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ORIGINAL ARTICLE

Aggressive interventions in terminally ill patients with solid tumors in China: a retrospective single center analysis

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Summary

Purpose: *Overtreatment in terminally ill cancer patients is very common worldwide, but whether patients will benefit from aggressive care remains obscure. This study aimed to explore the value of aggressive interventions in the end of life in adult patients with advanced solid tumors.*

Methods: *All adult patients who died from advanced solid tumors between 2011 and 2012 in Xiangyang Central Hospital were included. Detailed data concerning cancer types, therapy approach and outcome in the last three months of life were collected and assessed.*

Results: *263 patients with median age 63 years died of cancer between 2011 and 2012. In the last 3 months of life, 82.5% of the patients received aggressive care, especially chemotherapy and radiotherapy. Traditional Chinese medicine was widely used. Median survival from diagnosis of metastasis to death was 6.9 months for patients treated with aggressive care and 6.2 months for the others, respectively (p>0.05).*

Conclusion: *Despite their wide use, aggressive interventions in the last 3 months of life might have no benefit on survival. Radiotherapy provided significant symptom palliation of bone or brain metastases, but the short-course radiotherapy schedule was rarely used. Frequent reassessment of patients and making decision together with the patients is helpful to overcome the aggressive care. Appropriate tools to predict survival are needed to help design proper strategies for terminally ill cancer patients.*

Key words: *cancer, end-of-life care, palliative care, terminally ill patients*

Introduction

China is the only country with more than one hundred million aging population in the world. With the increasing number of deaths from cancer as a result of a growing and aging population, cancer has become a leading cause of death in China despite advances in early detection and treatment [1]. So the inevitable need for quality of end-of-life care has become a hot issue. Oncologists use to treat their patients with advanced cancer more and more aggressively even near the end-of-life irrespective of the disease' responsiveness to therapy, especially with the use of palliative chemotherapy [2-4]. In the aforementioned studies, a sizeable proportion of terminally ill cancer patients were subjected to aggressive therapy in their last months including chemotherapy, radiotherapy or surgery. But to our knowledge, there is no published data to investigate the use of aggressive care for terminal cancer patients in Mainland China.

Herein we present our retrospective study of a single hospital from January 2011 to December 2012. We aimed to survey the use of

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Table 1. Proportion of cancer patients receiving aggressive care

Aggressive care	*N*	*%*
Chemotherapy	151	57.4
Radiotherapy	110	41.8
Targeted therapy	21	8.0
Interventional therapy	7	2.7
Ablation therapy	4	1.5
Surgery	2	0.8
Radioactive particles implantation	1	0.4
More than two patterns	52	19.8

Of all the 263 cancer patients who died between 2011 and 2012 in Xiangyang Central Hospital, 217 (82.5%) received at least one aggressive care intervention 3 months before death. More than 50% of patients were treated with chemotherapy. 110 patients (41.8%) received radiotherapy and 52 (19.8%) received more than 2 aggressive care interventions. Twenty one patients (8.0%) received targeted therapy, especially tyrosine kinase inhibitors for lung cancer

aggressive interventions, especially chemotherapy or radiotherapy, in the end-of-life of adult patients with advanced solid tumors and to assess their value.

Methods

Study population

All adult patients with advanced solid tumors other than primary central nervous system cancer who died between 2011 and 2012 in Xiangyang Central Hospital, Hubei University of Arts and Science were included. Sex, age, Eastern Cooperative Oncology Group (ECOG) performance status score, date of diagnosis of metastatic disease and date of death were recorded. Chemotherapy regimens and cycles, radiotherapy schedule and surgery were recorded too. Patients younger than 18 years of age at diagnosis were excluded. Aggressiveness of end-of-life care was defined as at least one of the following actions: chemotherapy administration, radiotherapy, surgery, interventional therapy, targeted therapy, ablation therapy or radioactive particles implantation therapy 3 months before death. This study was approved by the Committee of Medical Ethics of our hospital. Written informed consent was waived.

Statistics

Statistical analyses were performed using SPSS software package (version 16.0). Significant differences between two groups were compared by using x^2 test or Student's t-test. Differences in Kaplan-Meier curves were compared with the log-rank test.

Results

There were 263 patients (166 men and 97 women) with advanced solid tumors who were treated and died in our hospital from 2011 to 2012, of which 217 (82.5%) received aggressive care including palliative chemotherapy, radiotherapy, surgery, interventional therapy, targeted therapy, ablation therapy or radioactive particles implantation therapy in their last 3 months of life (Table 1). The median age of the overall population was 63 years (range 32-81). Among those 217 patients, 151 (57.4%) received palliative systemic chemotherapy, 110 (41.8%) received radiotherapy, 21 (8.0%) received targeted therapy, 7 (2.7%) received interventional therapy (transcatheter arterial chemoembolization/TACE), and 4 (1.5%) received radiofrequency ablation therapy. Although surgery is suggested for patients with gastric cancer in terminal stage [5], only 2 patients (0.8%) underwent surgery because of intestinal obstruction. Only one patient received radioactive particles implantation therapy (Table 1). Fifty two patients (19.8%) received more than two kinds of treatment. All of them received traditional Chinese medicine therapy even until death. Almost all patients treated with targeted therapy were non-small cell lung cancer except for 2 colorectal cancer patients. Besides, 12 patients received intrapleural chemotherapy to control malignant pleural effusion.

Table 2. Diagnoses of all cancer patients

Diagnosis	*N*	*%*
Lung	99	37.6
Esophagus and stomach	67	25.5
Liver	29	11.1
Colorectal	23	8.7
Breast	16	6.1
Head and neck	5	1.9
Others	24	9.1
Total	263	100.0

Cancer diagnoses of all 263 adult patients with solid tumors, other than primary central nervous system cancer, who died in Xiangyang Central Hospital between 2011 and 2012

The most frequent tumor diagnosis was lung (37.6%), and then esophagus and stomach (25.5%), liver (11.1%) and colorectal cancer (8.7%) (Table 2). Of lung cancer patients 64.6% and 87.5% of breast cancer patients were treated with chemotherapy 3 months before death. More than half of gastrointestinal cancer patients received chemotherapy too (Table 3). The median time between the last administration of chemotherapy and death was 48 days (range 9-87). Among the 151 patients, who were administered chemotherapy 40 (26.5%) received

Table 3. Patients receiving chemotherapy according to the kind of cancer

Diagnosis	*N*	*%*
Lung	64	42.4
Esophagus and stomach	41	27.2
Liver	2	1.3
Colorectal	18	11.9
Breast	14	9.3
Head and neck	2	1.3
Others	10	6.6
Total	151	100

Of all 263 cancer patients who died in Xiangyang Central Hospital between 2011 and 2012, 151 patients (57.4%) received chemotherapy. 64.6% of lung cancer patients and 87.5% of breast cancer patients were treated with chemotherapy 3 months before death respectively. More than half of gastrointestinal tumor patients received chemotherapy too.

single-agent therapy and 111 (73.5%) doublet chemotherapy. No 3-agent regimen was administered. Thirty eight patients (14.4%) received chemotherapy 30 days before death. Among these 38 patients, 7 (18.4%) received first-line chemotherapy, 29 (76.3%) second-line chemotherapy, and 2 (5.3%) third-line chemotherapy. However, chemotherapy hardly had any effect on symptom palliation.

External beam radiation therapy was delivered to 110 patients. The most common radiotherapy target was whole brain and bone. Among the 110 patients, 38 patients (34.5%) were treated for brain metastases and 43 (39.1%) for bone metastases. Six (5.5%) patients received radiotherapy for metastatic lung or retroperitoneal cancer. The remaining 23 (20.9%) patients were irradiated for primary lesions. The median ECOG score of these patients was 3. Patients receiving radiotherapy had a poorer ECOG score than those receiving chemotherapy ($p < 0.05$). The mean radiotherapy duration was 34 days (range 6-50). The mean time between the beginning of radiotherapy and death was 47 days (range 10-86). The prescribed dose was 30-40 Gy in nearly 80% of cases. A dose of 1.8-2.0 Gy per fraction was applied in 93.6% of the cases. Single fraction of more than 4.0 Gy was never used. A proportion of patients (10.9%) didn't complete their radiotherapy regimen because of worsening performance status (Table 4). Radiotherapy could relieve pain and improve self-help ability for bone/brain metastasis in most cases.

The baseline clinical characteristics of the patients who received aggressive care or not while terminally ill are presented in Table 5.

Table 4. Characteristics of cancer patients treated with radiotherapy

Characteristics	*N*	*%*
Radiotherapy target		
Brain	38	34.5
Bone	43	39.1
Others	29	26.4
Schedule time (weeks)		
<4	7	6.4
≥4	103	93.6
Dose (Gy)		
≤40	84	76.4
>40	26	23.6
Fraction (Gy)		
1.8-2	103	93.6
3.0	7	6.4
≥4.0	0	0
Treatment completed		
Yes	98	89.8
No	12	10.2

110 terminally ill cancer patients received radiotherapy in Xiangyang Central Hospital between 2011 and 2012. Among these patients, 38 patients were treated for brain metastases and 43 for bone metastases. The remaining 29 patients received radiotherapy for metastatic lung/retroperitoneal cancer or primary lesions. Therapy schedule was > 4 weeks in most cases. The prescribed dose was 30-40 Gy in nearly 80% of cases. Dose of 1.8-2 Gy per fraction was applied in 93.6% of the cases. Single fraction > 4 Gy was never used. 10.9% of the patients didn't complete their radiotherapy because of worsening performance status.

There was no significant difference between the two groups in any of the variables, including gender, age, metastatic site and ECOG score. Of 46 patients who didn't receive aggressive care 3 months before death, 30 (65.2%) had received chemotherapy or targeted therapy before. The rest didn't receive aggressive care because of poor performance status or wish of the patients. For all the 217 patients who received aggressive care 3 months before death, the median survival time from the documentation of metastasis was 6.9 months (range 0.7-26.6). For the others who didn't receive any aggressive care 3 months before death, the median time was 6.2 months (range 0.5-33.2) ($p = 0.291$ by log-rank test; Figure 1).

Discussion

In clinical practice, selecting proper patients before treatment by distinguishing and assessing the clinical or genetic characteristics is helpful to achieve higher efficiency and fewer side effects for many kinds of cancer such as

Table 5. Clinical characteristics of cancer patients receiving or not aggressive care

Variables	*Aggressive care N (%)*	*No aggressive care N (%)*	x^2	*p-value*
Age, years, range (mean)	32-81 (62.6)	44-80 (64.3)	-0.920	0.358
Gender				
Male	132 (60.8)	34 (73.9)		
Female	85 (39.2)	12 (26.1)	0.791	0.470
ECOG PS				
≤2	185 (85.3)	39 (84.8)		
>2	32 (39.2)	7 (15.2)	0.007	0.935
Metastatic site				
Brain	42 (19.4)	9 (19.6)		
Bone	48 (22.1)	7 (15.2)		
Others	127 (58.5)	30 (65.2)	1.150	0.563

non-small cell lung cancer (NSCLC) [6]. For early-stage cancer, doctors are trying to avoid excessive treatment through some tools [7], while for terminally ill cancer patients, to treat or not is still a controversial issue.

Adoption of aggressive methods of cancer care near the end-of-life is intense over time worldwide [3,8-10]. Among patients who died of advanced cancer, 15-37% received chemotherapy in the last month of life [11,12]. For advanced NSCLC patients, chemotherapy within 14 days before death had no benefit on survival [13]. Meanwhile, 5.75% of cancer deaths resulted from toxicity, and 16% of the patients were hospitalized due to toxicity [11]. Similar to these studies, 82.5% of the patients received aggressive care including chemotherapy in our hospital. And continuing aggressive therapy within 3 months before death didn't prolong the survival (6.9 vs 6.2 months, p>0.05). Different from the aforementioned studies, the aggressive indicators in our study referred to antitumor measures rather than indirect indices such as emergency room visits or intensive care unit admissions. So our data reflected the true aggressive care near death. As almost 25% of the patients with incurable cancer received their last course of palliative chemotherapy within 31 days before death, researchers suggested that this was needed to design guidelines for the appropriate use of chemotherapy in advanced cancer patients with a short life expectancy [14,15].

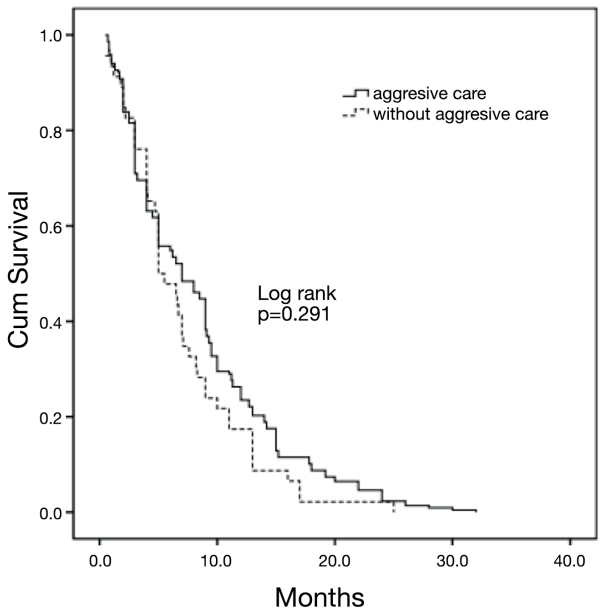

Figure 1. Kaplan-Meier survival curve of cancer patients with or without aggressive care 3 months before death. Median overall survival time from the date of metastasis was 6.9 months for patients with aggressive care and 6.2 months for those without (p=0.291 by log-rank test).

Palliative radiotherapy can improve the quality of life of cancer patients. External beam radiation therapy provides significant palliation of painful bone metastases in 50-80% of the patients, with up to one third of patients achieving complete pain relief at the treated site [16]. Compared to standard fractionation radiotherapy schedule, a single 8 Gy fraction yields similar pain relief for patients with previously un-irradiated painful bone metastases [17]. There were no additional significant risks in long-term side effects or acute toxicity from a single 8 Gy fraction for patients despite higher re-treatment to the same anatomic site due to recurrent pain [18,19]. Meanwhile, the single fraction treatment approach is more convenient than conventional radiotherapy with less cost, time and acute radiation reactions [20]. However, palliative care has traditionally been deliv-

ered late in the course of disease to inpatients. For example, in a study 52% were still on treatment at death, and 54% had completed less than half of their original radiotherapy plan at Indiana University [21].

Twenty to 40% of cancer patients will develop brain metastases during the course of their illness [22]. Various dose-fractionation schemes had no benefit compared to standard plan (30 Gy in 10 daily fractions or 20 Gy in 4 or 5 daily fractions) in terms of overall survival, neurologic function, or symptom control [23]. Short-course whole brain radiotherapy with 20 Gy in 5 fractions is preferable for most patients, because it is associated with similar survival as longer programs and is less time-consuming. The use of chemotherapy in conjunction with whole brain radiotherapy remains experimental. Radiosurgery boost with whole brain radiotherapy may improve local disease control in selected patients, although survival remains unchanged for patients with multiple brain metastases. For those patients with poor performance status, supportive care alone may be appropriate [24]. At our hospital, 10.9% of the patients didn't complete their radiotherapy until death. Single fraction of more than 4.0 Gy was never used despite its convenience and effectiveness.

Chinese believe that traditional Chinese Medicine can minimize the side effects of chemotherapy/radiotherapy and improve the quality of life and the patient immune function. However, randomized clinical trials didn't prove its effect in terms of survival benefit or quality of life [25,26]. Currently, traditional Chinese Medicine plays an indispensable role in cancer prevention and treatment and is widely used in China although scientific evidence for the effect needs to be established [27]. More rigorous trials are needed to explore both the underlying molecular mechanisms and the clinical efficacy.

The main reasons for overtreatment of terminally ill cancer patients in our hospital are listed as follows: patients' willing or their relatives' request, the fear for being involved in medical dispute, optimistic prediction of efficacy of aggressive therapy and life expectancy.

The attitudes to death vary strikingly across different regions and nations. Patients nearing the end of life often do not receive the care they prefer [28]. Admission of patients being aware that they are dying in a palliative care facility does not seem to influence their survival and is associated with less aggressive care [29,30]. Patients in general wards receive more inappropriate care near the end of life than in a palliative care unit [31]. But delivering realistic information about the different options of care and the likelihood of successful treatment or improvement of adverse effects is a difficult task for doctors [32]. Many terminal cancer patients receiving chemotherapy might not understand that chemotherapy is unlikely to be curative or even palliative, which could compromise their ability to make informed treatment decisions. In a study, 69% of lung cancer patients and 81% of colorectal cancer patients did not understand that chemotherapy was not at all likely to cure their cancer [33]. In China, influenced by filial piety of Confucianism, the relatives of patients often request doctors not to tell patients the truth and to treat at all costs regardless of little effectiveness of such efforts. Doctors will do their best to avoid being involved in medical dispute or being victims of violence in most cases [34]. Also, the high basic medical insurance coverage in China may be another reason for overtreatment.

An accurate survival estimate is prerequisite to avoid futile therapies. Overestimating survival may lead to inappropriate treatment schedules. Sometimes, doctors will persuade their patients to receive aggressive care due to incorrect prediction of life expectancy. Survival prediction is useful in selecting patients for palliative or active anticancer therapy. Unfortunately, physicians generally tend to provide optimistic prognoses for terminally ill patients [35]. In a systematic review comprising 1563 terminally ill cancer patients, 27% of the predictions overestimated survival by at least 4 weeks [36]. There are a few predictive scores intending to direct therapy decisions [37], and some new tools have been established to help physicians making decisions on clinical care at the end of life [38-40].

In all, this study reported the experience of a single general hospital during 2 years and showed that aggressive care was administered within 3 months of death in most terminally ill cancer patients in Mainland China. Aggressive care near death didn't prolong survival from the diagnosis of metastasis compared to best supportive care alone. All patients received traditional Chinese Medicine therapy even until death. Radiotherapy could relieve pain of metastatic bone disease but long-lasting sched-

ules were usually used. Patients included in this study came from one hospital only, which might lead to bias. The median survival time of patients with aggressive care seemed longer compared with those without such care (6.9 vs 6.2 months); however, the differences failed to reach statistically significance (Figure 1), probably due to the relatively small sample size and confounders such as different cancer types. Our study couldn't conclude that chemotherapy or radiotherapy had not a positive impact on survival for advanced cancer patients. Instead, many studies have verified that chemotherapy can prolong survival of advanced cancer patients compared to best supportive care. But the present study reminds us that we should pay more attention to stop futile aggressive care timely for terminally ill cancer patients. Further multicenter studies should be conducted to test and verify the value of aggressive care in China. We believe that doctors should make frequent patients' reassessments, focusing especially on the symptoms and performance status and come to a decision together with the patients to overcome the aggressive care. A few of new tools developed to predict survival more accurately may be helpful. We also should reinforce the follow-up procedures to discover the recurrence or metastasis of tumor so as to start palliative therapy as soon as possible. Proper treatment plan, for example short-course radiotherapy, is needed to save time and facilitate treatment for health caregivers and patients together.

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