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IMPROVING SURVIVAL IN ADVANCED GASTRIC CANCER: A QUALITATIVE APPROACH

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ABSTRACT

Purpose – Though the incidence and mortality numbers are comparatively less than other types of cancer, such as lung and breast cancer, overall survival in advanced gastric cancer cases is still very bleak, thus patients only receive palliative treatment. We sought to improve overall survival in gastric cancer patients by reviewing the various treatment protocols associated with advanced gastric carcinoma. Methodology- A retrospective analysis of several randomized trials and related literature collected from online medical databases was performed and all available regimens were evaluated for their influence on survival. Findings- Our analysis revealed chemotherapy followed by surgery to be the preferred protocol for treatment of gastric cancer(primary option), the exact selection of the agents and surgery involved being debatable. Immunotherapy and radiotherapy have recently been proved effective as adjunct and concurrent administration respectively in certain cases, thus appear as emerging treatment options. Second-line options, though limited, provide slight increment in survival. Thus, a possible treatment guideline has been proposed combining all facts. Research limitations/implications- For a more precise evaluation, more randomized trials over the past 10 years need to be analyzed. Thus more time is required. Practical implications- Our findings would enable us to accelerate the rather slow progress being made in the treatment of advanced gastric carcinoma and evaluate better treatment regimens and cost-effective ways in improving overall survival in such patients. Originality/value- Very few studies are available which review the effect of both chemotherapy and immunotherapy in advanced gastric cancer. Even less information or meta-analyses are available regarding radiotherapy and intraperitoneal chemotherapy in advanced gastric cancer, thus marking our study as a pivotal retrospective analysis.

INTRODUCTION

Though the incidence is much less compared to other types of cancer such as lung and prostrate carcinoma[1-3], gastric cancer is still the one of the leading causes of death due to cancer.[1, 3-6] Globally, gastric cancer accounts for 989,600 new annual cases.[2] Nearly two-thirds of the global gastric carcinoma burden is being shouldered by developing nations, with a staggering 42% in China alone.[7] In 2013, gastro-esophageal cancer accounted for 39590 new cases (2.38% of total new cases) in the United States with a corresponding 26200 deaths (4.51% of total).[8] In Europe, gastric cancer is the 5th most prevalent type of cancer with 159,900 reported new cases in 2006 and 118,200 deaths.[5] With an annual global death toll of 738,000 reported in 2008,[2] gastric cancer also possesses a high case-fatality-ratio (CFR) of 0.75, which is significantly higher than other major malignancies such as colon cancer (CFR 0.52), breast cancer (CFR 0.36) and prostate cancer. (CFR 0.33)[9] Despite the heterogeneity of nearly all types of cancer, adenocarcinoma consists of 95% of all gastric cancer cases and according to Lauren's classification, they can be further distinguished into 2 subtypes, intestinal and diffuse.[10] Intestinal-type gastric cancer is well differentiated and expands through the stomach wall.[11] Diffuse-type is normally poorly-differentiated, infiltrates throughout the stomach wall as discohesive cells and is associated with a loss of cell surface protein E-cadherin.[12] Occurrence of intestinal gastric cancer is predominant in areas of high incidence, such as China, and is majorly responsible for the ethnic variation across the globe.[13] The majority of the gastric cancer patients are normally diagnosed at a very late stage[14] and high rates of recurrence (40%- 60%) occur even in patients who have undergone curative resection.[15] As a result, systemic disease is inevitable. Compared to other solid-tumor or non-hematological malignancies like breast or colon, very little

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progress has been made in the treatment of this disease over the past few decades.[7] During this time, only a minimal improvement in the median overall survival of metastatic gastric cancer has been observed whereas survival period for breast cancer has at least doubled.[16, 17] Previously, best-supportive care (BSC) remained the preferred choice of treatment in advanced gastric cancer cases; however, several trials have proved the effectiveness of palliative treatment in prolonging survival[18] especially chemotherapy.[19] Cisplatin with 5-flurouracil (CFU) is normally preferred as a first-line treatment option, often with the addition of a third drug such as docetaxel, oxaliplatin, etc.[20, 21] Unfortunately, few patients receive second-line chemotherapy, mainly due to the limited availability of options and severe disease progression.[22]

The disparity becomes more apparent given the fact that there are no well-established immunotherapy regimens in gastric cancer despite the significantly improved knowledge of key-signalling pathways in our possession.[7] Surgery (either pre or post-chemotherapy) is considered the only possible curative treatment option for gastric cancer at any stage.[23] However, there is still debate over the preferred method of resection. Several Japanese trials have concluded that D2 dissection to be superior to D1 dissection.[24, 25] However, trials conducted in Europe concluded that D2 dissection leads to high morbidity due to pancreatico-splenectomy and no survival superiority over D1 dissection was observed.[26, 27] Outcomes are also dependent on location; tumors of the gastro-esophageal junction (GEJ) and cardiac region tend to have worse prognosis compared to the pyloric and curvature regions.[22]*H. pylori* infection is quite common with proximal-end tumors, and survival chances remain bleak after R0 resection in such tumors.[28]Given all of the above mentioned facts, treatment of advanced gastric cancer seems to be quite a depressive affair. There are certainly several challenges regarding treatment, however, recent advancements are being made. This study therefore aims to improve survival by reviewing all available treatment options for advanced gastric cancer and possibly provide an optimum treatment protocol

MATERIALS AND METHODS

The results from several randomized trials, reviews and meta-analyses were reviewed from MEDLINE, PUBMED and other journal databases.

Factors to be considered

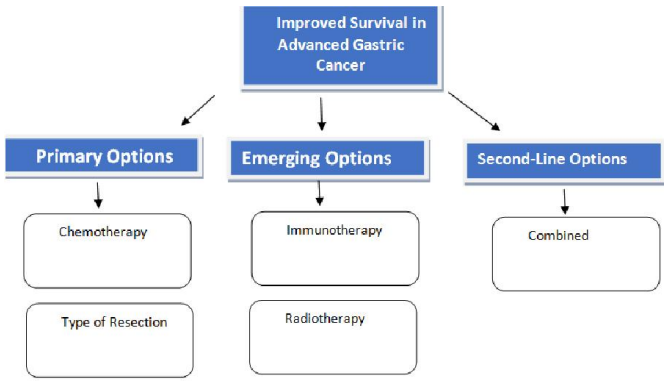

Figure 1. Treatment of Advanced Gastric cancer

Patient results or survival outcomes resulting from all of the 4 major treatment protocols or regimens used in the treatment of advanced gastric cancer were analyzed. Literature concerning operable gastric carcinoma was also taken into consideration. The effect of co-morbid and other prognostic factors such as age, gender, location, etc were excluded from the initial search due to limited availability of time and inferiority of magnitude of effect.The treatment regimens options can be categorized into 3 groups: (a) Primary options normally used for first-line therapy of advanced gastric cancer, (b) Emerging options, which have recently been used in adjunct with the regular first-line treatment regimens and Second-line options, which are used after failure of first-line therapy.

RESULTS AND DISCUSSION

Several meta-analyses and retrospective analyses involving advanced cases of gastric carcinoma have yielded both similar and contradicting results regarding an appropriate regimen or standard treatment method. For advances cases of gastric cancer, it can be assumed that the first-line treatment method involves chemotherapy, followed by gastrostomy. Immunotherapy and radiotherapy, previously left unexplored for decades have recently started emerging as potential modalities. Second-line treatment, though minimal in options, is similar to first-line treatment.

Primary Otions: Chemotherapy and Type of Resection

Chemotherapy is generally considered the first-choice or preferred intital treatment for advanced gastric cancer.[7] ECF is generally considered by many as the standard regimen with its optimum MOS, QoL and repetitive results.[18, 29, 30] The DCF regimen did provide a substantial improvement in MOS of such patients,[21] but QoL was compromised due to the high levels of grade 3-4 neutropenia caused by docetaxel.[31-34] Toxicity is reduced following a modified DCF regimen involving reduced dose of docetaxel with increased frequency.[35] One particular randomized trial compared ECF with DF+Carbopaltin (DF-Cb) where DF-Cb exhibited superior MOS of 12.4 months compared to 8.7 months in ECF.[36] Following this, the CLASSIC study quickly established the role of oxaliplatin and capecitabine in operable gastric carcinoma, following D2 dissection.[37] Both are currently recognized first-line treatment options for advanced disease.[31, 38, 39] Irinotecan-based regimens illustrated mixed results.[18] Therefore, a proper standard regimen for advanced gastric cancer has yet to be established. However, the retrospective analysis of several previous randomized trials, meta-analyses does confirm the following facts: (a) chemotherapy is effective in advanced gastric cancer, (b) triplet regimen containing CF and a third cytotoxic agent, such as oxaliplatin or docetaxel, illustrates optimum survival and QoL outcomes.

Another dilemma in the treatment of advanced gastric cancer is the choice of resection or gastrectomy involved. D1 resection involves removal of the perigastric nodes or group 1 lymph nodes, as according to the Japanese Gastric Cancer Association (JGCA); s1-s6 for lower middle and upper third localizations; s3, s4d, s5, s6 for lower third and duodenal localizations; s1, s3, s4sb, s4d, s5, s6 for middle third-lower localizations; s1–s6 for upper third-middle localizations; s1–

s3, s4sa, s4sb for upper third localizations.[40] D2 resection involves the additional removal of the pancreas, spleen and other regional lymph nodes; s1, s3, s4d, s4sb, s5–s7, s8a, s9, s11p, s12a for middle third localizations and s1, s3, s4d, s5–s7, s8a, s9, s11p, s12a, s14v for lower third-duodenal localizations.[40, 41] As previously stated, D2 dissection provided better outcome for Asian patients, particularly Japanese[24, 25] whereas no such survival superiority was ever observed in the Western counterparts.[42] Therefore the decision on the type of surgery required normally rests of the shoulder of the physician involved. In most cases of advanced gastric carcinoma, R0 resection is minimal.[15, 43, 44] R0 resection means the complete removal of the tumor, i.e. no microscopic trace of the tumor in the primary tumor bed. R1 resection means macroscopic removal of tumor, but leaving microscopic, residual tumor and R2 resection indicates gross residual disease with unresected gross residual tumor.[45] Given the low survival statistics following R0 resection, the need to improve the existing "curative resection" technniques is apparent. D'Annibale and colleagues then introduced a modified technique which involved robot-assisted gastrectomy with D2-lymphadenectomy.[46]

Successful surgery on 24 consecutive patients illustrated a low surgery-related morbidity of 8%, thirty day mortality of 0%, short median length-of-hospital-stay of 6 days and negative margins or complete R0 resections in all cases.[46] Therefore, robotic-assisted D2 dissection should be further explored. However, disease progression is often quickly followed after few cycles due to infiltration of the cancerous cells into the peritoneal cavity, leading to further nodal metastasis.[47] Due to the immense extent of the lymphatic spread, nearly 50% of advanced gastric patients will develop peritoneal carcinosis even after radical resection or gastrectomy.[48, 49] Post-operative intraperitoneal administration of chemotherapeutic drugs (IPC) in advanced gastric cancer patients has, therefore, been explored, but, with only marginal success.[50] One particular randomized trial showed positive response for early postoperative IP administration of mitomycin C and 5FU.[51] The results from four randomized controlled trials showed that 2-year mortality rate was significantly lowered in the surgery+IPC groups (OR= 0.28, 95% CI = 0.17-0.45)[52-55] Meta-analysis of several trials also showed that morbidity was significantly reduced in patients who received post-operative IPC.[49, 53, 56-59] Montori and colleagues, as well as several others have shown that cytoreductive surgery followed by HIPEC (hypperthermic intraperitoneal chemotherapy) significantly improves survival in post-operative gastric cancer patients.[60]

Emerging Options: Immunotherapy and Radiotherapy

In case of the application of immunotherapy, the ToGA trial[61] has established the role of trastuzumab in HER-2 positive advanced gastric carcinoma. Other phase II studies using targeted agents have since followed. Sun and colleagues have demonstrated the effectiveness of DC-sorafanib with a MOS of 14.9 moths.[62] Unfortunately, the optimism initially shown by phase II studies, especially concerning bevacizumab combined regimens could not be repeated in its first phase III trial. The AVAGAST trial involved 774 patients in which half received bevacizumab plus CF and the other half only received placebo and CF. MOS did increase for bevacizumab plus CF (12.1 vs 10.1 months; HR= 0.87) but was not statistically significant; only progression-free survival (6.7 months vs. 5.3 months) and overall response rate (46% vs 37.4%, p =0.0315) showed statistically significant improvements.[63] Despite not being able to achieve the primary end-point, the latter two achievements can be taken on a positive note. Catumaxomab, a monoclonal antibody with dual antigen specificity to epithelial cell adhesion molecule expressed frequently in gastric cancer, is being currently examined in a phase II trial.[64] Ramucirumab, a human IgG1 monoclonal antibody VEGFR-2 antagonist,[65](Spratlin et al., 2010) has been proved to be effective in second-line treatment.[66]

Due to the complexity of the organs situated in the abdomen and the sever disease progression, radiotherapy has been left almost completely unexplored in the advent of gastric cancer. Recent studies, however, have shown promising results. An initial randomized controlled trial conducted by Zhu and colleagues showed that concurrent chemoradiotherapy with 5FU and tetrahydrofolic acid slightly increase 1, 2, 3 year survival in operable gastric cancer patients, following either D1/ D2 dissection.[67, 68] Following their initial success, they conducted another trial, this time involving intensity-modulated radiotherapy (IMRT) plus concurrent chemotherapy versus chemotherapy alone after D2 dissection. The chemotherapy regimen used was 5FU and leucovorin. The IMRT group (IMRT-C) showed significantly improved outcomes, with a 58 months MOS compared to 48 months in the control group and progression-free survival increased from 36 months to 50 months; staging was found to be an independent prognostic factor.[69] Another prospective trial then explored the effect of RT in advanced carcinoma, where long-term efficacy of intraoperative electron radiotherapy (IOERT) followed by concurrent chemotherapy and external-beam radiotherapy (EBRT) in patients with T3 or T4 gastric adenocarcinoma.[70] Analysis revealed that high-dose IOERT provided improved locoregional control with manageable toxicities.[70] Therefore, further trials including concurrent chemoradiation or post-operative IMRT should be conducted.

Second-line treatment options

Once disease-progression has occurred after first-line therapy, performance status steadily decreases and death follows within 3-4 months.[18, 29-31, 34, 38, 39, 71-77] As a result, limited data is available for second-line treatment of advanced gastric cancer. This is completely the reverse in breast and colon cancer patients where 85% receive second and further-line chemotherapy treatment.[78, 79] Almost negligible phase III data is available for second-line therapy of metastatic gastric carcinoma, with a meager few studies comparing chemotherapy with BSC. In one such study, patients received eith BSC or monotherapy irinotecan; MOS of the irinotecan group was 4.4 months and 2.6 months for BSC.[80] Recently, Fuchs and colleagues have demonstrated the use of targeted agent monotherapy as a potential second-line treatment option. Ramucirumab, a human IgG1 monoclonal antibody VEGFR-2 antagonist,[65] was used to treat patients with gastro or gastro-esophageal cancer who have previously failed therapy with platinum and 5FU combinations. Compared to the group receiving placebo, the MOS of ramucirumab was significantly higher (5.2 months vs 3.8 months) and the survival benefit remained unchanged regardless of the prognostic factors.[66]

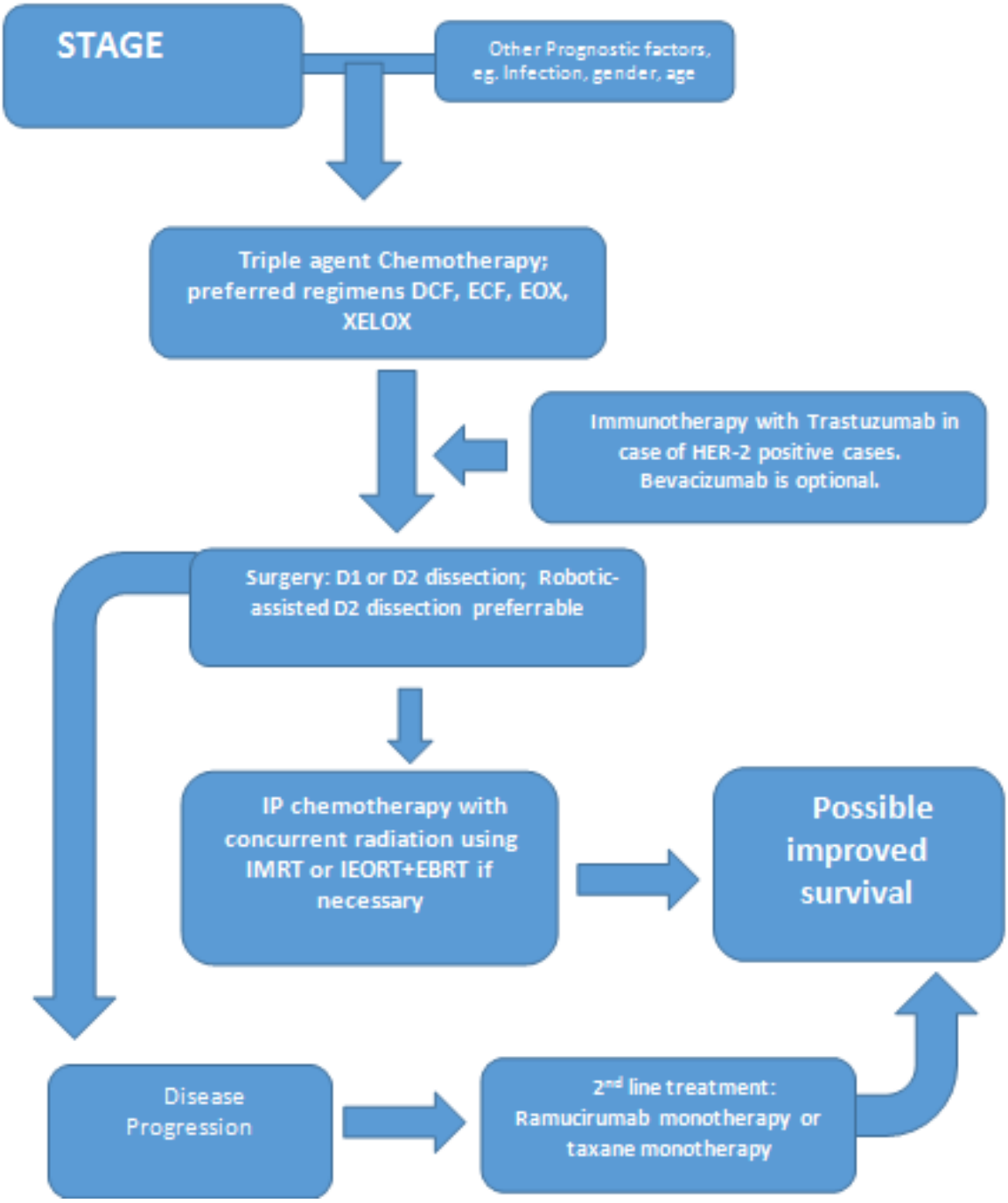

Figure 2. Possible guideline for treatment of advanced or metastatic gastric cancer

However, it should be noted the patient population for the ramucirumab (n= 237) was nearly double that of the control group (n= 117), thus this raises uncertainties regarding standardization. The test group also suffered from increased incidences of hypertension.[66] However, the implications of this pilot trial should be taken as a beacon of hope. A moderate, if no substantial, amount of phase II data is available regarding second-line chemotherapy treatment of advanced gastric cancer.[7, 81] Taxanes have proved to be more suitable for second-line treatment with either monotherapy or combinations, with similar MOS outcomes ranging from 6-8 months.[82, 83]Performance status of the patients greatly affects the toxicity profile during second-line chemotherapeutic treatment. Taxane monotherapy results in 18% incidence of Grade 3 / 4 neutropenia,[82, 84] whereas combination therapy increases the incidence to 30-40% and 11% incidence of febrile neutropenia[85-87] Studies concluded that overall toxicity profile of second-line regimens appear similar to the corresponding first-line therapeutic options.[82-84, 88] However, disease progression was inevitable and often QoL was compromised due to the toxicities. Thus, it is essential to formulate a second-line regimen without severe chemotherapy-related toxicity events.

Contribution and Insight

Despite some of the contradiction observed in the information from all of the above stated facts regarding advanced gastric cancer and its associated treatment,[1, 2, 5, 7, 16, 17, 24, 26, 31, 39, 56, 57, 61, 66, 69, 70, 74, 77, 87, 89-95] our analysis can reveal a few certain base guidelines.

a) Neoadjuvant chemotherapy is essential in case of advanced gastric carcinoma, with triplet regimen being the most superior.
b) Initial selection of triplet regimen depends on patient condition, tolerance, toxicity profile and choice.
c) After chemotherapy, gastrectomy is necessary for either curative or palliative purposes.
d) Either D1/ D2 dissection can be performed depending on the decision of the physician or the ethnicity of the patient. Robotic-assisted D2 dissection should be done if resources are available.
e) Following surgery, chemotherapy can be continued if necessary. Concurrent RT using IMRT can prove effective.
f) IP chemotherapy or HIPEC can be used to prevent peritoneal invasion and metastasis, thus reducing chances of recurrence.
g) If disease progression occurs, palliative therapy using CT (taxane monotherapy) or ramucirumab monotherapy.

Therefore, combining all of the above, a treatment guideline has been extracted and proposed in order to possibly improve survival Figure 2 illustrates our deductions in a flowchart below. Our deductions are plainly qualitative and is mostly a summarization of all the data analyzed. For a more accurate and precise evaluation, a prospective, randomized controlled trial needs to be conducted following the procedure given below.

Conclusion

Gastric cancer still remains an aggressive disease with high global mortality rate. Studies concerning chemotherapy in advanced gastric cancer have not been favorable and as a result, progress regarding this area had been stalled for many years whereas other treatment options for other solid-tumor malignancies have evolved significantly. However, the introduction of several new concepts have brought life back to what seemed a forever-sinking ship. The use of immunotherapy and radiotherapy as an adjunct or concurrent postoperative procedure respectively have shown modest improvements in survival. Given the high mortality regardless of R0 resection, robotic-assisted D2 dissection provides a new and safer approach of gastrectomy. It is still, however, advisable to revise the two surgical procedures involved due to the associated co-morbidities following the resection. Long term survival of 2 years or more may be a rarity but as studies have shown, they are still possible (15-20%).

First-line chemotherapy has already been proclaimed effective in reducing tumor mass and the addition of targeted agents such as trastuzumab provides extra survival benefits and also illustrates the heterogeneity of gastric carcinoma, which for years have not been studied. Our limited knowledge of the possible biological mechanisms concerning the disease is also a limiting factor, thus more histological or laboratory studies need to be conducted. The histology may vary according to ethnicity, location or other co-morbid factors as seen in more explored malignancies such as breast and colon cancer. Clinical parameters may help evaluate first-line and second-line outcomes but biological markers studies help enable us to understand the underlying and possible angiogenesis mechanisms involved in gastric carcinoma. Further research with large randomized, controlled trials need to be conducted involving all possible modes of therapy in order to properly evaluate the different treatment modes and establish a proper standardized treatment regimen. The protocol proposed based on our analysis may prove to be a pivotal landmark in the treatment of advanced gastric cancer. However, excessive optimism cannot be exercised.

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[1-67, 69-87, 89-113]

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