Journal of Geriatric Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Review article

Are phase I trials safe for older patients?

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ARTICLE INFO

Article history:
Received 12 April 2017
Received in revised form 13 July 2017
Accepted 23 August 2017
Available online xxxx

Keywords:
Phase I trial
Cancer
Drug development
Older patients
Toxicity

ABSTRACT

Phase I clinical trials in oncology primarily aim to assess the toxicity profile of new drugs and determine recommended phase II doses (RP2D). Since the cancer rate increases with age and our population is continually aging, RP2D must necessarily be assessed in older patients. Few clinical studies include older patients, however, and particularly few Phase I trials. We reviewed published data on the safety and efficacy of Phase I trials in older patients. The majority of studies included primarily young, fit patients, with age thresholds varying widely from 65 to 80 years. However, age does not seem to be associated with more toxicity or less efficacy. While Phase I trials seem feasible in fit older patients, geriatric-medicine score systems should be included in the clinical trial design in order to better characterize this population.

Contents

1. Introduction

The cancer rate increases with age. Due to the epidemiology of our aging population and increasing cancer incidence, cancer in the elderly is a major public health concern. Predictions for France estimate that 50% of all new cancer cases will be diagnosed in patients over 75 years old in 2050 [1]. Oncologists have to be aware of this issue and gain knowledge of how to treat older patients considering the complexity of their cases.

To better understand and adapt treatment for older patients, clinical trials should be conducted in this population. Unfortunately, only few older patients have so far been included into trials, despite general awareness of the need [2–6].

Ho et al. reported that patients over 70 years old are less eligible to enter early-phase trials, and particularly Phase I trials [6]. This may be due to the increased number of comorbidities, polypharmacy, physician perceptions, patient refusal, or lack of awareness about clinical trials [7]. Basche et al. reported that the older patients' unwillingness to be treated in an early-phase trial at a university cancer center was due to their concern about the loss of continuity with their primary oncologist, as well as about trying experimental treatments [8]. However, data from younger patients cannot be extrapolated without caution to the elderly,

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http://dx.doi.org/10.1016/j.jgo.2017.08.012
1879-4068/

given that aging proves to be a complex process with multiple changes. Pharmacokinetics and pharmacodynamics are modified in these populations, especially due to altered renal and hepatic functions.

Prospective studies and Phase I trials are thus required to be performed in the elderly in order to better understand drug metabolism in this population. This review sought to discuss the safety and efficacy data available from Phase I trials conducted in older patients.

2. Pharmacology of Anticancer Drugs in the Elderly

2.1. Pharmacokinetics and Pharmacodynamics

As people age, numerous physiological changes occur. These modifications may impact anticancer drug metabolism, altering absorption, distribution, metabolism, or excretion, thereby resulting in increased toxicity and lower efficacy. These alterations are outlined in Fig. 1.

Older patients exhibit variable pharmacokinetic profiles, particularly due to gastrointestinal modifications and body mass composition changes. Drug absorption can be affected by decreased gastrointestinal motility, splanchnic blood flow, liver mass, secretion of digestive enzymes, and mucosal atrophy observed in older patients [9,10].

Body composition, which is known to significantly influence pharmacokinetics, also changes with age. Increasing body fat combined with decreasing lean body mass and total body water result in increased volume of distribution, prolonged half-life for liposoluble drugs, and decreased volume of distribution for hydrosoluble drugs [11]. Muscle mass has been reported to decline 1–3% per decade in men starting by age 30 and 2–3% per decade after age 60, whereas fat mass has been reported to increase by 2% per year after age 65 in men [12–15]. Moreover, malnutrition with decreased albumin concentration is often associated with aging. The progressive reduction of albumin serum concentration ranges between 0.08 and 0.17 g/L (0.2–0.5%) per year with greater reductions in men than in women [16]. This explains the increased exposure to drugs that bind to albumin, such as paclitaxel. Lichtman et al. demonstrated that while mean paclitaxel exposure was highest in the oldest patient cohort (75 years or older; $p = 0.01$) compared to the youngest (<75 years), owing to hypoalbuminemia, this did not result in higher toxicity, except for Grade 3 neutropenia [17].

Reduction in the number of nephrons is also associated with aging, possibly influencing the body's elimination of drugs. Denic et al. showed that the nephron number decreases by 7.3% per age decade [18]. Two-thirds of patients exhibit decreased creatinine clearance with age [19], which may be linked to an increased area under the plasma concentration curve (AUC) of certain drugs, as well as enhanced toxicity. The 2007 SIOG guidelines for adjusting doses in older cancer patients were defined with these issues in mind [20]. Dose adjustments are described according to drug and renal function. Renal function needs to be calculated for each patient using aMDRD (Modification of the Diet in Renal Disease) or Cockroft-Gault formulae prior to treatment initiation.

Finally, absorption of oral cancer treatments, such as tyrosine kinase inhibitors (TKIs) or capecitabine, increases in correlation with rising gastric pH values, potentially resulting in increased toxicity. Pepsin, both basal and stimulated secretions decline after 70 years of age (divided by four between 70 and 90) which resulted in increased gastric pH [21]. Crombag et al. reported the impact of aging on the pharmacokinetics of cytotoxic agents like taxanes, anthracyclines, vinorelbine, capecitabine, and platinum in breast cancer patients [9,22–24]. There is very little data available, however, on the safety and efficacy of oral cancer drugs in the elderly.

Pharmacodynamics depends on drug concentration and response at the receptor, in addition to post-receptor events within cells and homeostatic mechanisms. All these pharmacodynamic mechanisms can be affected by aging. Older age is associated with increased sensitivity to cardiovascular medications, anticoagulants, benzodiazepines and drugs used in anesthesia [25,26]. Evidence is scarce regarding pharmacodynamics of cancer therapies with age. A retrospective study showed that age >80 years old was associated with increased risk of congestive heart failure in patients treated with trastuzumab [27]. Further studies are needed to better describe pharmacodynamics of cancer drugs in the elderly.

2.2. Polypharmacy

Age is associated with an increasing intake of concomitant medications due to prescriptions being poorly monitored, in addition to comorbidities increasing with age. Polypharmacy is defined as the consumption of more than five concomitant medications, resulting in an increased risk of interactions between concomitant medications [28,29]. This is a major concern in the elderly, with potentially altered pharmacokinetics and pharmacodynamics. Metabolic pathways are likely to be manipulated in the elderly by polypharmacy. For example, cytochrome p450-mediated drug-drug interactions (DDI) were reported in a prospective cohort study was among 275 consecutive new patients aged 65 years and older with polypharmacy (>5 drugs) admitted to a community hospital. The prevalence of a potential hepatic cytochrome enzyme-mediated DDI was 80%. Addition of each medication to a 5-drug regimen conferred a 12% increased risk of a potential CYP-mediated DDI after adjustment [30]. Furthermore, for patients with cancer the majority of TKIs are metabolized via CYP3A4, which is an enzyme involved in around 80% of the drugs metabolism making the risk of DDI very high. Polypharmacy has also been reported to affect a patient's nutritional status. In a prospective cohort study of 294 survivors from the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly Study, excessive polypharmacy was associated with declined nutritional status evaluated through mini nutritional assessment. In the excessive polypharmacy group, the proportion of malnourished or at risk of it was 50%. This may affect drug distribution and therefore its activity and toxicity [31].

Oncologists should be aware of inappropriate drug use and adverse drug reactions, since the number of older patients with cancer is increasing, with polypharmacy being a common feature of this population [32]. Two analytical tools are commonly used to detect prescription errors in the elderly by means of the Beers criteria: Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert Doctors to Right Treatment criteria (START). Both tools have recently been updated and can prove useful to verify interactions between concurrent medications. Of note is, however, that there is surprisingly no data available regarding anti-tumor agents [33].

Furthermore, polypharmacy may be associated with frailty, and one of the G8 items is specifically focused on polypharmacy, demonstrating the latter's relevance in older patients. In addition, polypharmacy may be a risk factor for poor tolerance and associated poor treatment adherence [34].

Drug interactions are particularly relevant for Phase I studies, given that they likely alter both drug metabolism and tolerance, potentially preventing us from establishing correct dose levels for the subsequent Phase II studies. Therefore, drug interactions in older patients are very common; they must thus be searched for and recorded at each patient Visit.

3. Phase I Trials in the Elderly

3.1. Safety (Table 1)

Phase I trials are designed to assess pharmacokinetics and recommend dose levels for the subsequent Phase II studies. This is of special interest in the elderly for the aforementioned reasons. Nevertheless, only five of the currently ongoing Phase I trials are specifically dedicated to older patients (NCT02735057; NCT02467946; NCT03129828; NCT02799550; NCT02228772).

One Phase I trial is particularly noteworthy, specifically involving older patients who were stratified according to age into two groups:

Please cite this article as: Baldini C, et al, Are phase I trials safe for older patients? J Geriatr Oncol (2017), http://dx.doi.org/10.1016/j.jgo.2017.08.012