short review

memo (2021) 14:11–14
https://doi.org/10.1007/s12254-020-00668-z

memo
magazine of european medical oncology

Pharmacokinetic considerations in geriatric cancer patients

Martin Hohenegger

Received: 14 September 2020 / Accepted: 11 November 2020 / Published online: 3 December 2020

Summary Pharmacological anticancer therapy in elderly people has to account for pharmacokinetic aspects in view of age-related changes in organ function and disease-related alterations. Age-related changes in organ function might still be physiological and have to be discriminated from concomitant diseases and their pharmacotherapy. Although efficacy is retained with pharmacological anticancer therapies in elderly patients, plasma drug concentrations and the incidence of adverse reactions often increase. Thus, altered organ function in elderly will be reviewed with respect to clinically relevant outcomes. Furthermore, possible consequences of therapeutic drug monitoring will be discussed focusing on novel targeted therapies with small molecules. Examples of therapeutic drug monitoring during targeted therapies may represent an easy tool to overcome the individual pharmacokinetic situation of elderly cancer patients and may contribute to enhanced safety, when implemented in clinical routine.

Keywords Pharmacokinetics · Gene polymorphisms · Targeted anticancer therapies · Therapeutic drug monitoring · Health services for the aged

Abbreviations

C_{min}	Minimal plasma concentrations
C_{trough}	Trough concentration

M. Hohenegger (✉)
Centre for Physiology and Pharmacology, Institute of Pharmacology, Medical University of Vienna, Währingerstraße 13A, 1090 Vienna, Austria
martin.hohenegger@meduniwien.ac.at

Introduction

In Western countries the incidence of cancer increases with age (≥65 years) and consequently is associated with life expectancy [1]. Elderly benefit from chemotherapies similar to other age groups, implying that age per se does not represent a limitation to access an anticancer therapy. Conversely, drug side effects occur more often and are related to age-related changes in organ function, concomitant diseases or drug plasma concentration below or above therapeutic relevant recommendations [2]. The pronounced heterogeneity in health conditions of elderly cancer patients maximizes individualisation of targeted anticancer therapies. The introduction of targeted anticancer therapies has improved the overall outcome in cancer patients including elderly [3, 4]. Beside better prognosis, the incidence and severity of adverse effects have been reduced so that benefit–risk evaluation of novel targeted therapies gradually contribute to favourable overall survival rates including the elderly.

Pharmacokinetic changes in the elderly

The performance status of the elderly is dependent on age, comorbidities and their therapies. Aged patients suffer from decreased symptom awareness, which often implicates psychological distress, anxiety or depressive symptoms. Reduced communication may also result from oral and dental problems. Consequently, patients may be categorized simply into fit, vulnerable and fragile or based on a subtly depicted comprehensive geriatric assessment (Karnofsky index or ECOG score) [5]. In accordance with this risk assessment therapeutic consequences may result in reduced intensification or avoidance of anticancer therapy. Conversely, reduction of polypharmacy may also

represent a prerequisite for initiation of chemotherapy in order to prevent drug–drug interactions and decrease the number of side effects (www.deprescribing.org) [6]. In support of this correlation, the geriatric performance status has been identified as a key predictor of chemotherapy-related toxicity, therapy discontinuation and survival [7, 8].

At rest, age-related changes in organ function do not generally result in reduced organ function. Conversely, in response to physical activity, psychological stress or disease related situations reduced organ functions decline with the age. In response to exercise the cardiovascular system also progressively declines with age [9].

Age-related changes in splanchnic blood flow involve reduction in gastrointestinal motility and secretory gland activity. As a consequence mucosal atrophy is observed, which not only increases the risk for gastric and duodenal ulcerations, but also reduces the intestinal surface for drug absorption. However, to what extent drug absorption is affected solely by age-related alterations in the gastrointestinal tract remains to be elucidated.

Similarly, reduced liver mass, liver perfusion and related metabolism have been reported [10]. Interestingly, reduced levels of enzymes of the cytochrome P-450 system have been described for CYP2E1, CYP3A4 and NADPH cytochrome c reductase [10]. However, age-related alterations in liver parameters and function are not superior to drug metabolisation related to individual polymorphisms in liver enzymes or consecutive drug–drug interactions on the level of hepatic metabolisation [11].

In accordance with the age-related performance status one has to bear in mind that aging is roughly associated with a ~1% reduction in skeletal muscle mass per year. Thus, serum creatinine is not predictive for glomerular filtration rate or renal function in this age group. Hence, various algorithms have been established to determine the glomerular filtration rate indirectly from serum creatinine. The Cockroft–Gault formula has been used extensively, but sometimes underestimates glomerular filtration rate [12]. Alternatively, serum concentration of urea has been evaluated as a sensitive indicator for renal function in the elderly. Thus, using serum urea levels the Levey algorithm provides an accurate estimation of renal clearance [13]. Nevertheless, the Cockroft–Gault formula has been recently confirmed to be accurate and safe to adopt pharmacotherapy to reduced renal function (creatinine clearance <50 ml/min) in lung cancer patients [14].

As soon as the creatinine clearance drops below 50 ml/min one has to consider dose reduction independent of age [12]. Moreover, drugs with an extrarenal elimination below 50% require considerable dose reduction. A rapid and practicable approach is provided under the web link www.dosing.de (Clinical Pharmacology and Pharmacoepidemiology Department, Medical University Heidelberg, Germany). The databank summarizes pharmacokinetic parameters and dose recommendations according to renal function for the most commonly used drugs including anticancer therapeutics. Nevertheless, renal function is the central dosing relevant parameter in the elderly and thus should be considered essential for therapeutic concepts [12, 15].

Given this various changes in organ and tissue function, the interindividual variability in drug disposition is large in elderly persons. Hurria and Lichtman have summarized chemotherapeutic studies including elderly with reduced performance and found in 5 out of 18 studies an age-related decrease in drug clearance [16]. Thus, geriatric performance status, comorbidity and polypharmacy represent higher risk factors than age alone.

Comorbidities

Comorbidities in elderly cancer patients are associated with a poor prognosis, which may reflect reduced survival and outcomes. Consequently, these patients are generally not included in randomized clinical trials, leaving the published data on this population vague and limited [6]. Thus, comorbidities in the elderly may include kidney diseases, latent infections or impairments of blood cell counts. In addition, polypharmacy is highly prevalent in the elderly and often related to diabetes, lipidemia, hypertension and coronary heart disease [9, 11]. Besides the aforementioned interactions in various organ systems, cardiovascular interactions, in particular ischemic complications and reduction in cardiac ejection fraction, are often seen in high-dose chemotherapy [17]. The spectrum of cardiovascular side effects is not restricted to classical chemotherapeutics, but also observed with novel targeted chemotherapies. The cardiac toxicity of anthracyclines has been well-described for a long time and prevented by dose limitation. Similarly, high doses of cyclophosphamide or ifosfamide predispose to the development of reversible heart failure and arrhythmias. With respect to specific anticancer strategies, antibody-based targeted therapies (trastuzumab, bevacizumab and alemtuzumab) and tyrosine kinase inhibitors (imatinib, sunitinib, lapatinib and dasatinib) are associated with heart failure, hypotension, or hypertension [17]. Thus, patients with pre-existing cardiovascular risks may substantially improve from referral to a cardiologist for close monitoring of cardiovascular parameters and exclusion from cardiotoxic chemotherapies. Conversely, early detection of a decline in cardiovascular function may facilitate dose adjustments and pharmacological counter manoeuvres.

Genetic polymorphisms and therapeutic drug monitoring

Genetic polymorphisms may contribute to additional heterogeneity in the population of elderly patients. However, a defined polymorphism does not necessarily translate into a clinical relevant consequence. Such a defined mutation in a drug-metabolizing enzyme might be silent in adult individuals because the function is totally compensated by other isoforms or related enzymes. In elderly, due to reduced liver function and consequently reduced protein synthesis such compensation mechanisms might be uncovered and become clinically relevant. Of course, such an assumption is currently strictly hypothetical and needs further investigations.

In order to escape this conundrum one would circumvent these ill-defined, but individual risk factors by adapting cancer therapy to plasma drug concentrations. If predefined, one may adapt chemotherapeutics according to plasma levels defined as a therapeutic window between minimal efficacy and the risk of overdosage.

There is cumulating evidence that surveillance of plasma concentrations of kinase inhibitors and other small molecules used in anticancer strategies improves efficacy and reduced the risk of side effects [18, 19]. From a pharmacological point of view monitoring of the plasma concentration over 2–4 half-lives would be perfect to account for individual bioavailability and clinical efficacy. Due to the work load, turnaround times and costs, such an approach is not feasible in clinical routine or ambulant chemotherapy. Novel developments using on-site biosensor technologies may overcome these limitations and enable future implementation in clinics [20]. Hence, the minimal plasma concentrations (C_{min}) or trough concentration (C_{trough}) of drugs immediately before the next drug application have been established as a single pharmacokinetic parameter, sufficient to circumvent underdosing or overdosing, once there are established C_{min} values available for all anticancer drugs [21].

Due to regular practice C_{trough} values were used in therapeutic drug monitoring, in particular through clinical trials to monitor for example the efficacy and adverse effects during application of novel tyrosine kinase inhibitors [22, 23]. Investigation of outpatients treated with tyrosine kinase inhibitors like imatinib, erlotinib or sunitinib did not reach the recommended C_{trough} values in 73.2%, 11.1% and 48.6%, respectively [24].

A C_{trough} value for imatinib of 1 µg/ml was defined to reflect efficacy in CML patients. In two randomized controlled trials, only 33% of the patients reached this value. Consecutive dose adjustment enhanced response rates after 12 months from 37% to 63% [23, 25]. Interestingly, C_{trough} values have been also defined for nilotinib and dasatinib in imatinib-resistant chronic myeloid leukemia patients and resulted in significantly improved response rates [26, 27]. Together, these results corroborate the efficacy of therapeutic drug monitoring of tyrosine kinase inhibitors and the importance of dose optimization to obtain therapeutic success.

In a real-world cohort study (454 patients), comparing tyrosine kinase inhibitors exposed to two age groups (<70 years and ≥70 years) only dabrafenib showed significantly higher exposure in older patients. Conversely, erlotinib, imatinib, pazopanib, sunitinib and vemurafenib exposure was not affected by age of patients [28]. Importantly, one third of total patients did not reach the proposed target concentration of their tyrosine kinase inhibitor, indicating that individual drug monitoring may improve cancer therapy independent of age. Hence, individual drug monitoring in cancer therapy and particular elderly populations is recommended to reach effective plasma concentrations [29]. However, therapeutic drug monitoring is not implemented in the daily routine given the cost, time and manpower consuming hurdles.

Conclusion

The complexity of interactions between comorbidities, polypharmacy and age-related changes in pharmacokinetics justifies the general rule “start low, go slow” in aged individuals. However, one can foresee that therapeutic drug monitoring of targeted therapies may regain efficacy and safety particularly in elderly patients.

Take-home message

Heterogeneity in health status of geriatric cancer patients maximizes individualisation of anticancer therapies. Hence, implementation of therapeutic drug monitoring of targeted therapies may regain efficacy and safety.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest M. Hohenegger declares that he has no competing interests.

References

1. Denson AC, Mahipal A. Participation of the elderly population in clinical trials: barriers and solutions. Cancer Control. 2014;21(3):209–14.
2. Power DG, Lichtman SM. Chemotherapy for the elderly patient with colorectal cancer. Cancer J. 2010;16(3):241–52.
3. Losanno T, Gridelli C. Recent advances in targeted advanced lung cancer therapy in the elderly. Expert Rev Anticancer Ther. 2017;17(9):787–97.
4. Zhang Q, Wang Z, Guo J, Liu L, Han X, Li M, et al. Comparison of single-agent chemotherapy and targeted therapy to first-line treatment in patients aged 80 years and older with advanced non-small-cell lung cancer. Onco Targets Ther. 2015;8:893–8.
5. Balducci L, Colloca G, Cesari M, Gambassi G. Assessment and treatment of elderly patients with cancer. Surg Oncol. 2010;19(3):117–23.
6. Lee L, Cheung WY, Atkinson E, Krzyzanowska MK. Impact of comorbidity on chemotherapy use and outcomes in solid tumors: a systematic review. J Clin Oncol. 2011;29(1):106–17.
7. Wildes TM, Ruwe AP, Fournier C, Gao F, Carson KR, Piccirillo JF, et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. J Geriatr Oncol. 2013;4(3):227–34.
8. Phaibulvatanapong E, Srinonprasert V, Ithimakin S. Risk factors for chemotherapy-related toxicity and adverse events in elderly thai cancer patients: a prospective study. Oncology. 2018;94(3):149–60.
9. Lakatta EG. Age-associated cardiovascular changes in health: impact on cardiovascular disease in older persons. Heart Fail Rev. 2002;7(1):29–49.
10. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18(11):837–51.
11. Mannheimer B, Eliasson E. Drug-drug interactions that reduce the formation of pharmacologically active metabolites: a poorly understood problem in clinical practice. J Intern Med. 2010;268(6):540–8.
12. Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol. 2010;5(2):314–27.
13. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (〉70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. Scand J Urol Nephrol. 2004;38(1):73–7.
14. Hubner RA, Goldstein R, Mitchell S, Jones A, Ashley S, O'Brien ME, et al. Influence of co-morbidity on renal function assessment by Cockcroft-Gault calculation in lung cancer and mesothelioma patients receiving platinum-based chemotherapy. Lung Cancer. 2011;73(3):356–60.
15. Feliu J, Jiménez-Munárriz B, Basterretxea L, Paredero I, Llabrés E, Antonio-Rebollo M, et al. Predicting Chemotherapy Toxicity in Older Patients with Cancer: A Multicenter Prospective Study. Oncologist. 2020 Apr 23;25(10):e1516–24. https://doi.org/10.1634/theoncologist.2019-0701.
16. Hurria A, Lichtman SM. Pharmacokinetics of chemotherapy in the older patient. Cancer Control. 2007;14(1):32–43.
17. Monsuez JJ. Detection and prevention of cardiac complications of cancer chemotherapy. Arch Cardiovasc Dis. 2012;105(11):593–604.
18. Yu H, Steeghs N, Nijenhuis CM, Schellens JH, Beijnen JH, Huitema AD. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. Clin Pharmacokinet. 2014;53(4):305–25.
19. Klumpen HJ, Samer CF, Mathijssen RH, Schellens JH, Gurney H. Moving towards dose individualization of tyrosine kinase inhibitors. Cancer Treat Rev. 2011;37(4):251–60.
20. Ates HC, Roberts JA, Lipman J, Cass AEG, Urban GA, Dincer C. On-site therapeutic drug monitoring. Trends Biotechnol. 2020;38(11):1262–77.
21. Ward MB, Reuter SE, Martin JH. How 'optimal' are optimal sampling times for tyrosine kinase inhibitors in cancer? Practical considerations. Clin Pharmacokinet. 2016;55(10):1171–7.
22. Eechoute K, Fransson MN, Reyners AK, de Jong FA, Sparreboom A, van der Graaf WT, et al. A long-term prospective population pharmacokinetic study on imatinib plasma concentrations in GIST patients. Clin Cancer Res. 2012;18(20):5780–7.
23. Gotta V, Widmer N, Decosterd LA, Chalandon Y, Heim D, Gregor M, et al. Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. Cancer Chemother Pharmacol. 2014;74(6):1307–19.
24. Lankheet NA, Knapen LM, Schellens JH, Beijnen JH, Steeghs N, Huitema AD. Plasma concentrations of tyrosine kinase inhibitors imatinib, erlotinib, and sunitinib in routine clinical outpatient cancer care. Ther Drug Monit. 2014;36(3):326–34.
25. Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, et al. Long-term follow-up of the French stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. J Clin Oncol. 2017;35(3):298–305.
26. Giles FJ, Yin OQ, Sallas WM, le Coutre PD, Woodman RC, Ottmann OG, et al. Nilotinib population pharmacokinetics and exposure-response analysis in patients with imatinib-resistant or -intolerant chronic myeloid leukemia. Eur J Clin Pharmacol. 2013;69(4):813–23.
27. Shah NP, Guilhot F, Cortes JE, Schiffer CA, le Coutre P, Brummendorf TH, et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. Blood. 2014;123(15):2317–24.
28. Crombag MBS, van Doremalen JGC, Janssen JM, Rosing H, Schellens JHM, Beijnen JH, et al. Therapeutic drug monitoring of small molecule kinase inhibitors in oncology in a real-world cohort study: does age matter? Br J Clin Pharmacol. 2018;84(12):2770–8.
29. Knezevic CE, Clarke W. Cancer Chemotherapy: The Case for Therapeutic Drug Monitoring. Ther Drug Monit. 2020;42(1):6–19.