original reports

Computerized Approach to Creating a Systematic Ontology of Hematology/Oncology Regimens

abstract

Purpose The systemic treatment of cancer is primarily through the administration of complex chemotherapy protocols. To date, this knowledge has not been systematized, because of the lack of a consistent nomenclature and the variation in which regimens are documented. For example, recording of treatment events in electronic health record notes is often through shorthand and acronyms, limiting secondary use. A standardized hierarchic ontology of cancer treatments, mapped to standard nomenclatures, would be valuable to a variety of end users.

Methods We leveraged the knowledge contained in a large wiki of hematology/oncology drugs and treatment regimens, HemOnc.org. Through algorithmic parsing, we created a hierarchic ontology of treatment concepts in the World Wide Web Consortium Web Ontology Language. We also mapped drug names to RxNorm codes and created optional filters to restrict the ontology by disease and/or drug class.

Results As of December 2017, the main ontology includes 30,526 axioms (eg, doxorubicin is an anthracycline), 1,196 classes (eg, regimens used in the neoadjuvant treatment of human epidermal growth factor receptor 2–positive breast cancer, nitrogen mustards), and 1,728 individual entities. More than 13,000 of the axioms are annotations including RxNorm codes, drug synonyms, literature references, and direct links to published articles.

Conclusion This approach represents, to our knowledge, the largest effort to date to systematically categorize and relate hematology/oncology drugs and regimens. The ontology can be used to reason individual components from regimens mentioned in electronic health records (eg, R-CHOP maps to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and also to probabilistically reconstruct regimens from individual drug components. These capabilities may be particularly valuable in the implementation of rapid-learning health systems on the basis of real-world evidence. The derived Web Ontology Language ontology is freely available for noncommercial use through the Creative Commons 4.0 Attribution-NonCommercial-ShareAlike license.

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INTRODUCTION

The field of hematology/oncology is generally acknowledged for its complexity and encompasses many disparate diseases. Over the past 70 years, a large body of knowledge has evolved around single-drug and multidrug treatment regimens. Because of the complexity of many of these regimens, clinicians rarely document specific drugs and instead use commonly understood acronyms or shorthand. Unfortunately, this hampers the secondary use of electronic health records (EHRs), such as retrospective studies on the cause of specific adverse effects of specific drugs within regimens. Although several general purpose medical extraction natural language processing algorithms currently exist (eg, cTAKES[1] and MedEx,[2] both introduced in 2010; MedXN,[3] introduced in 2014; and CLAMP,[4] introduced in 2017), they typically rely on the presence of drug names, routes, and doses in the narrative. Recently, the complexity of the field has been increasing exponentially,[5] aided by exploding scientific knowledge and a concomitant rapid escalation of drug approvals. For example, a recent estimate found more than 2,000 cancer immunotherapy drugs in the development pipeline.

The National Cancer Institute (NCI) has worked for many years to compile variables to ease both clinical application and research analysis in hematology/oncology. The main product of this work, the NCI Thesaurus[6] (NCIT), does have formal representations of some chemotherapy regimens (eg, the R-CHOP regimen [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone] is represented by NCIT code C9760). The NCIT also includes terms and properties, synonym details, relationships, and mappings. However, the relationships in the NCIT are limited to the component drug names and a small number of partially contextual assertions (eg, R-CHOP is used in the treatment of diffuse large B-cell lymphoma [DLBCL], whereas a fully contextual assertion would state that R-CHOP is used with curative intent in the treatment of previously untreated DLBCL). Additional details such as similarity to other regimens, use of alternate medications (eg, prednisolone substituted for prednisone in R-CHOP[7]), supportive medications (eg, filgrastim in R-CHOP[8]), regimen relevance (eg, m-BACOD [methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone] in the treatment of untreated DLBCL[9] is obsolete), and literature references are not provided. We sought to improve the status quo by creating a formal domain ontology, as defined in the field of information science,[10] based primarily on HemOnc.org content. Specifically, we sought to create a self-contained information model establishing the relationships between antineoplastic drugs and regimens and the contexts in which they are used.

METHODS

Data Source

Our source, HemOnc.org, has been previously described.[11] Briefly, HemOnc.org was created in 2011 and is now the largest freely available wiki Web site of drugs and regimens relevant to hematology/oncology. HemOnc.org has become an increasingly used resource, with more than 170,000 visitors from 179 countries within the past year. The site includes a large number of single- and multidrug regimens, including details concerning antineoplastic drug administration instructions, regimen variants, and associated supportive medications. All included regimens are referenced, with direct links to the original manuscript, PubMed or conference abstract, and PubMed Central version (when available). The content of HemOnc.org is the property of HemOnc.org LLC, which was cofounded by two of the authors (P.C.Y. and J.L.W.) in 2017. Although we considered using other data sources of chemotherapy regimens (eg, National Comprehensive Cancer Network or CancerTherapy Advisor.com), these sources either are not machine readable (eg, National Comprehensive Cancer Network guidelines are PDF based) and/or are proprietary.

HemOnc.org Web Crawler for Existing Metadata

HemOnc.org is structured in MediaWiki with the semantic mediawiki extension.[12] This format allows for structured categorization of pages and sustained connections via hyperlinks. This creates an implicit ontology that the project extracted and enhanced. A Web crawler was created that started at the top-level page index and traversed every page to gather data and analyze connections. The first step of this process was filtering redirect pages, which allow people to use multiple search terms to find the same page (eg, "AML" redirects to "Acute Myeloid Leukemia"). This involved tracing the page request and verifying that it was a direct connection with no redirects or diversions. The remaining pages were then run through a recursive function that traverses hyperlinks until they lead to a dead end or to a familiar page. Sequential storage of all new connections (ie, memoization[13]) was further used to increase efficiency and reduce repeats. The Web crawling function consisted of three sections: identification of all possible connections, categorization of those connections, and calling a function on all new connections. After identifying the categories that each concept falls under, those categories are rerun through a function to identify their lineage. The result was a general structure where the base classes and axioms (relationships) made up the ontology.

Parsing Treatment Regimens

Once the page-level structure had been identified, recursion was used again to identify pages including cancer regimens. The structure of the Web site was used to guide the program through the extraction of the following eight items: regimen names; regimen links, if part of a multipart regimen; regimen context (eg, neoadjuvant, adjuvant, salvage, first-line metastatic); regimen type (eg, chemotherapy, immunotherapy, chemoradiotherapy); drugs contained within the regimens; reference shorthand (eg, Smith et al

Table 1. Subclasses of the Drug Index Class With Representative Examples

Concept	Drug or Subsubclass Example
Drugs by chemical composition	
Antibody medications	Anti-CD20 antibodies
Drugs by approval status	
FDA-approved drugs	Drugs FDA approved in the 21st century
Investigational	Barasertib (AZD1152)
Drugs by prescribing specialty	
Pediatric oncology medications	Neuroblastoma medications
Drugs by class effect	
Immunotherapy	T-cell activators
Drugs by disease characteristic	
Mutation-specific medications	Erlotinib
Drugs by availability	
OTC medications	Aspirin
Drugs by route	
Subcutaneous medications	Omacetaxine
Drugs by disease site	
Site-specific medications	Breast cancer medications
Site-agnostic medications	Larotrectinib (LOXO-101)
Supportive medications	
Antihistamines	H2 receptor antagonists
Miscellaneous	
WHO essential cancer medicines	Doxorubicin
Biosimilars	Bevacizumab-awwb

Abbreviations: FDA, US Food and Drug Administration; OTC, over the counter.

2010); study names if available (eg, CALGB [Cancer and Leukemia Group B] 9732,[14] DSHNHL [German High-Grade Non-Hodgkin Lymphoma Study Group], RICOVER-60[15]); and URLs for the research article(s). Drugs were additionally assigned one of four properties (ie, antineoplastic, CNS directed, immunosuppressive, or supportive component), depending on the context in which they were used. The parsing process was simplified through the creation of a function that once given the page and expected structure around the keyword, identified the keyword by doing multiple searches that gradually identified the result. Regimens that span multiple cancer conditions and/or contexts were archived separately to gather all variants and later combined into a single concept with multiple parents.

Drug Indexing

To increase the standardization of the ontology and to allow integration with other data sources, we mapped HemOnc.org medication names to RxNorm[16] codes, which are widely used by the international standards community and are required for EHR certification under the meaningful use regulations.[17] RxNorm codes were added to all drugs within the ontology, when they were available. This was done through the use of the RxNorm application programming interface, which the program sent requests to for every identified drug. The program searched for the commercial name, the technical name, and the compound name if applicable; drugs that returned no match were manually reviewed.

Ontology Filtering

After the creation of the overarching ontology, it became apparent that the ontology must be filtered into manageable facets for specific research purposes, such as the incorporation of rules engines. To start the filtration process, the goal needs to be defined and vital data need to be specified. For the goals of this project, the team determined that vital information for a cancer type includes all conditions, regimens, and accompanying drugs that are contained in any of the regimens. The class structure for drugs will remain only for those drugs that are used in any regimen that is used for the specific cancer

Table 2. Distinct Treatment Regimens by Class

Class of Regimen	No. of Distinct Regimens
Chemotherapy regimens	982
Chemoimmunotherapy regimens*	12
Chemoradiotherapy regimens	48
Endocrine therapy regimens	38
Growth factor therapy regimens	2
Immunosuppressive therapy regimens	20
Immunotherapy regimens	27
Radiotherapy regimens	15
Other regimens	102

NOTE. A regimen that appears in multiple disease contexts (eg, R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone]) would only be counted once in this table.

*Our definition of chemoimmunotherapy includes regimens that combine cytotoxics (conventional or targeted therapy with an intended direct cytotoxic effect) along with immune system modulators such as anti–programmed death-1 antibodies, interferon, and interleukin-2; regimens that simply contain monoclonal antibodies, which have sometimes been referred to as chemoimmunotherapy or biologics, are not included.

Table 3. Distinct Chemotherapy Regimens by Therapeutic Context

Subcontext	No. of Distinct Regimens
Curative, upfront, predefinitive	
Induction	237
Neoadjuvant	69
Curative, upfront, definitive*	
Not specified	37
Curative, upfront, postdefinitive	
Adjuvant	159
Consolidation	74
Maintenance	30
Curative, salvage therapy	
Not specified	73
Curative, salvage, postreinduction	
Consolidation	13
Maintenance	4
Noncurative, first line	
Induction	12
Consolidation	30
Maintenance	39
Not specified	241
Noncurative, second line	
Induction	0
Consolidation	4
Maintenance	15
Not specified	38
Noncurative, third line	
Induction	0
Consolidation	0
Maintenance	0
Not specified	1
Noncurative, any line†	
Not specified	490
All lines of therapy‡	
Not specified	123
Local therapy	
Not specified	19

*Definitive therapy for cancer is usually surgical, which is with few exceptions not captured in the HemOnc.org content. Definitive here typically refers to a chemoradiotherapy approach, which may or may not have preceding and subsequent associated treatments.

†This category is exclusive of regimens labeled as first line, second line, or third line.

‡Regimens assigned directly to this parent category do not belong to any other category.

type. As a demonstration of this capability, we filtered the ontology by two restriction dimensions: restriction by drug class and restriction by disease subtype. We illustrate these filters by restricting to the class of anti-CD20 antibody-containing regimens and the disease DLBCL (described in Results).

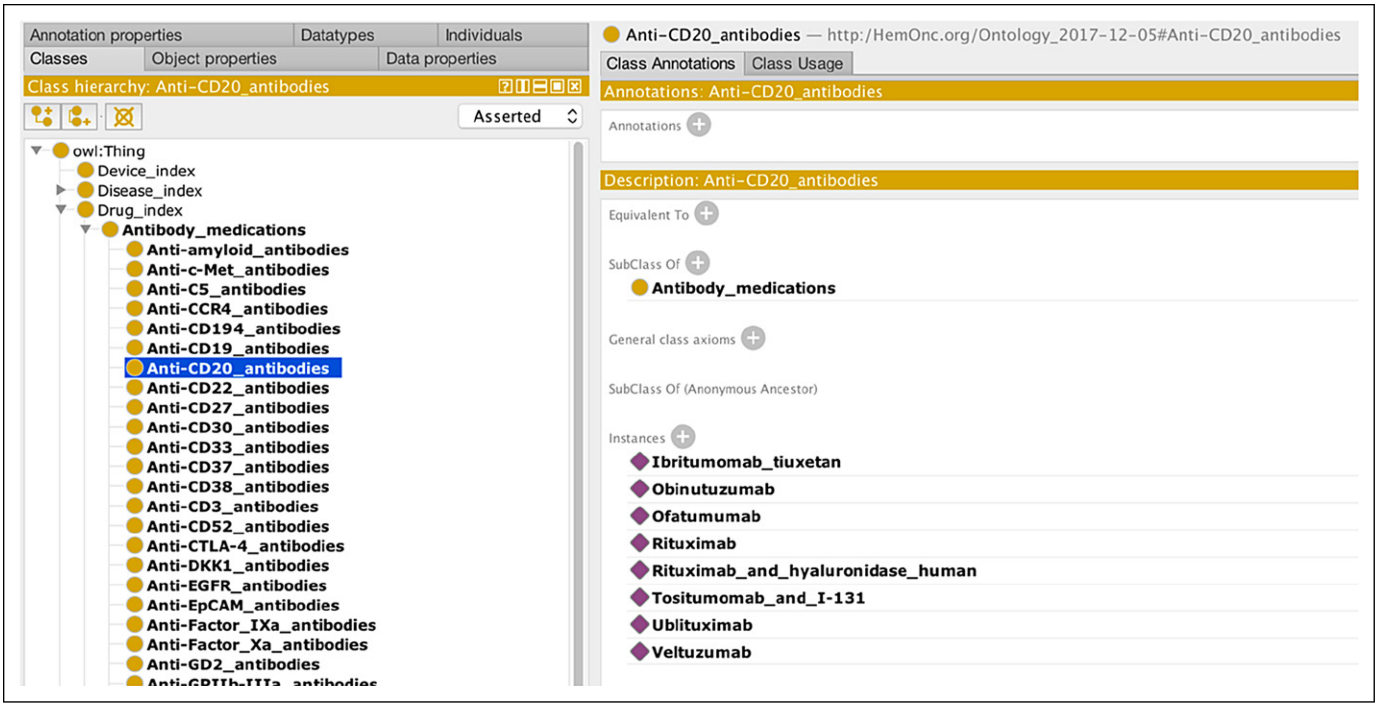
Output and Validation

The output of the parser was stored in the World Wide Web Consortium Web Ontology Language (OWL) format.[18] OWL was selected because of its widespread use in the ontology community as well as its compatibility with the Protégé ontology browser.[19] Our team subsequently used Protégé (version 5.2.0) to validate and interact with the results. Axiomatic relationships between ontology concepts were visualized using the OntoGraf Protégé plugin.[20]

Regarding general availability, the entire OWL ontology and/or subontologies filtered by the parameters we have described are freely available to noncommercial users through the Creative Commons 4.0 Attribution-NonCommercial-ShareAlike license[21]; commercial uses will be considered on a case-by-case basis.

RESULTS

A total of 613 (79%) of 753 Web pages, representing 284,000 lines (27.1 million characters) of content, were parsed by the algorithm. Excluded Web pages did not have regimen or drug content (eg, general reference pages about the site). As of December 5, 2017, the main HemOnc.org ontology includes 30,526 axioms, 1,196 classes (categories of regimens, drugs, devices, and diseases), and 1,728 entities (individual regimens/drugs). It furthermore contains 4,439 drug-to-regimen relationships, of which 3,334 are antineoplastic components, 34 are immunosuppressive components, 88 are CNS therapy components, and 983 are supportive medication components. There are 402 links tying multipart regimens together (eg, cisplatin plus radiotherapy has seven possible preceding treatments, depending on the context). The ontology contains 3,790 literature references, all but nine of which have an accompanying reference URL, for a total of 7,571 literature references and URLs for regimens. Finally, it includes 338 RxNorm codes for drugs; the remainder that



- owl:Thing
  - Device_index
  - Disease_index
  - Drug_index
    - Antibody_medications
      - Anti-amyloid_antibodies
      - Anti-c-Met_antibodies
      - Anti-C5_antibodies
      - Anti-CCR4_antibodies
      - Anti-CD194_antibodies
      - Anti-CD19_antibodies
      - Anti-CD20_antibodies
      - Anti-CD22_antibodies
      - Anti-CD27_antibodies
      - Anti-CD30_antibodies
      - Anti-CD33_antibodies
      - Anti-CD37_antibodies
      - Anti-CD38_antibodies
      - Anti-CD3_antibodies
      - Anti-CD52_antibodies
      - Anti-CTLA-4_antibodies
      - Anti-DKK1_antibodies
      - Anti-EGFR_antibodies
      - Anti-EpCAM_antibodies
      - Anti-Factor_IXa_antibodies
      - Anti-Factor_Xa_antibodies
      - Anti-GD2_antibodies
      - Anti-GPIIb-IIIa_antibodies

Anti-CD20_antibodies — http:/HemOnc.org/Ontology_2017-12-05#Anti-CD20_antibodies

SubClass Of: Antibody_medications

Instances:
- Ibritumomab_tiuxetan
- Obinutuzumab
- Ofatumumab
- Rituximab
- Rituximab_and_hyaluronidase_human
- Tositumomab_and_I-131
- Ublituximab
- Veltuzumab

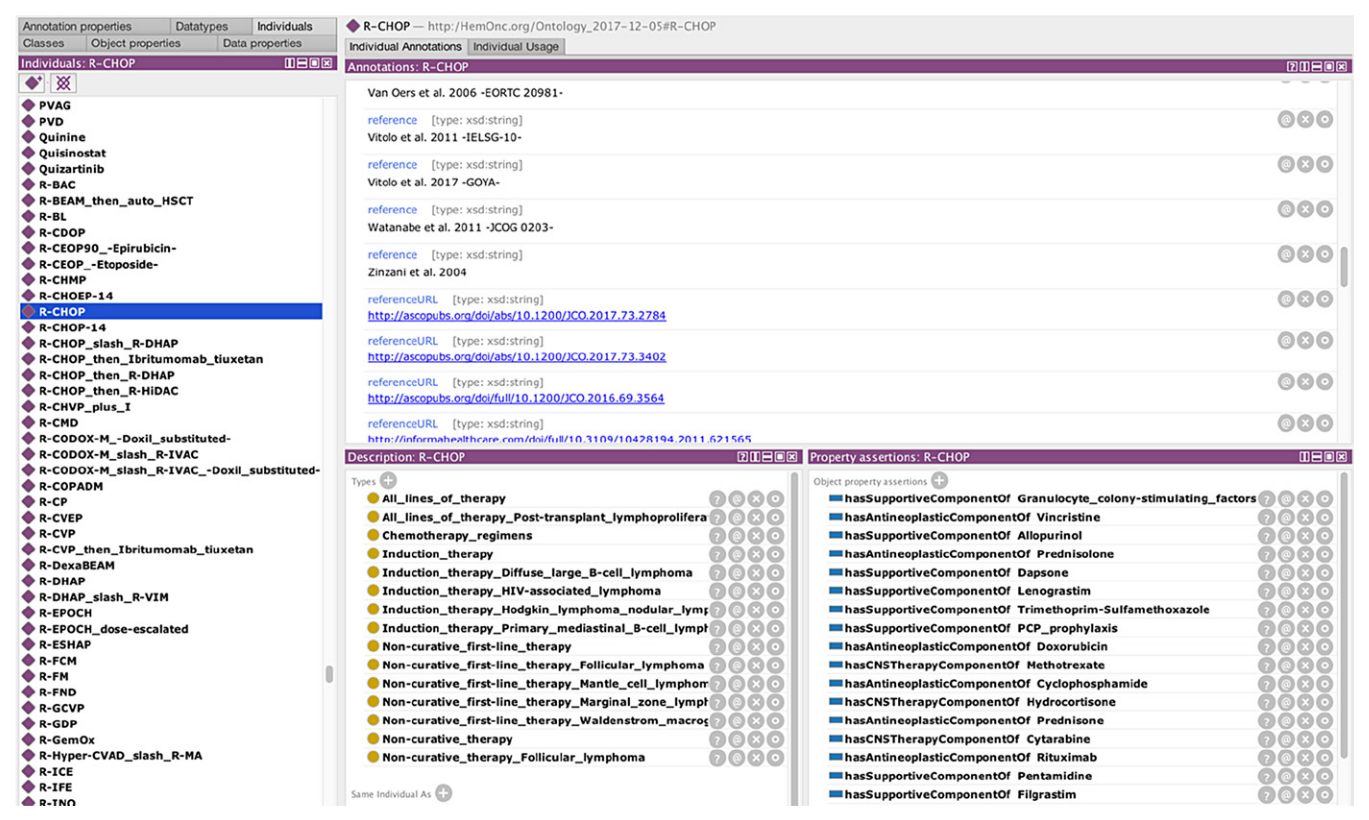
Fig 1. Screenshot of Protégé with the class "anti-CD20 antibodies" loaded. The left panel shows the other antibody medication classes as well as several other subclasses of drug index. The bottom right panel shows the eight instances of anti-CD20 antibodies included on HemOnc.org (seven approved and one investigational).

were not successfully mapped were manually reviewed and were either at the investigational stage or newly approved and not yet accepted by the RxNorm ontology. There are four parent classes in the HemOnc.org ontology: drug index, device index, disease index, and regimen index. As an example of the complex polyhierarchy of the ontology, categorizations of drug index and examples are listed in Table 1. Numbers of regimens categorized by the major axes regimens by class and regimens by context are listed in Tables 2 and 3.

Application of the filters we have described resulted in smaller but substantial subontologies. For example, restriction to anti-CD20 antibody-containing regimens began with the eight drugs shown in Figure 1. The ontology remains substantial, because any regimen that has one or more of these eight drugs will be included, along with its context(s). For example, there are 152 regimens within the ontology that contain the drug rituximab; one of these, the R-CHOP regimen, is shown in Figure 2. A tabular representation of the drug components of the R-CHOP regimen is shown in Table 4. This regimen is found in 10 different contexts: as induction therapy for DLBCL, HIV-associated lymphoma, nodular lymphocyte-predominant Hodgkin lymphoma, and primary mediastinal B-cell lymphoma; as noncurative first-line therapy for follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia; as noncurative therapy (ie, administered other than in first line) for follicular lymphoma; and in all lines of therapy for post-transplantation lymphoproliferative disorder. More information on the ontology is available in the Data Supplement.

DISCUSSION

Using HemOnc.org as a fairly comprehensive source, this project works to create chemotherapy ontologies, with one broad ontology and a filtering mechanism that can focus on specific key drugs, drug classes, regimens, and regimen classes and their relation to the rest of the ontology. Therefore, the ontologies allow for the mapping of the interrelation between regimens, drugs, and general categories to contextualize hematology/oncology regimens. The information made available through the ontology may be useful to a variety of users, including practicing oncologists, trainees, creators of consensus guidelines, insurance providers, and terminology experts. In particular, the resulting ontologies could support the use of retrospective studies and data mining of real-world evidence (RWE) to identify links between drugs, drug categories, conditions, and regimens. As an illustration, the



PVAG
PVD
Quinine
Quisinostat
Quizartinib
R-BAC
R-BEAM_then_auto_HSCT
R-BL
R-CDOP
R-CEOP90_-Epirubicin-
R-CEOP_-Etoposide-
R-CHMP
R-CHOEP-14
R-CHOP
R-CHOP-14
R-CHOP_slash_R-DHAP
R-CHOP_then_Ibritumomab_tiuxetan
R-CHOP_then_R-DHAP
R-CHOP_then_R-HiDAC
R-CHVP_plus_I
R-CMD
R-CODOX-M_-Doxil_substituted-
R-CODOX-M_slash_R-IVAC
R-CODOX-M_slash_R-IVAC_-Doxil_substituted-
R-COPADM
R-CP
R-CVEP
R-CVP
R-CVP_then_Ibritumomab_tiuxetan
R-DexaBEAM
R-DHAP
R-DHAP_slash_R-VIM
R-EPOCH
R-EPOCH_dose-escalated
R-ESHAP
R-FCM
R-FM
R-FND
R-GCVP
R-GDP
R-GemOx
R-Hyper-CVAD_slash_R-MA
R-ICE
R-IFE
R-INO

R-CHOP — http:/HemOnc.org/Ontology_2017-12-05#R-CHOP

Van Oers et al. 2006 -EORTC 20981-

reference [type: xsd:string]
Vitolo et al. 2011 -IELSG-10-

reference [type: xsd:string]
Vitolo et al. 2017 -GOYA-

reference [type: xsd:string]
Watanabe et al. 2011 -JCOG 0203-

reference [type: xsd:string]
Zinzani et al. 2004

referenceURL [type: xsd:string]
http://ascopubs.org/doi/abs/10.1200/JCO.2017.73.2784

referenceURL [type: xsd:string]
http://ascopubs.org/doi/abs/10.1200/JCO.2017.73.3402

referenceURL [type: xsd:string]
http://ascopubs.org/doi/full/10.1200/JCO.2016.69.3564

referenceURL [type: xsd:string]
http://informahealthcare.com/doi/full/10.3109/10428194.2011.621565

All_lines_of_therapy
All_lines_of_therapy_Post-transplant_lymphoprolifera
Chemotherapy_regimens
Induction_therapy
Induction_therapy_Diffuse_large_B-cell_lymphoma
Induction_therapy_HIV-associated_lymphoma
Induction_therapy_Hodgkin_lymphoma_nodular_lymp
Induction_therapy_Primary_mediastinal_B-cell_lymph
Non-curative_first-line_therapy
Non-curative_first-line_therapy_Follicular_lymphoma
Non-curative_first-line_therapy_Mantle_cell_lymphom
Non-curative_first-line_therapy_Marginal_zone_lymph
Non-curative_first-line_therapy_Waldenstrom_macroç
Non-curative_therapy
Non-curative_therapy_Follicular_lymphoma

hasSupportiveComponentOf Granulocyte_colony-stimulating_factors
hasAntineoplasticComponentOf Vincristine
hasSupportiveComponentOf Allopurinol
hasAntineoplasticComponentOf Prednisolone
hasSupportiveComponentOf Dapsone
hasSupportiveComponentOf Lenograstim
hasSupportiveComponentOf Trimethoprim-Sulfamethoxazole
hasSupportiveComponentOf PCP_prophylaxis
hasAntineoplasticComponentOf Doxorubicin
hasCNSTherapyComponentOf Methotrexate
hasAntineoplasticComponentOf Cyclophosphamide
hasCNSTherapyComponentOf Hydrocortisone
hasAntineoplasticComponentOf Prednisone
hasCNSTherapyComponentOf Cytarabine
hasAntineoplasticComponentOf Rituximab
hasSupportiveComponentOf Pentamidine
hasSupportiveComponentOf Filgrastim

Fig 2. Screenshot of Protégé with the regimen concept “R-CHOP” (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) loaded. The left panel shows some other entities, in alphabetic order. The top right panel shows some of the 36 references and 36 reference URL annotations for R-CHOP. The bottom middle panel shows the 15 types to which R-CHOP belongs, which are primarily contextual. The bottom right panel shows all drugs that are found in one or more of the R-CHOP regimens, including supportive medications and intrathecal prophylaxis (eg, methotrexate).

ontology can be used in two important use cases: the decomposition of regimens referred to only by acronym or reference in narrative EHR text into their component drugs and the composition of regimens from component drug references in narrative or structured EHR data. As an example of the former, a reasoning system built on the HemOnc.org ontology could take the following phrase, “The patient received R-CHOP per the RICOVER-60 protocol,” and determine that the patient received dose-dense R-CHOP with granulocyte colony-stimulating factor support (R-CHOP-14), as described by Pfreundschuh et al.[15] As an example of the latter, a system could take mentions of the individual drugs gemcitabine and cisplatin from the EHR of a patient with pancreatic cancer and infer that the patient received the regimen cisplatin plus gemcitabine as first-line treatment for advanced pancreatic cancer per a small number of possible protocols.[22-24]

A system that can recognize drug names and regimens to this level of specificity could help make use of the abundant RWE available within EHR systems. For example, 3,952 patients at Vanderbilt University Medical Center have the terms R-CHOP, RCHOP, CHOP-R, or CHOPR present in their EHR, whereas only 1,560 (39%) of these have rituximab or the brand name Rituxan (Genentech, South San Francisco, CA) in their EHR. Although some of these may represent false positives (eg, “R-CHOP was considered but not given due to frailty”), it is highly likely that many of them are true positives; natural language processing negation algorithms such as NegEx[25] could be used in conjunction with our ontology to reduce the risk of false positives. Precisely detecting regimens and their component drugs within EHRs could help physicians and researchers detect patients’ therapeutic histories. Extraction of these rich data could help with discovering potential new indications for drugs that have been used in an off-label fashion[26,27] and/or have had off-target effects,[28] help in the detection of drug resistance patterns across populations of patients, and associate regimens with adverse effect profiles—all focuses of US Food and Drug Administration efforts to take advantage of RWE.[29] Toward this end, we are working to integrate parts of the ontology into DeepPhe, which was recently described.[30] The recognition of drug regimen names could also help current patients. Clinical

Table 4. Expansion of the Regimen Concept R-CHOP Into Its Component Medications

Class*	Medication Name	Route	Dose
Antineoplastics			
Anti-CD20 antibodies	Rituximab	IV	375 mg/m^2
	Rituximab and hyaluronidase human	SC	1,400 mg
Alkylating agents	Cyclophosphamide	IV	750 mg/m^2
Anthracyclines	Doxorubicin	IV	50 mg/m^2
Vinca alkaloids	Vincristine	IV	1.4 mg/m^2 (maximum, 2 mg)
			1.4 mg/m^2 (no cap)
			2 mg
Steroids	Prednisone	PO/IV	40 mg/m^2
			50 mg/m^2
			60 mg/m^2
			100 mg
			100 mg/m^2
	Prednisolone	PO	40 mg/m^2
Antifolates	Methotrexate	IT	12 mg
			12.5 mg
			15 mg
Deoxycytidine analogs	Cytarabine	IT	40 mg
Supportive medications			
Xanthine oxidase inhibitors	Allopurinol	PO	300 mg
G-CSF†	Filgrastim†	SC	‡
	Lenograstim†	SC	‡
Steroids	Hydrocortisone	IT	20 mg
PCP prophylaxis	Trimethoprim and sulfamethoxasole	PO	80/400 mg 160/800 mg
	Dapsone	PO	‡
	Pentamidine	IH	300 mg

NOTE. Medication category, class, and name are available directly from the ontology; routes and doses were manually abstracted from the respective HemOnc.org disease pages. R-CHOP is standard-dose R-CHOP administered every 21 days.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IH, inhaled; IT, intrathecally; IV, intravenously; PCP, pneumocystis pneumonia; PO, orally; SC, subcutaneously.

*Class in this case refers to the immediate parent class with a mechanism of action. Most of these medications have multiple parent classes.

†Only a few R-CHOP regimens specify precise drug ingredients for WBC support (filgrastim, lenograstim); others specify the category of G-CSF, which can be inferred to mean any of six G-CSF medications, with the caveat that some of these may not have been approved at the time that a particular regimen was studied or published (eg, filgrastim-sndz).

‡Doses for these medications are not defined in the published R-CHOP regimens.

trials have stringent inclusion and exclusion criteria, which can include a history of exposure to one or more particular chemotherapy regimens. By better recognizing the therapies a patient has received, a system built on our ontology could help with identifying appropriate clinical trials for hematology/oncology patients at scale and could complement clinical trial matching efforts such as MatchMiner.[31]

An inherent challenge in creating this ontology is our ever-changing understanding of cancer and hematologic diseases. Therefore, it is important for such an ontology to be updated frequently and remain dynamic rather than static. Our ontology is highly dynamic as it draws on data from HemOnc.org, which is updated by direct contribution or indirect suggestions to contributors on a daily or weekly basis. A limitation of this approach is that HemOnc.org may have biases in content coverage and/or completeness; the user is referred to the Web site tutorial[32] for a discussion of the approach to curation. Despite this limitation, it has been shown that crowd-sourced knowledge bases increase in their comprehensiveness over time, including in the medical domain.[33,34] In this light, our ontology is primed to remain up to date as new relationships and concepts are introduced into the field of oncology. New concepts, relations, instances, and axioms can be integrated within the ontology as information is added to the wiki.

Being able to keep up with the rapidly growing and evolving field of hematology/oncology is quite challenging for clinicians.[5] Our ontology will be able to adapt and grow as changes are made to HemOnc.org; however, keeping track of the growing amount of evidence and literature upon which the ontology is based is nearly impossible for an individual clinician. Critically, our ontology captures the evidence and support for the regimen and drug instances found within. The practice and growth of hematology/oncology relies on comparing evidence of new therapeutics with former strategies, whether directly through randomized controlled trials or through other indirect means. By tracking the references associated with particular instances, our ontology preserves the provenance of knowledge.

Our work has several limitations. In particular, we do not yet account for variants of chemotherapy regimens on the basis of dosages or substitution of similar drugs. Even a seemingly uniform concept such as R-CHOP can in fact be quite complex. As summarized in Table 4, only some of the component medications have an unambiguous route and dose. Vincristine and prednisone dosing in particular is variable across published regimens and in common practice. Nevertheless, a formal ontologic representation of this concept can enable rational decomposition from acronym representation as well as synthesis from component medications. We elected to map to RxNorm codes so as to increase the standardization of the content; however, a sizeable minority of medications did not have an assigned RxNorm code. It is possible that some of these are available in other structured databases (eg, the National Drug Code Directory[35] or the National Drug File Reference Terminology)[36]; future work will seek to search these databases for drugs lacking RxNorm codes.

We do not yet account for most nomenclature variation. For example, the terms R-CHOP, RCHOP, CHOP-R, and CHOPR are potentially interchangeable but not formally accounted for as aliases in the present ontology. Conversely, the regimens R-CHOP and R-CHOP-14 (as described earlier in Discussion) are distinct in the ontology, as are CHOEP (etoposide plus CHOP) and EPOCH (infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), which contain the same antineoplastic drugs but have different dosing and infusion parameters. In parallel with this work, we are formulating a standardized chemotherapy regimen nomenclature, including synonyms, which can then be introduced into the ontology. We also do not account for the linkage of multipart protocols. For example, the RICOVER-60 protocol previously mentioned has a prephase of vincristine and prednisone administered for 1 week before the main R-CHOP portion; other protocols such as GIMEMA AIDA-2000 (Gruppo Italiano per le Malattie Ematologiche dell'Adulto All-*Trans*-Retinoic Acid and Idarubicin) for acute promyelocytic leukemia are much more complex.[37] In its current state, the HemOnc.org ontology could be used to link linear protocols such as RICOVER-60 but not branching protocols such as AIDA-2000, which uses risk-adapted consolidation therapy. Future work will include formalization of the links between multipart protocols. The fact that the ontology is not yet finished, in a sense, describes its emergent (ie, bottom-up) and conceptual properties, akin to efforts such as the Systematized Nomenclature of Medicine–Clinical Terms.[38,39] Whether evolution toward a realist ontology, such as the Gene Ontology,[40] occurs will depend on our clinical and research use cases and those of our users.

In conclusion, we have presented an initial attempt to formalize the relationships between medications, regimens, and treatment contexts in hematology/oncology. The resultant large ontology can be used for a number of applications and will be iteratively improved over time. The product is freely available for noncommercial use and represents a substantial step forward in the formalization of hematology/oncology treatments.

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