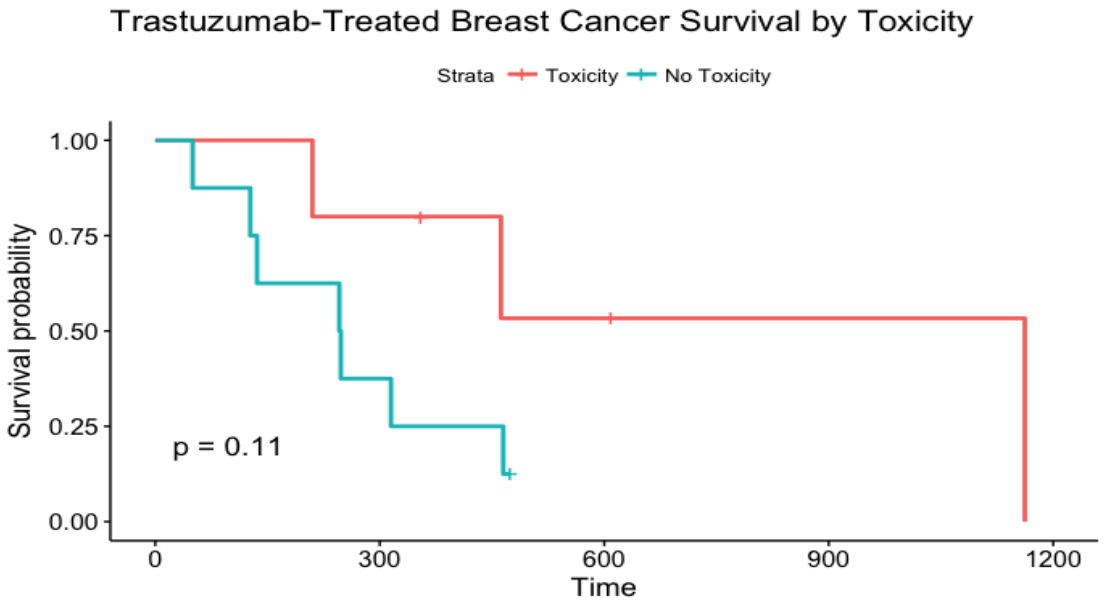
For patients with lymphomatous meningitis (all of the patients receiving intraventricular rituximab), median survival was 348 days [95% CI: 263-730]. Survival among those who experienced and did not experience toxicity were 290 vs. 405 days (Wilcoxon p = .62).

Figure 3.



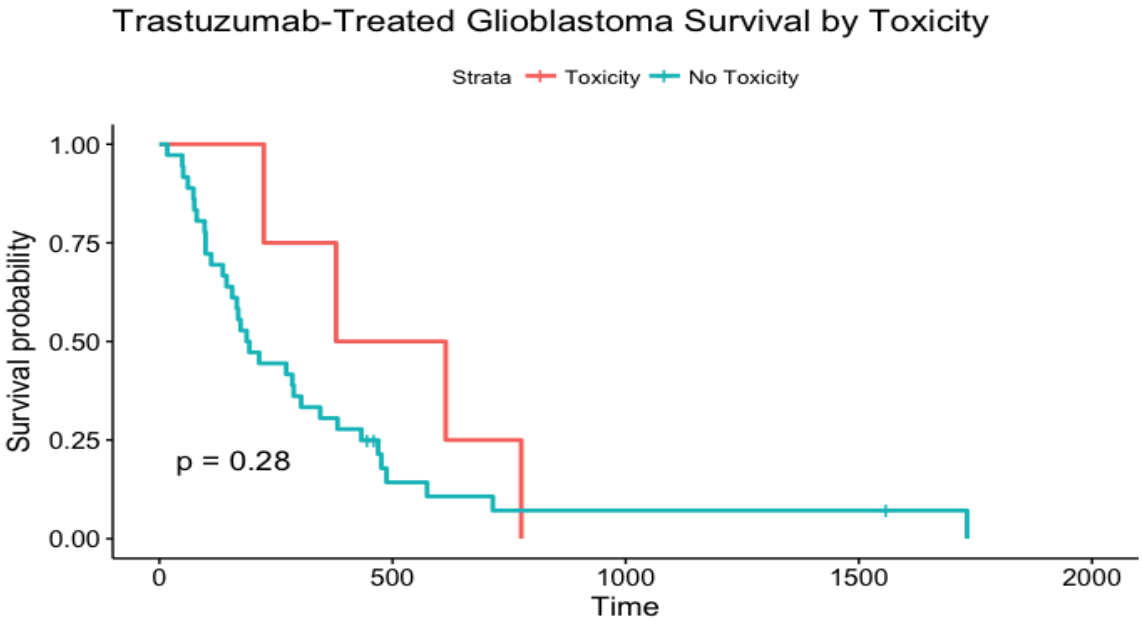
Due to significantly different clinical outcomes, the survival and the effects of toxicity in patients suffering from breast cancer-derived and glioblastoma multiforme-derived NMs were evaluated separately. For patients with NM from HER-2+ breast cancers (all of whom received intraventricular trastuzumab), median survival was 315 days [95% CI:210-NA]. Survival among those who experienced and did not experience toxicity were 1162 vs 247 days (log rank p = .11).

Figure 4.



For patients with NM from glioblastomas, median survival was 219 days [95% CI:166-382]. Survival among those who did and did not experience toxicity were 496 vs. 190 days (log rank p = .28).

Figure 5.



DISCUSSION

Patients with NM are frequently burdened by multiple neurologic deficits, and must often also contend with treatment- and disease-related symptoms caused by their systemic chemotherapy and extraneural cancer. Clinicians are frequently reluctant to add intrathecal chemotherapy to the treatment regimens of these patients both because of doubts regarding therapeutic benefit and concerns about additional toxicity which might interfere with systemic treatment and compromise quality of life. Complicating the decision about whether to initiate intrathecal chemotherapy further is the paucity of published experience regarding the intrathecal administration of all but a few chemotherapeutic agents. As a result, even if the decision to begin treatment is made, the armamentarium from which most clinicians select is limited to a few agents, including methotrexate, cytarabine, and liposomal cytarabine. Occasionally, thiotepa and rituximab are also used, but the range of malignancies for which these agents are best suited is relatively small. Information which would allow clinicians to confidently expand this armamentarium to include not only rituximab, but additional biological agents such as trastuzumab, panitumumab, and alpha-interferon would broaden the range of tumors for which potentially effective intrathecal therapy exists. In this paper we present evidence that these four biologic agents – rituximab, trastuzumab, panitumumab, and alpha-interferon – are safe when administered intrathecally to patients with NM from a range of primary tumors including lymphoma, breast cancer, lung cancer, melanoma, and primary brain tumors. In a cohort which included 110 patients and 568 cycles of therapy, we identified no episodes of grade IV or V toxicity, and observed a frequency of grade III toxicity of only 5.8%. More specifically, this included grade III toxicity rates of 4.6% in 57 patients (350 cycles) treated with intrathecal

trastuzumab, and 8.8% in 45 patients (193 cycles) treated with rituximab. In addition, in 15 of the 33 episodes of grade III toxicity, the biologic agent (trastuzumab or rituximab) was administered together with a second chemotherapy agent. The observed toxicity might, therefore, have been related to the second agent, or to the combination of drugs. Although our numbers were small (2 patients and 3 cycles for panitumumab, 7 patients and 22 cycles for alpha-interferon) we saw no grade III, IV, or V toxicity in any patient receiving either of these two agents.

Although the primary focus of our study was to report on the toxicities associated with intraventricular administration of biologic agents in patients with NM, the question of efficacy is also a critical component of the decision to use these drugs. Overall survival for our entire cohort of 110 patients was 297 days, substantially better than for patients with NM participating in any randomized controlled trial (range 56-84 days), and this pattern persisted irrespective of tumor histology. Our study was not designed to show a difference in survival between cohorts of patients receiving or not receiving intraventricular biologic agents, and we cannot claim that the impressive survival results seen in our patients were causally related to those agents. Nevertheless, these results do suggest that toxicity is not increased, and survival is not compromised by such therapy.

Although the number of episodes of grade III toxicity was small, we did not identify any predictors of toxic events, including age, gender, or performance status. Overall, and for each biologic agent individually except for rituximab, survival was longer (though not statistically significantly longer) in patients who experienced grade III toxicity compared to those who did

not. This may simply be a chance observation, or may reflect the presence of a more vigorous immune response in patients who experienced some form of toxicity.

The list of chemotherapeutic agents which can safely be administered into the cerebrospinal fluid is quite limited compared to the armamentarium available for systemic administration. Based on our experience, we suggest that rituximab, trastuzumab, panitumumab, and alpha-interferon should be added to that list. While these four agents are not relevant to all tumor histologies, they are applicable to several large and important tumor types which commonly involve the CSF. Overall, diffuse large B-cell lymphomas invade the CSF in approximately 7% of cases, but depending on a variety of clinical and laboratory features, this number can be many times higher [21,24-40]. Almost all these tumors are amenable to treatment with a CD-20-targeted agent such as rituximab. Since almost no rituximab reaches the CSF when administered systemically[19, 41, 42] this constitutes an important addition to intrathecal armamentarium. Patients with HER2-positive breast cancer represent a subset of breast cancer patients with a high frequency of NM (as high as 30-40%) [9, 43]. Trastuzumab is an important therapeutic agent for the approximately 30% of breast cancer patients harboring this molecular abnormality[6, 44, 45], and for the much smaller cohorts of patients with HER2-positive tumors involving the gastrointestinal tract[45], but trastuzumab does not penetrate the CSF in clinically meaningful concentrations following intravenous administration [9]. HER2 positivity (at least immunochemically) is also very common in adults with malignant primary brain tumors, including glioblastomas, anaplastic gliomas, and medulloblastomas [7]. Although EGFR exon 19 mutations are relatively uncommon in patients with lung cancer (10-26%) [47, 48], when present, panitumumab has the potential to substantially improve the outcome of therapy[8], and, like rituximab and trastuzumab, does not achieve

clinically relevant concentrations following systemic administration. Finally, alpha-interferon has been a mainstay of therapy for malignant melanoma[49, 50], a disease with a very high frequency of leptomeningeal metastases (1-5%)[1, 49]. We hope that our observations of modest toxicity and promising treatment outcomes will stimulate the necessary prospective evaluations of rituximab, trastuzumab, panitumumab, and alpha-interferon in appropriate patient populations, and will encourage investigators to explore the safety and efficacy of intrathecal administration of other targeted agents.

APPENDIX A

Table 3.

Therapeutic Combinations by Treament Cycle					
Treatment	Rituximab	Trastuzumab	Alpha-Interferon	Panitumumab	Total
Methotrexate	111	77	0	1	189
Topotecan	5	137	0	0	142
Etoposide	30	2	20	0	52
Liposomal Cytarabine	5	1	0	1	7
Other	0	3	2	1	6
Mono-Therapy	42	130	0	0	172
Total	193	350	22	3	568

Note. This table summarizes the concurrent intrathecal treatments received by treatment cycle for each biologic agent

Table 4.

Treatment by Cancer Type					
Treatment	Rituximab	Trastuzumab	Alpha-Interferon	Panitumumab	Total
Breast Cancer	0	13	0	0	13
Esophageal Cancer	0	1	0	0	0
Gastric Cancer	0	1	0	0	1
Lung Cancer	0	1	0	2	3
Non-Hodgkin Lymphoma	28	1	0	0	29
Glioblastoma Multiforme	0	40	0	0	40
Primary CNS Lymphoma	16	0	0	0	16
Renal Cancer	0	0	1	0	1
Melanoma	0	0	6	0	6
Other	1	0	0	0	1
Total	45	57	7	2	111

Note. This table reports the histology of the underlying tumor for patients treated with each biologic agent.

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ACADEMIC VITA

Aaron Bernstein
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Education

Master of Philosophy in Epidemiology
The University of Cambridge
Supervisor: Dr. Antonis Antoniou
Graduation: August 2019

Bachelor of Science in Pre-Medicine
Schreyer Scholar
The Pennsylvania State University, University Park
Graduation: May 2018

Awards

National Cancer Institute Cancer Research Training Award — **May 2018**
Eberly College of Science Student Marshal — **March 2018**
Gates Cambridge Finalist — **December 2017**
Schreyer Honors College Internal Scholarship — **December 2017**
Ruth E. Duffy Pre-Medicine Endowment Scholarship — **August 2017**
Schreyer Honors College Gateway Admission — **May 2015**
The President's Freshman Award — **January 2015**

Research Experience

NIH Cancer Research Training Award Fellowship — **May 2018- September 2018**
The National Cancer Institute, Shady Grove, MD
Supervising Researchers: Dr. Montserrat Garica-Closas
- Prevalence and clinical significance of SNPs in the emergence of breast cancer

Thesis Research — **2016- present**
The Pennsylvania State University, Hershey Medical Center, Hershey, PA
Supervising Researchers: Dr. Michael Glantz
- Toxicity of intrathecal administration of panitumumab, trastuzumab, rituximab, and a-IFN in the treatment of neoplastic meningitis
- Response of BRAF V600E-mutated primary CNS neoplasms to dual BRAF/MEK inhibition
- Novel diagnostic and prognostic indicators for neoplastic meningitis

Summer Undergraduate Research Fellowship — **Summer 2016**
Mayo Clinic, Rochester, MN
Supervising Researchers: Dr. Larry Karnitz and Dr. Arun Kanakanthara
- Interaction study between BRCA1 associated proteins

Summer Undergraduate Research Fellowship — **Summer 2015**
Mayo Clinic, Rochester, MN
Supervising Researchers: Dr. John Hawse and Dr. Malayannan Subramaniam
- Proposed and investigated novel mechanism for endoxifen resistance in MCF7 breast cancer cells

Independent Research **2015- 2016**

The Pennsylvania State University, University Park, PA

Supervising Researcher: Dr. Joseph Reese

- Elucidation of Spt5's mechanism in defense against RNA Polymerase II transcriptional arrest

Leadership, Healthcare, and Service Experience

Database Contributor/Analyst, Registry of Neoplastic Meningitis Patients **2017-Present**

- Responsible for expansion and maintenance of the registry

Initiator/Coordinator, Hershey Undergraduate Research Program **2017- Present**

- Proposed, designed, and advocated for formation of program dedicated to connecting undergraduates from University Park with faculty at Hershey, for the purpose of promoting research
- Supported by The Pennsylvania State University Hershey Chair of Medicine, Chair of Surgery, Chair of Ophthalmology, Vice Chair of Radiology, and Department of Neurosurgery
- Established a formal roster of participating faculty

Volunteer, Oregon Palliative Care Advisory Council **June 2017-Present**

- Created a comprehensive database of palliative care facilities in Oregon
- Assisted in the design, development, distribution, and analysis of a survey investigating Oregon's palliative care availability and capability

Founder/President, Science Journal Club **2017-Present**

- Designed club to teach students how to read and present scientific literature
- Responsible for appointing officers, holding meetings, and approving schedules

Teaching Assistant, Biology 472: Mammalian Physiology **Fall 2017**

- Responsible for office hours, leading pre-exam question sessions, and lecturing in the professor's absence

Volunteer, Milton S. Hershey Medical Center Emergency Room **2017**

- Assisted nurses and doctors with replacing oxygen tanks, and pushing wheel chairs

Volunteer, Milton S. Hershey Medical Center Clinical Simulation Center **2017**

- Assisted set-up for medical school classes
- Responsible for checking physiological accuracy for impromptu clinical scenarios

Publications

Abstracts

- **BERNSTEIN A**, MROWCZYNSKI OD, STROWD RE, CREAM L, RUDÀ R, JEYAPALAN S, EBY R, BLACK D, PATRIKIDOU A, HOFER S, FERRERI A, GLANTZ MJ. Safety and Efficacy of Intraventricular Biologic Agents as Part of a Multi-Agent Intraventricular Treatment Regimen for Patients with Neoplastic Meningitis. Neuro-Oncology. 2017 Nov; Accepted for poster presentation at the Society for Neuro-Oncology Annual Meeting.

- **BERNSTEIN A**, MROWCZYNSKI OD, KHALSA A, RYAN S, CHUNG C, GLANTZ MJ. Dual BRAF/MEK Therapy for Patients with BRAF V600E-Mutated Tumors: Dramatic

Clinical and Radiographic Responses and a Reduction in Cutaneous Toxicity. Neuro-Oncology. 2017 Nov; Accepted for poster presentation at the Society for Neuro-Oncology Annual Meeting.

Papers

- **BERNSTEIN A**, MROWCZYNSKI OD, STROWD RE, CREAM L, RUDÀ R, JEYAPALAN S, EBY R, BLACK D, PATRIKIDOU A, HOFER S, FERRERI A, GLANTZ MJ. Safety and Efficacy of Intraventricular Biologic Agents as Part of a Multi-Agent Intraventricular Treatment Regimen for Patients with Neoplastic Meningitis. In progress.

- **BERNSTEIN A**, MROWCZYNSKI OD, KHALSA A, RYAN S, CHUNG C, GLANTZ MJ. Dual BRAF/MEK Therapy for Patients with BRAF V600E-Mutated Tumors: Dramatic Clinical and Radiographic Responses and a Reduction in Cutaneous Toxicity. In progress.

- ALI A, ZOCCOLI C, BLACK D, **BERNSTEIN A**, ZACHARIA B, TULCHINSKY M, GLANTZ MJ. Inadvertent Under-dosing of Intraventricular Chemotherapy in Patients with Neoplastic Meningitis: Shooting to Kill or Getting Shot in the Foot?. The Journal of Clinical Oncology; Submitted.

Research Presentations

- **BERNSTEIN A**, MROWCZYNSKI OD, STROWD RE, CREAM L, RUDÀ R, JEYAPALAN S, EBY R, BLACK D, PATRIKIDOU A, HOFER S, FERRERI A, GLANTZ MJ. (2017). Safety and Efficacy of Intraventricular Biologic Agents as Part of a Multi-Agent Intraventricular Treatment Regimen for Patients with Neoplastic Meningitis. Accepted for poster presentation at Society for Neuro-Oncology Annual Meeting, San Francisco, California.

- **BERNSTEIN A**, MROWCZYNSKI OD, KHALSA A, RYAN S, CHUNG C, GLANTZ MJ. (2017). Dual BRAF/MEK Therapy for Patients with BRAF V600E-Mutated Tumors: Dramatic Clinical and Radiographic Responses and a Reduction in Cutaneous Toxicity. Accepted for poster presentation at the Society for Neuro-Oncology Annual Meeting, San Francisco, California.

- ALI A, TULCHINSKY M, BLACK D, RYAN S, ZOCCOLI C, **BERNSTEIN A**, ZACHARIA B, GLANTZ MJ. (2017). Inadvertent Under-dosing of Intraventricular Chemotherapy in Patients with Neoplastic Meningitis. Oral presentation delivered by Ayesha S. Ali at the World Federation of Neuro-Oncology Societies Quadrennial Conference, Zurich, Switzerland.

- **BERNSTEIN A**, KANAKKANTHARA A, JOSHI PM, KARNITZ LM. (2016). CDK12 and ZC3H18: An Interaction Study of BRCA1 Regulatory Proteins; Oral presentation delivered to the Mayo Clinic Department of Molecular Pharmacology and Experimental Therapeutics, Rochester, Minnesota.

- JONES CJ, MUELLER KG, **BERNSTEIN A**, BRUINSMA ES, SUBRAMANIAM M, HAWSE JR. (2016). Role of the Progesterone Receptor in Endocrine Resistant Breast Cancer. Poster presented by Calley J. Jones at Scientific Innovation through Diverse Perspectives Symposium, Rochester, Minnesota.

- **BERNSTEIN A**, KANAKKANTHARA A, JOSHI PM, KARNITZ LM. (2016). CDK12 and ZC3H18: An Interaction Study of BRCA1 Regulatory Proteins. Poster presented at the Mayo

Clinic SURF Poster Event, Rochester, Minnesota.

- **BERNSTEIN A**, JONES CJ, BRUINSMA ES, PITEL KS, REESE JM, SUBRAMANIAM S, HAWSE JR. (2015). Repression of Progesterone Receptor: A Mechanistic Explanation for the Emergence of Endocrine Resistance. Poster presented at the Mayo Clinic SURF Poster Event, Rochester, Minnesota.