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Review article

The Evolving Challenges of Polypharmacy Amongst Patients with Cancer Diagnosis: A Narrative Perspective on Current Trends

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Abstract

Across patient populations increasing pill burden per patient often defined as polypharmacy is becoming a worrying therapeutic morbidity. In cancer patients, this becomes more challenging because of lack of clarity on its key themes. These includes its definitional threshold, dichotomization of cancer polypharmacy into those due related chemotherapy, those related to a complication of chemotherapeutic drugs, and those employed for general comorbidities. In this narrative review we have explored the outstanding uncertainties with regard to the varying phenotypes of polypharmacy in patients with cancer with the view to determining exact patient cohorts that will benefit from targeted interventions.

Keywords: *Cancer, Neoplasm, Polypharmacy.*

Introduction

Polypharmacy' refers to the use of multiple medications. The most commonly reported definition of polypharmacy was the numerical definition of five or more medications daily (1). Exact prevalence rates vary but it is estimated to range between 25-35% across hospital and community-based databases (2). Despite significant amount of ongoing work involving various patients' populations, its key determinants as well as themes critical to its adjudication (such as definitions, prevalence etc.) remains uncertain (3). For example, until recently the medication threshold that exactly defines what constitutes polypharmacy was the subject of intense debate (4). For patients in the general population, polypharmacy is defined as intake of five or more medications over a period of at least 4 months (4). This unifying definition has had a tremendous impact in advancing our understanding as well as adoption of mitigation strategies to deal with polypharmacy since it was advanced in 2017(4). In organ specific morbidities (such as patients with cancer) this uncertainty still subsist, as are the factors which exacerbate it. In patients with cancer (particularly the elderly cohort) prevalence estimates of polypharmacy range between 10-90% (5); placing an additionally huge therapeutic burden on a population that is physiologically disadvantaged ab initio from the pharmacokinetic and pharmacodynamics consequences of drugs.

The significant improvement seen recently in cancer patients' survival across patient demographics was principally due novel therapeutics amongst other factors. Very often these drugs were delivered in cocktails and various treatment regimen which inevitably add to patients' overall medication count (6). Unlike the numerical phenotype of polypharmacy in the general population, dichotomous cancer related polypharmacy may not necessarily be detrimental to overall patient health. Chemotherapeutic agents often rely on bespoke genetic epitopes and markers as mechanisms of their action (7). Polymorphisms involving these receptors therefore increases the risks of development of adverse consequences (such as adverse drug reactions [ADR]). This therefore makes Cancer patients particularly more vulnerable to downstream consequences of polypharmacy including drug-drug, drug-food, and pharmacogenetic interactions (7). The consequences of these are ADRs, which have thus far been reported to account for up to 6.4-12% of all hospital admissions (8). In elderly cancer

patients the occurrence of certain ADRs is inescapable and the appropriate therapeutic strategy in this case may clinically come down to how this could be mitigated rather than eliminated (9).

Is all Cancer polypharmacy deleterious?

Recent advances in the field of flow cytometry have provided a therapeutic platform for the development of several targeted treatments of especially hematological malignancies. These drugs have conferred increased survival benefits on some patient cohorts with designated malignancies as well as improved quality adjusted life years in others (10) (11–13). Unfortunately, polymorphisms of genes encoding proteins involved in the bio-disposition of these drugs meant that drug interactions sometimes become an inevitable consequence of their use (14–17). And the more these drugs are deployed in patient settings with rising medication counts, the greater the multiplicative risks of these interactions and their sequelae. Very often the remedy lies in ascertaining the attributable risk of possession of these polymorphisms and the risk of clinically significant downstream toxicity; this is with the view to quantifying the benefit of relevant enzyme assays to identify vulnerable individuals. In cancer morbidities that require Azathioprine as part of their treatment regimen for example, prior assay for the genotypes of the critical enzyme (thiopurine methyl transferase [TPMT]) has proven both clinically and economically effective in reducing the burden of toxicity associated with exposure to azathioprine in these cohorts of patients (18–20).

Although still a matter of ongoing debate, the clear dichotomy into the various therapeutic risks pheno-groups that constitutes cancer polypharmacy is necessary in order to adequately deploy clinical and non-clinical resources to address it. Figure 1 shows a suggested outline of where current evidence lies and the potential for improvement on current uncertainties.

Duration of polypharmacy

In the general population the duration of exposure to multiple medications above a given numerical threshold defines polypharmacy. This is going to be challenging in patients with cancer diagnosis due to the transitory nature of some the key chemotherapeutic regimens. The traditional threshold of intake of at least five or more medications over 4 months may not strictly hold as discussed above. Despite this, there is an increasing body of emerging work in this area; but still limited by amongst others the duration of drug exposure. This is a perspective that may need exploration by future systematic studies.

Cancer and non-cancer related polypharmacy

The exact relationship between PIMs and mortality in cancer patients remains uncertain. In an examination of a cohort of patients with non-Hodgkin's lymphoma, Lin et al (21) reported significant correlations between all-cause mortality and treatment-related toxicities with the use of PIMs. Subsequent published reports have both supported and disputed this this association (22). It remains a matter of therapeutic debate whether these associations were consequent upon the underlying disease process (aggressive hematological malignancies) and not the possible therapeutic effect of multiple medication census. It is for example very interesting that varying significant and insignificant polypharmacy-themed point estimates have been reported depending on whether the underlying cancer morbidity was a breast cell carcinoma compared to a colorectal cancer (23). Recent comprehensive meta-analysis of Associations of polypharmacy and potentially inappropriate medications with adverse outcomes in older Cancer patients did establish that polypharmacy was associated with several adverse outcomes including hospitalization and all-cause mortality in older cancer patients (24). To date this remains the most comprehensive examination of this relationship.

Future perspectives

Going forward, as cancer related novel therapies continue to expand, the over clinical phenogroups of PIMs and ensuing polypharmacy and their consequences are likely to significantly change in these cohorts' patients. How refinement of specific drug epitopes will impact on this burden remains unknown. What has been evident from other clinical morbidities was that as improvement in drug delivery systems (such as sustained released medications) increases, the total pill count is likely to geometrically reduce; expected decrease in polypharmacy aa its positive sequelae. The federal and drug administration (FDA) have recently approved a relatively few nanotechnology-derived small molecule drugs in cancer chemotherapy; despite this apparent inertia, this number is expected to exponentially increase with

the rising interest in this field of therapeutics (25). Furthermore, increased survival seen with some phenotypic cancers meant that the overall numerical burden of polypharmacy is likely to significantly change going forward. This will therefore call for a more rigorous proactive prospective databases examining key determinant themes of polypharmacy in this vulnerable population

Conclusion

With increasing survival of patients across cancer phenotypes, there is a commensurate increase in the risk of polypharmacy and its attendant sequalae. But unlike in the general population, therapeutic uncertainty remains across various themes of polypharmacy in these cohorts of patients and will require exploration by future prospective studies. This will include a revaluation of the exact numerical threshold that defines polypharmacy in patients with Cancer; its prevalence and global trend of socio-demographic factors that drive it; as well as whether a dichotomized phenotype of polypharmacy in cancer patient cohorts (cancer and noncancer related polypharmacy) has the propensity to more robustly identify cohorts that would most adequately respond to therapeutic interventions.

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