Evaluating Outcomes of FLOT protocol in Elderly Patients with Locally Advanced Gastric Adenocarcinoma

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ABSTRACT **Background:** Locally advanced gastric adenocarcinomas are treated with neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy. Since 2019 the standard of care for perioperative chemotherapy has been FLOT protocol. Concerns regarding the use of FLOT in elderly patients ≥ 65 years of age emerged due to the relatively high toxicity of this protocol.

Objectives: To evaluate the toxicity profile of FLOT and clinical outcome in elderly patients.

Methods: We conducted a retrospective analysis of patients with locally advanced gastric adenocarcinomas treated with FLOT between 2017–2023 at the Sheba Medical Center. The cohort was stratified by age (≥ or < 65 years). The primary outcome was overall survival (OS). Secondary outcomes were treatment-related toxicity. Kaplan-Meier analysis and Cox proportional hazard regression model were used to analyze the effect of exposure variables on OS.

Results: The study cohort included 91 patients. The median age was 60 years (IQR 50–67); 32 patients were included in the ≥ 65 years group, and 59 patients were included in the < 65 years group. Median follow-up was 40 months (IQR 17–58). Patients ≥ 65 years old received fewer cycles of FLOT compared to those < 65 years old (4.5 vs. 7 cycles, respectively, $P = 0.03$). Despite the difference in treatment intensity and cumulative chemotherapy dose, there was no difference in median OS between patients ≥ 65 years old compared with those < 65 years old ($P = 0.68$).

Conclusions: Elderly patients with locally advanced gastric adenocarcinomas received fewer cycles of perioperative FLOT without compromising clinical outcomes.

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KEY WORDS: age, FLOT, gastric cancer, overall survival, toxicity

Gastric cancer is the fifth most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths worldwide, with approximately 970,000 cases diagnosed and 660,000 deaths in 2022. The incidence of gastric cancer shows wide geographic variation, with particularly high rates in South-East Asia (https://gco.iarc.fr).

Until the early 2000s, the main treatment for locally advanced gastric adenocarcinomas (LAGAs) was surgical resection. However, disease recurrences were frequent and posed a major risk for death. The first evidence for a survival benefit of perioperative chemotherapy came from the MAGIC study, in which the addition of perioperative ECF chemotherapy (epirubicin, cisplatin, and 5-FU) was shown to increase 5-year overall survival (OS) from 23% to 36% [1]. Later studies, including the ACCORD 07 [2], CALGB 80101 [3], and OE05 [4] suggested that a doublet chemotherapy, excluding epirubicin, may suffice. Therefore, ECF was replaced by FOLFOX (5-FU plus oxaliplatin) as the preferred regimen in the perioperative setting [5].

In 2019, the FLOT4 phase III study showed superiority of the FLOT (docetaxel, oxaliplatin and 5- FU) protocol over ECF, improving median disease-free survival (DFS) (30 months vs. 18, respectively) and median OS (50 vs. 35 months, respectively) [6]. Therefore, FLOT was considered standard-of-care in perioperative therapy for LAGA [7]. However, FLOT is considered to be a relatively more toxic protocol compared with FOLFOX, due to the addition of docetaxel [8,9]. Two small retrospective studies comparing the toxicity of FLOT versus FOLFOX in the perioperative setting suggested that FLOT is associated with higher rates of neutropenia [10,11] and infection [11].

The choice between FLOT and FOLFOX perioperative regimens is mainly based on performance status, co-morbidities, and age. FLOT is preferred in patients with very good performance status, lack of co-morbidities, and younger age, while FOLFOX is reserved for patients with good to moderate performance status, significant co-morbidities, or older age.

The aim of the current study was to evaluate the correlation between elderly age and FLOT-related toxicity, and overall survival.

PATIENTS AND METHODS

PATIENT POPULATION

Our study population included a cohort of consecutive LAGA patients who initiated FLOT chemotherapy at the Sheba Medical Center during the years 2017–2023. We excluded patients with known metastasis, mismatch-repair deficiency, or microsatellite instability, as well as patients initiating chemotherapy following surgery. The study was approved by the institutional review boards of Sheba Medical Center and Israeli Ministry of Health (SMC-5899-19 and MOH 201910550, respectively).

OUTCOME VARIABLES

The primary outcome of interest was OS. Follow-up started at the initiation of chemotherapy and ended at either disease progression, death, loss to follow-up, or data cutoff in April 2024. OS was assessed comparing patients ≥ 65 years old versus < 65 years old. Secondary outcome included adverse events (AEs) noted during the period of chemotherapy administration. Adverse events included leukopenia, neutropenia, anemia, thrombocytopenia, and abnormal liver function tests. Common Terminology Criteria for Adverse Events version 5.0 was used to record AEs.

EXPOSURE VARIABLES

Demographic and basic clinical information included age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status score defined as a dichotomous variable (i.e., 0–1 vs. ≥ 2). All patients were initially treated with FLOT, which was either continued until the end of therapy or downgraded by omitting oxaliplatin or docetaxel. Chemotherapy intensity was defined by the number of FLOT cycles, total number of chemotherapy cycles, and actual dose of oxaliplatin as a percentage of the planned dose.

STATISTICAL ANALYSIS

Continuous variables were described as median and IQR, while categorical variables were described as number and percentage. Kaplan-Meier analysis and univariate Cox proportional hazard regression model were used to analyze the effect of all exposure variables on OS. A multivariable model was generated using Cox proportional hazards regression modeling. A two-sided P-value < 0.05 was considered statistically significant. Statistical analyses were performed using R Statistical Software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study cohort included 91 consecutive LAGA patients, treated at the Sheba Medical Center between the years 2017–2023. Median age was 60 years (IQR 50–67). Median follow-up time was 40 months (IQR 17–58). Baseline characteristics of patients are presented in Table 1. There was no difference in tumor, node, metastasis staging between the two age groups (data not shown).

Table 1. Patient characteristics

Characteristic	N=91
Age*	60 (50–67)
Age group, n (%)	
≥ 65 years	32 (35%)
< 65 years	59 (65%)
T stage, n (%)	
1	5 (5.5%)
2	15 (16.4%)
3	26 (28.6%)
4	15 (16.4%)
Unknown	30(33%)
N stage, n (%)	
0	45 (49.5%)
1	24 (30%)
2	15 (16.5%)
3	4 (4.4%)
Unknown	3(3.3%)
Number chemotherapy cycles*	8 (6–8)
Number FLOT Cycles*	7 (4–8)
Percent of oxaliplatin*	89 (70–98)

*Median (IQR)

Patients ≥ 65 years old received significantly fewer cycles of FLOT compared with those < 65 years old (4.5 vs. 7.0 cycles, respectively, $P = 0.03$) and fewer cycles of any chemotherapy (7.0 vs. 8.0 cycles, respectively, $P = 0.01$). In addition, patients ≥ 65 years old received a significantly lower total dose of oxaliplatin, compared with those < 65 years old (76% vs. 93% of the planned dose, respectively, $P = 0.004$) [Table 2]. There were no differences in the incidence of leukopenia, neutropenia, anemia, thrombocytopenia and elevated liver enzymes between the two age groups (data not shown).

Table 2. Comparison of treatment intensity between patients ≥ 65 years old versus < 65 years old

	≥ 65 years, N=32*	< 65 years, N=59*	*P*-value**
Number of FLOT cycles	4.50 (4.00–8.00)	7.00 (4.00–8.00)	0.030
Number of chemotherapy cycles	7.00 (5.50–8.00)	8.00 (7.00–8.00)	0.011
Percent of oxaliplatin	76 (52–93)	93 (80–99)	0.004

*Median (IQR)
**Wilcoxon rank sum test

Overall survival stratified by age showed no significant difference between patients ≥ 65 years old versus those < 65 years old [Figure 1]. In a multivariable analysis, overall survival was not affected by age, sex, number of cycles of FLOT, number of cycles of chemotherapy, or dose of oxaliplatin [Table 3].

DISCUSSION

In this retrospective analysis of 91 patients with LAGA, patients ≥ 65 years old received fewer cycles of perioperative FLOT and lower dose intensity compared to patients < 65 years old, without compromising clinical outcome and without increased toxicity.

While there is lack of evidence regarding the association between the number of chemotherapy cycles and survival outcome in LAGA, in the metastatic setting there is evidence that a lower dose of chemotherapy does not impair efficacy of treatment. The phase III GO2 study randomized 514 elderly and/or frail patients with untreated advanced gastroesophageal adenocarcinomas to either standard dose CAPOX, or reduced dose CAPOX (80% and 60% dose levels), and showed that the lowest dose was less toxic while maintaining non-inferiority in terms of PFS [12].

Figure 1. Overall survival comparison of patients ≥ 65 years old versus < 65 years old

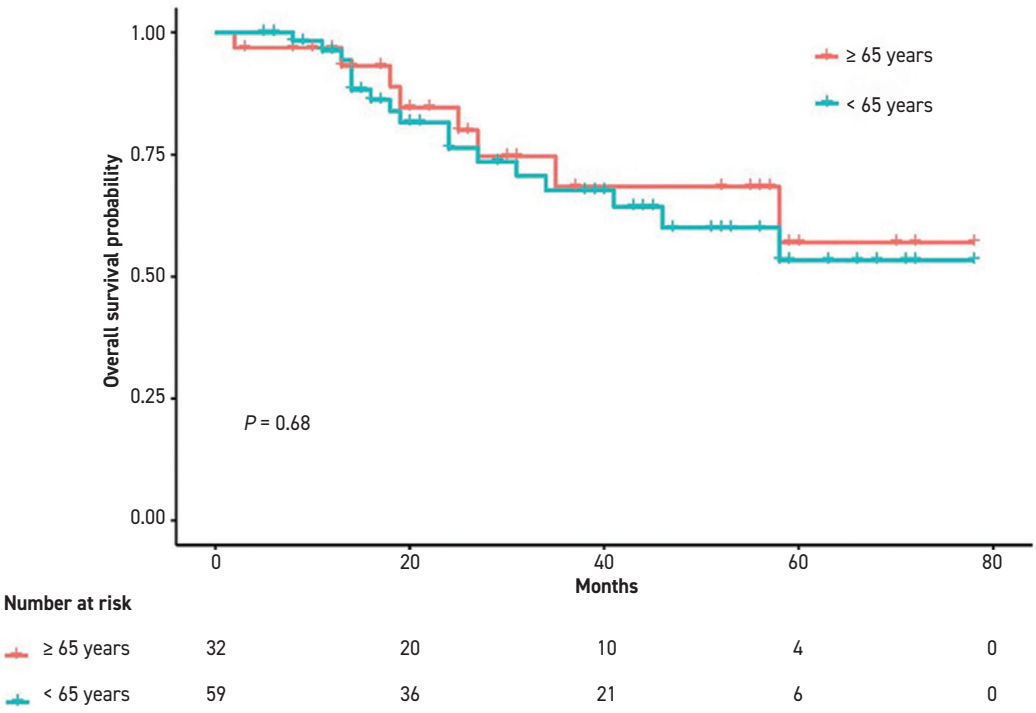

Table 3. Multivariate analysis for overall survival in LAGA patients treated with FLOT

Characteristic	HR	95% CI	*P*-value
Age group			
≥ 65 years	–	–	
< 65 years	1.24	0.49–3.14	0.6
Sex			
Female	–	–	
Male	1.43	0.60–3.39	0.4
Number of FLOT cycles	1.18	0.84–1.66	0.3
Number of chemotherapy cycles	0.58	0.23–1.48	0.3
Percent of oxaliplatin	1.03	0.95–1.11	0.5

95%CI = 95% confidence interval, HR = hazard ratio, LAGA = locally advanced gastric adenocarcinomas

In the landmark FLOT4 study, median OS was 50 months [6], which is comparable to our results, in which median OS was not reached in both age groups. Notably, median follow-up time was also similar between the FLOT4 study and ours (43 and 40 months, respectively).

There are several limitations in our study. Our cohort included a relatively small sample size; all treated in a single center. Due to these limitations, we could not perform further subgroup analyses such as survival outcome according to specific dose reductions and number of chemotherapy cycles. In addition, we did not have available data on ECOG performance status, restricting our capacity to account for this characteristic as a confounding factor.

CONCLUSIONS

Elderly patients with LAGAs received fewer cycles of perioperative FLOT, without compromising clinical outcome or increasing toxicity.

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No fathers or mothers think their own children ugly; and this self-deceit is yet stronger with respect to the offspring of the mind.

Miguel de Cervantes (1547–1616), Spanish writer best known for his novel Don Quixote