Elderly patients with gastrointestinal stromal tumour (GIST) receive less treatment irrespective of performance score or comorbidity – a retrospective multicentre study in a large cohort of GIST patients

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Abstract (250 words, max 250)

Objective Although gastrointestinal stromal tumours (GIST) predominantly occur in older patients, data on treatment patterns in elderly GIST patients are scarce.

Methods Patients registered in the Dutch GIST Registry from January 2009 until December 2016 were included. Differences in treatment patterns between elderly(≥75 years) and younger patients were compared. Multivariate analyses were conducted using logistic regression.

Results Data of 145 elderly and 665 non-elderly were registered (median age 78 and 60 years respectively). In elderly, performance score and age-adjusted Charlson comorbidity index were significantly higher (p=0.05; p<0.001), and albumin level significantly lower (p=0.04).

Hundred-and-nine (75.2%) elderly and 503 (75.6%) non-elderly had only localised disease. Surgery was performed in 57% of elderly versus 84% of non-elderly (p=0.003, OR:0.26, 95% CI:0.11-0.63). No differences in surgery outcome or complications were found. Thirty-eight percent of elderly with an indication for adjuvant treatment did receive imatinib versus 68% of non-elderly (p=0.04, OR:0.47, 95% CI:0.23-0.95).

Thirty-six elderly and 162 non-elderly had metastatic disease. Palliative imatinib was equally given (mean dose 400 mg) and adverse events were mostly minor (p=0.71). In elderly, drug-related toxicity was in 32.7% reason to discontinue imatinib versus 5.1% in non-elderly (p=0.001, OR 13.5, 95% CI 2.8-65.0). Median PFS was 24 months in elderly and 33 months in non-elderly (p=0.10). Median OS was 34 months and 59 month

s respectively (p=0.01).

Conclusions Elderly GIST patients with localised disease receive less surgery and adjuvant treatment, irrespective of comorbidity and performance score. Drug-related toxicity results more often in treatment discontinuation. This possibly results in poor outcome.

Key words

Gastrointestinal stromal tumours; GIST; elderly; imatinib

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours in the gastrointestinal tract. Annual incidence is estimated to be between 11 and 19.6 per million worldwide [1]. The highest incidence is found in the age group of 60-74 years, closely followed by patients 75 years of age and older.[2] The latter age group is growing as life-expectancy continues to increase. Besides, patients 75 years of age and older have an estimated life expectancy of up to 12 years.[3] Nevertheless, studies on treatment strategies in elderly GIST patients are scarce.

Since the introduction of imatinib, a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, KIT and PDGFR, treatment of patients with advanced GIST has been spectacularly improved. Up to 85% of GIST patients with advanced disease derive clinical benefit

from imatinib.[4] One retrospective study in GIST patients 75 years of age and older with advanced disease found survival rates similar to survival rates described in the overall GIST population.[5]

In patients with resectable localised disease, primary therapy consists of surgery. For patients with high-risk of recurrence, adjuvant treatment with imatinib is recommended.[6,7] Despite this recommendation, a prior study showed that adjuvant treatment with imatinib in patients with high-risk disease is significantly less frequently given in patients 65 years of age and older.[8] As frailty, disability and multimorbidity are more common in the elderly population, treatment decisions might be influenced.[9] The aim of this study was to assess differences in treatment strategies between elderly patients (aged ≥75 years) and younger patients (<75 year old) with GIST.

Methods

Patients

All patients entered in the Dutch GIST Registry (DGR) were included in this cohort analysis. This database includes all GIST patients treated between January 2009 and September 2016 in one of 5 GIST expert centres in the Netherlands: the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Leiden University Medical Centre, Erasmus University Medical Centre, Radboud University Nijmegen Medical Centre and the University Medical Centre Groningen. Data acquisition was approved by local independent ethics committees, and the study was conducted in accordance with the Declaration of Helsinki.

Variables

Baseline demographic data, such as gender, age, ethnic origin, baseline World Health Organization Performance Score (WHO PS) and baseline albumin level, and comorbidities, were retrieved from the DGR. Comorbidities were scored using the Charlson Comorbidity Index (CCI).[10] Tumour specific data, such as location, size, mitotic rate and mutation status were also retrieved from this database. Tumour measurements were derived from computed tomography (CT) scans, positron emission tomography (PET) scans, and magnetic resonance imaging (MRI).

For systemic treatment, the database includes treatment objective, treatment type (imatinib, sunitinib, regorafenib or other), dose, duration of treatment and reasons for treatment interruptions. Also, adverse events during systemic treatment were entered and assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. For surgery, reason for surgery, surgery technique (endoscopy, laparoscopic and open laparotomy), extent of surgery and surgery outcome have been registered.

Statistical analyses

Statistical analyses were executed using IBM SPSS Statistics 23. Cut-off date for clinical outcome was 28 December 2016. For this analysis patients with a lower age limit of 75 years or older were defined as elderly, in accordance to prior studies in both GIST and general geriatric oncology.[5,11,12] Analyses on adjuvant treatment strategies were assessed only in patients who had a high-risk (>50% risk of recurrence according to Miettinen's criteria) GIST resected and who had a registration date starting from March 2011.[13] From this date adjuvant imatinib treatment was officially implemented in the Netherlands.[14] Differences between elderly patients and younger patients were assessed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Variables with a p-value <0.05 in univariate analyses were included in the multivariate analyses using a logistic regression model. Progression free survival (PFS) was calculated in patients receiving systemic treatment with palliative intent and was defined as the time from start of treatment until disease progression, death or last patient contact. Overall survival (OS) was calculated in patients with localised disease and patients with metastatic disease separately and was defined as the time of registration in the hospital until death or last contact. Survival analysis was conducted using the Kaplan-Meier method. All tests were two-sided and a p-value of <0.05 was considered significant.

Results

Demographic characteristics

In total 810 patients were entered in the DGR of whom 145 (17.6%) patients were 75 years of age and older. Table 1 shows differences in demographic characteristics between elderly and non-elderly patients. Baseline WHO PS and age-adjusted CCI score were significantly higher in elderly patients, albumin level was significantly lower. (Table 1)

Patients with localised disease

In total 109 elderly and 503 non-elderly in the DGR had non-metastatic disease. Surgery was performed in 57% of the elderly compared to 84% in the non-elderly (p<0.001). (Table 2) No significant differences in surgery technique, type, surgical outcome or complications were found. (Table 3) In multivariate analyses, elderly were still less likely to receive surgery (p=0.003, OR 0.26, 95% CI 0.11-0.63).

Furthermore, 8 out of 20 (38%) of elderly patients with an indication for adjuvant treatment did receive imatinib in adjuvant setting compared to 78 out of 112 (68%) of the non-elderly (p=0.03). (Table 2) Also in multivariate analyses adjuvant treatment was initiated less in elderly (p=0.04, OR 0.47, 95% CI 0.23-0.95). In addition, in univariate analyses elderly patients with localised disease were more likely to receive imatinib with palliative intent (p=0.05), but multivariate analysis showed no significant difference (p=0.07, OR 1.70, 95% CI 0.73-3.96).

Fifteen elderly with localised disease (10.3%) received no treatment at all, compared to 20 non-elderly (3.0%; p<0.01). Follow-up was terminated in 44 elderly (41.1%) and in 89 non-elderly (17.8%). Median follow-up time in elderly was 30 months (95% CI 23.23-36.32) and was 74 months (no 95% CI could be calculated) in non-elderly (p<0.001). (Figure 1)

Sixteen elderly with localised disease (15.0%) died during follow up, of whom 6 of disease progression (5.6%). In the non-elderly group 39 patients (7.8%) died, 12 of disease progression (2.4%). Median OS was not reached.

Patients with metastatic disease

In total, 36 elderly had metastatic disease at registry entry. Imatinib was given in 86% of elderly patients. (Table 4) The mean daily dose of imatinib was 400 mg for elderly compared to 395 mg for non-elderly (p=0.33). Also, second- and third-line therapy were given equally in elderly and non-elderly. (Table 4) Adverse events were equally common in elderly and non-elderly (71.4% and 69.4% respectively). Most adverse events in both groups were grade 1 or 2 (54.5% and 58.7% respectively) and no differences were found in occurrence of grade ≥3 adverse events (p=0.71). (Table 5) In 28 (57.1%) elderly with metastatic disease imatinib treatment was discontinued compared to 75 (38.3%) non-elderly (p=0.017). The most common reason to end imatinib treatment in elderly patients was an adverse event (57.1%). In non-elderly this was 13.3% (p<0.001). In elderly, progressive disease was in 38.1% of cases reason to end systemic treatment compared to 77.6% of non-elderly. In multivariate analysis, corrected for WHO PS, CCI, and albumin level, this difference was still significant (p=0.001, OR 13.5, 95% CI 2.8-65.0).

No difference in progression-free survival (PFS) was found (p=0.70). Median PFS was 24 month (95% CI 13.3- 34.7) in elderly compared to 33 months in non-elderly (p= 0.1, 95% CI 27.4-38.6). (Figure 2) Multivariate Cox regression including WHO PS, baseline albumin level, and CCI still did not show any significant differences in PFS (p=0.81).12 elderly (33.3%) and 31 non-elderly (19.1%) with metastatic disease have died during follow up. Nine elderly (25.0%) and 26 non-elderly (16.0%) have died of disease progression. Median OS was 34 months in elderly patients (95% CI 13.0-55.0) and 59 months in non-elderly (no 95% CI could be calculated) and was significantly shorter in elderly patients (p=0.01). (Figure 3)

Discussion

GISTs have a high incidence in the age group of 75 years of age and older.[2] However, studies on treatment strategies in elderly GIST patients are scarce as, in general, elderly cancer patients are underrepresented in trials.[12] This is a problem since life-expectancy is increasing. Currently in the Netherlands, elderly patients ≥75 years have an average life-expectancy of up to 12 years.[3] As frailty, disability and comorbidity are more common in the elderly population, treatment decisions may very well be influenced by these factors.[9] In our study we indeed found that elderly patients had worse WHO PS and lower albumin level. However, irrespective of performance status or comorbidity, elderly GIST patients with localised disease received less treatment.

Surgery was significantly less performed in the elderly. Meanwhile, in elderly patients who did receive surgery no difference in occurrence of major complications was found. One might argue that this is caused by successful selection of patients eligible for surgery. Especially since in our study almost 90% of surgery was conducted by open laparotomy. Meanwhile,

recent studies suggest that less invasive surgery, like laparoscopic and even endoscopic resection, is feasible and safe for poor PS elderly patients.[15,16] This might be an option for elderly patients who are deemed not eligible for open surgery.

In addition, adjuvant treatment was given significantly less in elderly patients after resection of a high-risk tumor. Our findings are similar to a prior study, where adjuvant treatment with imatinib in high-risk patients was significantly less given in patients 65 years of age and older.[8] However, it is well known that recurrence in hig-risk patients often occurs and studies showed that adjuvant treatment with imatinib for 36 months increased 5-year recurrence free survival from 36% to 65.6%.[17,18] Considering the increasing life-expectancy in elderly patients, adjuvant imatinib treatment might be beneficial, even in this age group. Besides, occurrence of adverse events related to imatinib treatment and dose of imatinib in our study was equal in the elderly and non-elderly group, suggesting equal tolerance to imatinib. Considering the low number of events, no recurrence free survival could be calculated in our cohort. However, slightly more elderly with localised disease have died of disease progression. An earlier study on age-related risk factors in GIST patients has also found worse disease specific survival rates in elderly patients compared to patients younger than 50 years of age.[19] Similar to our study they did not find any differences in tumour characteristics, suggesting that worse disease specific survival rates can be explained by lack of treatment in elderly patients. Moreover, in our registry less than 18% of the GIST patients are 75 years of age and older at diagnosis, while in the Netherlands this is estimated to be approximately 25% annually.[2] This suggests that a relatively large proportion of elderly GIST patients are not referred to a GIST centre, possibly resulting in a greater number of elderly GIST patients who do not receive treatment. It is unclear why less treatment is given in our elderly population with localised disease. One explanation might be that besides the physician's expert opinion, the elderly patient himself might be less motivated for treatment.

In contrast to elderly with localised disease, elderly patients with metastatic disease are treated similarly to non-elderly patients. Consistent with a prior study in elderly GIST patients aged ≥75 years with advanced disease, we found that first, second, and third line treatment are equally initiated in the elderly and non-elderly group.[5] Also, no difference in treatment efficacy or occurrence of adverse events was found. Similar to the study of Italiano et al, adverse events were mainly of grades 1 and 2. In their study they mention that most adverse events were medically manageable and dose reduction occurred in almost 50% of the cases.[5] In our study, however, mean imatinib dose was 400 mg in the elderly, suggesting that dose reductions rarely occurred in our population. It seems that adverse events were more often managed by treatment interruption rather than reducing imatinib dose. This might have caused a significantly shorter overall survival in elderly. Meanwhile, in the abovementioned study a dose reduction seemed not to result in worse survival rates. On the other hand, there is evidence that imatinib underexposure is associated with worse treatment outcome.[20,21] This might explain why in our study in case of an adverse events dose reduction rarely occurred. Also, rather than a decision made by the clinician, this might also be a patient motivated decision. An earlier study on compliance to treatment in GIST patients found that older GIST patients showed more non-compliance to therapy.[22] A dose reduction might improve compliance to therapy in elderly patients.

Moreover, considering the large interpatient variability, imatinib plasma levels give more insight in drug efficacy in the individual patient than dose does. Therapeutic drug monitoring (TDM) might therefore be useful in elderly patients with adverse events and might result in dose reduction without reducing treatment efficacy. Considering earlier findings, in our opinion a dose reduction seems to be a better advice than discontinuation of treatment.[5,23]

In conclusion, primary resection and adjuvant imatinib treatment seem feasible and effective treatments in elderly GIST patients with localised disease. However, irrespective of PS or comorbidity these patients receive less treatment. An objective evaluation of comorbidity using the CCI might improve the decisions-making process in elderly GIST patients. In case of adverse events during imatinib treatment a dose reduction is preferred rather than treatment discontinuation.

Conflicts of Interest Statement

Neeltje Steeghs received a research grant for the Dutch GIST Registry from Novartis, Pfizer and Bayer.

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