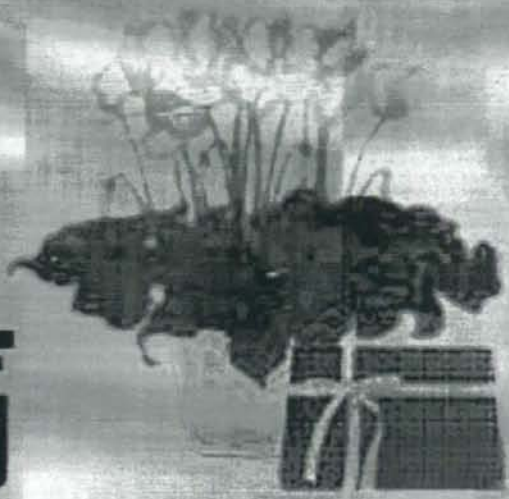
あなたの看護をサポートする

Nursing Mook



いつでも どこでも がん疼痛マネジメント

編集
林 章敏 聖路加国際病院緩和ケア科医長

痛みに応じた治療とケアの基本がわかる!

- がん疼痛の考え方　がん疼痛のアセスメント
- がん疼痛マネジメントの基本
- がん疼痛に対する薬物療法
  - がん疼痛薬物療法の基礎／非オピオイド鎮痛薬／オピオイド鎮痛薬／鎮痛補助薬
- 薬物療法以外のがん疼痛治療　放射線治療／神経ブロック／神経破壊薬
- がん疼痛ケアの実際　事例から考えるがん疼痛治療とケア
- 薬物の安全な取り扱いと対策
- がん疼痛治療に使用する主な薬剤一覧

Gakken

「胃がん・大腸がんを薬で抑えましょう」と言われた時

北海道大学病院腫瘍センター 准教授 小松嘉人 編

協力 NPO法人 北海道消化器癌化学療法研究会（HGCSG）

これから化学療法を受ける
患者さんのために

ヴァンメディカル

14. 気持ちがくじけてしまいそうです。どうしたらいいのでしょうか？

治療を続けていく中で，治療そのものの苦痛や治療の副作用に対する苦痛などから，これ以上治療を続けていくことができないという辛い思いでいっぱいになることがあります。そのうえ，病気や治療のために仕事を辞めたり休まなければならなくなったり，家族にこれ以上迷惑をかけることはできないと思ったり，このまま治療を続けても将来に対する見通しを立てることができないと感じたり，様々なことで不安になったり，抑うつ的になったりします。なかには今の状況を，非現実的に極端に悪い方向に考えてしまい，さらに気持ちが落ち込むことがあります。

あなたの気持ちを，話せる人に話せるだけ打ちあけましょう

このような気持ちになったら，まず，１人で悩まずに，話せる人にこの気持ちを話せる内容だけ話すようにしましょう。話す相手は家族，友人など，どなたでもかまいません。たとえ，今，目の前にある問題が解決できないとしても，他人に話をするだけで，自分の気持ちが落ち着いたり，思考がまとまったりすることがあります。

病院のスタッフにも相談して下さい

病院を訪れた時にも，主治医や看護師に，今の気持ちを相談しましょう。治療について不安な点やわからない点があれば，遠慮なく尋ねましょう。それだけでも，心が落ち着くことがあります。場合によっては，心のケアの専門家である精神科医の診察を受けたり，心理士と話をすることもひとつの方法です。気持ちが落ち込むことは決して恥ずかしいことではなく，誰もがそうなるかもしれないことなのです。大切なことは，１人で辛い気持ちを抱えこみ，悩まないことです。

また，日頃から気分転換を心がけ，心身ともにリラックスできるように心がけましょう。たとえば，ゆっくりと深呼吸をして，身体の力を抜くようにするだけでも心が軽くなることがあります。そして，積極的に自分の好きなことをしましょう。たとえば，本を読んだり，お花を見たり，家族と語らうなど，治療が続く日常生活の中に，自分にとってささやかな楽しみをもつようにしましょう。

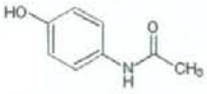
【岩満優美】

2. 解熱鎮痛薬（アセトアミノフェン）

伊勢雄也

シクロオキシゲナーゼ（cyclooxygenase：COX）

アセトアミノフェン（acetaminophen）



アセトアミノフェン
acetaminophen

非ステロイド性抗炎症薬（nonsteroidal anti-inflammatory drugs：NSAIDs）

解熱鎮痛薬は，炎症局所ではシクロオキシゲナーゼ（cyclooxygenase：COX）阻害作用が弱いため，鎮痛・解熱効果は強いが抗炎症効果はほとんどない．しかしながら，解熱鎮痛薬であるアセトアミノフェン（acetaminophen）は非ステロイド性抗炎症薬（nonsteroidal anti-inflammatory drugs：NSAIDs）と比較して消化管障害等の副作用を懸念することなく使用できるため，がん疼痛に対しても使用頻度は高い．

本邦において使用されている解熱鎮痛薬としては，アセトアミノフェン，スルピリン，イソプロピルアンチピリン等があるが，本稿ではがん疼痛に対する適応が認められており，臨床においても繁用されているアセトアミノフェンについて述べる．

1. アセトアミノフェン（ピリナジン®，カロナール® 他）

1）構造，剤形

アセトアミノフェンは，アセトアニリドまたはフェナセチンをヒトに投与したときの主要代謝産物である．白色の結晶または結晶性の粉末で，メタノールや95%エタノールに溶けやすく，水にやや溶けにくく，ジエチルエーテルに極めて溶けにくい．また，水酸化ナトリウム試液に溶ける．原末，シロップ，坐剤，錠剤等の剤形がある．錠剤は200 mg/錠，300 mg/錠が使用可能である．

2）作用部位

アラキドン酸からプロスタグランジンを産生する経路の律速酵素であるCOXを阻害することにより解熱鎮痛作用を生じる．しかし，抗炎症作用はほとんどない．解熱鎮痛作用はサリチル酸類と同様に中枢性で，体水分の移動と末梢血管の拡張とが相まって起こる発汗を伴う解熱と，視床と大脳皮質の痛覚閾値の上昇効果とによる．平熱時にはほとんど体温に影響を及ぼさず，発熱時には投与3時間後前後で最大効果を発現する．しかし，前述したように抗炎症作用はごく弱く，炎症部位のような高濃度の過酸化物の存在下ではCOXをほとんど阻害できないと一般的には考えられているが，この点につ

中枢性
発汗を伴う解熱
痛覚閾値の上昇効果

Antipyretic analgesic : acetaminophen

Yuya Ise（Department of Pharmacy Services, Nippon Medical School Hospital）

いては十分に検証されていない．健常人全血を用いた *ex vivo* の評価では，COX-1 と COX-2 の両方が約 50%阻害される．解熱作用は，脳で局所的に COX の阻害が起こるためであるとされてきた．COX-1 のスプライスバリアントがイヌの脳で同定されて COX-3 と名づけられ，*in vitro* でアセトアミノフェンによりある程度阻害されることが示された．しかし，このスプライスバリアントがヒトの脳に存在しているか，また，その阻害がアセトアミノフェンのヒトでの効果と関連しているかについては現在のところ明らかではない．アセトアミノフェンの単回または反復治療用量の投与では，心循環系と呼吸系，血小板，および凝固系への影響はない．酸－塩基の変化や尿酸排泄効果はなく，サリチル酸塩の投与後に起こる胃の刺激，びらんまたは出血も生じない．

3）薬物動態

経口投与されたアセトアミノフェンはほぼ完全に吸収される．血漿中濃度は 30～60 分で最高に達し，治療用量を用いた場合の血漿中半減期は約 2 時間である．全身クリアランスおよび分布容積は，それぞれ 5 ml/分/kg，0.95 l/kg であるが，肝障害時には全身クリアランスは低下し，また投与量が 2 g を超えると非線形動態を示す．アセトアミノフェンはほとんどの体液中に比較的均等に分布する．血漿蛋白質に対する結合は変動しやすいが，NSAIDs よりは少なく，急性中毒時の濃度でも 20～50%が結合しているのみである．治療用量では薬物の 90～100%が主として肝臓でグルクロン酸（約 60%），硫酸（約 35%）またはシステイン（約 3%）と抱合された後，投与された日のうちに尿に回収される．少量の水酸化および脱アルカリ化された代謝物も検出される．小児は成人よりも薬物をグルクロン酸抱合する能力が低い．アセトアミノフェン服用時には肝薬物代謝酵素を介する N-水酸化を経て，高い反応性を持った中間体である **N-アセチル-*p*-ベンゾキノンイミン（N-acetyl-*p*-benzoquinoneimine：NAPQI）** が形成されるが，通常，この代謝物は **グルタチオン（glutathione：GSH）** のスルフィドリル基と反応し無毒化される．しかし，大量のアセトアミノフェンを服用した後は，肝臓のグルタチオンを枯渇させるのに十分な量の代謝物が形成され，過剰量を投与した場合の毒性の原因となる．

N-アセチル-*p*-ベンゾキノンイミン（N-acetyl-*p*-benzoquinoneimine：NAPQI）
グルタチオン（glutathione：GSH）

4）用　法

通常，原末または錠剤では成人としてアセトアミノフェン 1 回 300～500 mg，1 日 900～1,500 mg を経口投与する（通常，乳児，幼児および小児にはアセトアミノフェンとして，体重 1 kg あたり 1 回 10～15 mg を経口投与する．投与間隔は 4～6 時間以上とし，1 日総量として 60 mg/kg を限度とする．ただし，成人の用量を超えない）．なお，年齢，症状により適宜増減する．しかしながら，ここで示した本邦の成人での用量，用法ではがん疼痛

に対して有効な除痛が得られない可能性がある．海外における投与方法は，1回500～1,000 mg，1日最大4,000 mg程度，4～6時間ごととなっている．一方，本邦における高用量アセトアミノフェンの安全性は確認されていないため，その際は定期的な肝機能モニタリングを行うことが望ましい．

5）副作用

①発疹・アレルギー

推奨される治療投与量では，アセトアミノフェンの副作用は起こりにくい．稀に皮膚発疹と他のアレルギー反応が起こる．発疹は，通常は紅斑性または蕁麻疹様であるが，さらに重症になり，薬物による発熱と粘膜損傷を伴うことがある．サリチル酸塩に対し過敏症反応を示す患者が，ごく稀にアセトアミノフェンに対し過敏症を示すことがある．アセトアミノフェンの使用により，好中球減少症，血小板減少症および汎血球減少症が起こった例もある．

肝臓障害

②肝臓障害

アセトアミノフェンの過量投与による最も重篤な急性の有害作用は，致命的になりうる肝臓壊死である．腎尿細管壊死と低血糖性昏睡も起こることがある．アセトアミノフェンの過量投与が肝細胞の損傷と死亡をもたらす機序には，毒性のある代謝物NAPQIに変換されることが関係している．グルクロン酸塩および硫酸塩と抱合経路が飽和し，肝薬物代謝酵素によるN-hydroxylationによりNAPQIへの変換が増加する．この中間体はGSHとの抱合によりすみやかに分解され，その後，さらにメルカプツール酸に代謝されて尿に排泄される．しかし，過量のアセトアミノフェンの場合には，肝細胞のGSH量が枯渇している．反応性に富むNAPQIは細胞の高分子と共有結合するため，酵素反応系が抑制され，細胞の構造と代謝が正常な状態を保てなくなる．さらに，細胞内GSHの枯渇により，肝細胞が酸化ストレスを受けやすくなり，細胞死が起こりやすくなる．

成人では，10～15 g（150～250 mg/kg）のアセトアミノフェンを一度に内服すると肝臓毒性が起こり，20～25 gまたはそれ以上では致命的になる可能性がある．薬物代謝酵素誘導が起こる条件（アルコールの過剰摂取など）やGSH枯渇が起こる条件（空腹や栄養失調など）では肝臓が障害を受けやすくなり，稀ではあるが，治療用量域で肝毒性が起こった例も報告されている．アセトアミノフェンによる急性中毒で最初の2日間に起こる症状は，消化器症状（悪心，腹痛，食欲不振）で中毒の深刻さを思わせるものではない．服用12～36時間後に血漿トランスアミナーゼが上昇し始め，その上昇が極めて顕著な場合もある．肝障害の臨床的な診断は，中毒量を内服して2～4日以内に，右の肋骨下の痛み，圧痛を伴う肝腫，黄疸，凝固障害により明らかになる．腎障害や明らかな腎不全が起こることもある．肝臓の酵素の異常は一般には服用72～96時間後に起こる．これより後に肝性脳障害や凝固障

害の悪化が起こると予後が悪い．肝臓の生検では，門脈周囲部を除いて小葉中心性壊死がみられる．死に至らなかった症例では，肝障害は数週ないし数カ月かけて回復する．

③ 過量投与に対する処置

アセトアミノフェンの過量投与には緊急の対策が必要である．アセトアミノフェンの血漿濃度が内服後4時間で300 μg/ml より多いか，または15時間で45 μg/ml より多い患者の90%で重篤な肝障害が起こる．薬物濃度が内服後4時間で120 μg/ml より少ないか，または12時間で30 μg/ml より少ない時は，最小限の肝障害にとどまる．アセトアミノフェンの過量投与を治療する場合には，早期診断が大切である．適切な治療が行われなければ，おそらく中毒患者の10%が重篤な肝障害を起こし，そのうち10～20%はその後に十分な処置を施したとしても肝不全のために死亡する．服用4時間後までに活性炭を与えることができれば，アセトアミノフェンの吸収を50%～90%まで抑制することができる．胃洗浄は一般的に推奨されない．肝障害の危険がある時にはN-アセチルシステイン（N-acetylcysteine：NAC）が処方される．アセトアミノフェン中毒の疑いがある場合には血液検査の結果を待たずにNACによる治療を開始し，血漿中のアセトアミノフェンの測定値から肝毒性の危険性の低いことが示されたならば，治療を終了する．NACはGSH量を回復させ，GSHに置換してNAPQIと結合することにより，NAPQIの毒性作用を消失させる．アセトアミノフェン中毒の症例で，NACの抗酸化および抗炎症作用によって肝以外の障害が抑制された例が報告されている．活性炭存在下でもNACはよく吸収されるので，相互作用を懸念して活性炭の投与をやめたり，NACの投与を遅らせたりしてはならない．NACの有害反応としては，皮膚発疹，悪心，嘔吐，下痢等があり，稀にアナフィラキシー反応が起こることがある．初回経口投与量は140 mg/kgで，その後4時間毎に70 mg/kgを17回投与する．可能であれば静脈内投与量として150 mg/kgを100 mlの5%デキストロース溶液250 mlに溶解して15分以上かけて点滴静注し，次に50 mg/kgを250 mlの5%デキストロース溶液250 mlに溶解して4時間以上かけて点滴静注し，さらに100 mg/kgを5%デキストロース溶液500 mlに溶解して16時間以上かけて点滴静注する．

N-アセチルシステイン（N-acetylcysteine：NAC）

NAC療法に加えて，集中的に支持的な治療を行う必要がある．これには，肝不全や腎不全が起こった場合の対応，意識混濁の場合の挿管などがある．肝不全により低血糖が起こることがあるため，血漿中グルコースをモニターすべきである．劇症肝炎の場合は肝臓移植が必要であり，NAC療法を行っても重篤な肝障害が進行する場合は肝臓移植のできる医療機関に連絡をすべきである．

6）相互作用

NSAIDs（インドメタシン，イブプロフェン等）は腎のプロスタグランジン合成を抑制するため，炭酸リチウムとの併用によりリチウムの血中濃度が上昇したとの報告がある．逆にこの機序により水，塩類貯留が生じ，チアジド系利尿剤の作用を減弱させる可能性があるため，アセトアミノフェンとこれらの薬剤を併用する際にも注意が必要である．また，アルコール常飲やフェノバルビタール，フェニトイン，プリミドン，リファンピシン，イソニアジド等の薬物代謝酵素を誘導する薬物によりアセトアミノフェンから肝毒性を持つNAPQIへの代謝が促進される可能性があるため，アルコール多量常飲者やこれらの薬物を服用中の患者にアセトアミノフェンを服用させる際は肝障害の発現に十分に注意する必要がある．一方，クマリン系抗凝血薬と血漿蛋白質結合部位において競合することで抗凝血薬を遊離させ，その抗凝血作用を増強させる可能性があるため，ワルファリンカリウムと併用する際には減量するなど慎重に投与する必要がある．また，機序は不明だが，抗菌剤との併用により過度の体温下降を起こす頻度が高くなることから，併用する場合には観察を十分に行う必要がある．

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SHORT COMMUNICATION

Palliative care needs of cancer outpatients receiving chemotherapy: an audit of a clinical screening project

Tatsuya Morita · Koji Fujimoto · Miki Namba · Naoko Sasaki · Tomoko Ito · Chika Yamada · Arisa Ohba · Motoki Hiroyoshi · Hiroshi Niwa · Takeshi Yamada · Tsuneo Noda

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Abstract
Purpose Although more and more cancer patients are receiving chemotherapy in outpatient settings in their advanced stage and could have a broad range of palliative care needs, referral to the specialized palliative care service is often delayed. The primary aim of this study is to explore the usefulness of a combined intervention for cancer patients in identifying patients with underrecognized palliative care needs and referring them to the specialized palliative care service. The intervention consisted of (1) introducing the specialized palliative care service when starting chemotherapy, (2) using screening tools, and (3) providing on-demand specialized palliative care service.
Materials and methods All cancer patients newly starting chemotherapy with primary tumor sites of the lung, gastrointestine, pancreas, bile duct, breast, ovary, and uterus were included. As routine practice, at the first instruction about chemotherapy, pharmacists provided information about the role of the specialized palliative care service using a pamphlet and handed out screening questionnaires. Screening questionnaires were distributed at every hospital visit. Treating physicians and/or nurses checked the questionnaire before examining the patients. The patients were referred to the palliative care team, if (1) the patients voluntarily wished for the specialized palliative care service or (2) the treating physicians clinically determined that, on the basis of the screening results, the patients had physical or psychological needs appropriate for referral to the specialized palliative care service. The screening questionnaire included an open-ended question about their greatest concerns, the severity of 11 physical symptoms, overall quality-of-life, the distress thermometer, help for information about the treatment and decision-making, economic problems, nutri-

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tion, daily activities, and wish for help from the specialized palliative care service.

Results Of 211 patients who newly started chemotherapy, 5 patients refused to complete the questionnaire (compliance rate, 98%). We obtained 1,000 questionnaires from 206 patients. The percentages of missing values ranged from 2.7% to 7.0%. Of 206 patients, 38 (18%) were referred to the palliative care team due to newly recognized problems, in addition to 10 patients with problems well-recognized by primary physicians. The total percentage of patients receiving specialized palliative care service was thus 23% of all patients. Frequently identified problems were oral problems (20%), insomnia (20%), help with information and decision-making (16%), psychological distress defined as the distress thermometer (14%), severe fatigue (9.0%), and severe appetite loss (8.8%). As a whole, problems were identified in half of all questionnaires.

Conclusion The combined intervention of introducing the specialized palliative care service, using screening tools and providing on-demand specialized palliative care service, was feasible as part of the routine clinical practice for all cancer patients starting chemotherapy. It might be useful in identifying patients with underrecognized palliative care needs and referring them to the specialized palliative care service at the appropriate time.

Keywords Palliative care team · Neoplasms · Screening · Chemotherapy head · Outpatient

Introduction

The recent literature indicates that more and more cancer patients receive chemotherapy in outpatient settings in their advanced stage [1]. They have a broad range of palliative care needs including physical symptoms, psychological distress, help with decision-making, and economical and practical support [2–7]. Conceptually, palliative care can and should be provided for all patients along with disease-modifying treatment [8]. Referral to the specialized palliative care service is, however, often delayed because patients regard receiving palliative care as an *alternative*, not an additional, resource of anticancer treatment [9–11]. Introducing the specialized palliative care service as an additional resource to improve the quality-of-life of all patients at the earlier stage of cancer treatment, focusing on patient distress not on the stage of the disease, can be a useful strategy to provide adequate palliative care [12]. Several intervention trials have suggested that the routine use and feedback to the treating physicians of quality-of-life measurements or symptom assessment scales could contribute to improving physician recognition of patient quality-of-life aspects with some beneficial effects on patient psychological well-being [13–17]. On the other hand, some clinical trials including more intensive interventions, such as cognitive behavior intervention with systematic identification of patient needs, have demonstrated positive outcomes in patient physical well-being, not only psychological issues [18–22]. In addition, multidisciplinary intervention by specialized palliative care teams in outpatient settings could contribute to enhancing patient quality-of-life [23–26]. These findings suggest that a combined intervention of (1) introducing the specialized palliative care service at the earlier stage of disease trajectory, (2) using screening tools, and (3) providing on-demand specialized palliative care might contribute to a better quality-of-life for cancer patients receiving active anticancer treatment.

The primary aim of this project is to explore the usefulness of such intervention in identifying patients with underrecognized palliative care needs and referring them to the specialized palliative care service. An additional aim was to clarify the prevalence of physical and psychological symptoms and concerns among a heterogeneous sample of cancer patients receiving outpatient chemotherapy in a regional cancer center.

Materials and methods

This brief descriptive study included all cancer patients newly starting chemotherapy with primary tumor sites of the lung, gastrointestine, pancreas, bile duct, breast, ovary, and uterus from April to October 2006. We had decided to include the patients receiving adjuvant chemotherapy because they might receive some benefit from professional emotional support by a member of the palliative care team (the leading department of this project is the Department of Palliative and Supportive Care). As part of the routine practice, at the first instruction about chemotherapy, pharmacists provided information about the role of the specialized palliative care service using a pamphlet and handed out screening questionnaires with coaching on how to complete them. Screening questionnaires were thereafter distributed at every hospital visit. If the patients refused to complete

the questionnaire or recognized no need, they were not obliged to complete the questionnaire.

Treating physicians and/or nurses checked the screening questionnaire before examining the patients. The patients were referred to the palliative care team, if (1) the patients voluntarily wished for the specialized palliative care service or (2) the treating physicians determined that, on the basis of the screening results, the patients had physical or psychological needs appropriate for referral to the specialized palliative care service. Although we instructed the physicians to consider the scores of 5 or more as a threshold for the screening, the decision whether the treating physicians referred patients to the palliative care team was clinically made due to no established cutoff points. In addition, a research nurse provided brief feedback about the screening results via the electronic medical recording system.

Palliative care team activity is widespread throughout our hospital and could respond to all consultations within a few days [27, 28].

Screening questionnaire

The study group constructed the screening questionnaire on the basis of existing validated instruments [29–33]. As the primary intention of this activity was to identify patients with underrecognized needs and facilitate their referral to the specialized palliative care service within the routine clinical practice, not to clarify the exact prevalence of each need, we decided to make the questionnaire as simple and short as possible.

The screening questionnaire included (1) an open-ended question about the greatest concerns of patients; (2) 0–10 numeric rating scales of 8 physical symptoms (pain, dyspnea, nausea, appetite loss, somnolence, fatigue, constipation/diarrhea, numbness) adopted from the Japanese version of the M.D. Anderson Symptom Inventory (MDASI) after modification of the interval (24 h to 1 week) and the timing (worst to average severity) [29]; (3) presence or absence of oral problems, fever, and insomnia; (4) 0–7 numeric rating scale of overall quality-of-life adopted from item 29 of the EORTC-C30 [30]; (5) the distress thermometer [31, 32]; (6) presence or absence of help in 4 areas, i.e., information about the treatment and decision-making, economic problems, nutrition, and daily activities [33]; and (7) wish for help of the specialized palliative care service (see Appendix).

Our hospital required no Institutional Review Board approval for the retrospective analysis of clinical activity, but admitted patients gave written consent that their clinical information could be used for clinical research.

Analyses

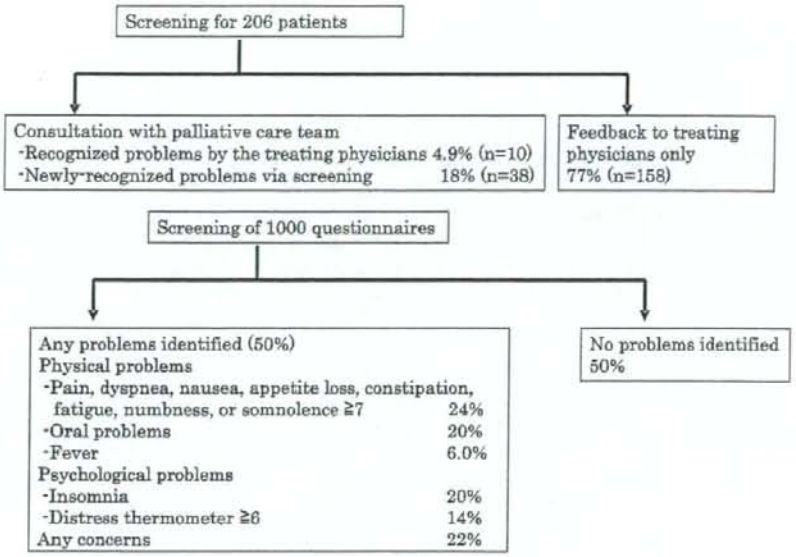
The primary endpoint was the number of patients referred to the palliative care team after treating physicians and/or nurses recognized patient needs via the screening questionnaire.

As additional endpoints, the prevalence of problems was calculated for each visit. For calculations, we adopted ad hoc definition of moderate and severe symptom intensities for the MDASI items as 4–6 and 7–10, respectively. We used cutoff points on the distress thermometer of 6 or more following the previous findings [31, 32]. We determined that a patient had problems if he/she had either MDASI symptoms of 7 or more, oral problem, fever, insomnia, distress thermometer of 6 or more or any help with

Table 1 Patient backgrounds (n=206)

Summary of patient backgrounds	
Age	62±11 years
Sex	
Male	41% (n=84)
Female	59% (n=122)
Primary sites	
Lung	30% (n=62)
Breast	27% (n=56)
Colon, rectum	15% (n=31)
Stomach	13% (n=26)
Uterus, ovary	10% (n=21)
Pancreas, bile duct	2.9% (n=6)
Others	3.9% (n=8)
Chemotherapy regimens	
Taxanes	27% (n=55)
Carboplatin and taxanes	19% (n=39)
Doxorubicin and cyclophosphamide	12% (n=25)
Oral tegafur gimeracil oteracil	11% (n=22)
Fluorouracil	10% (n=21)
Gemcitabin	3.4% (n=7)
Irinotecan with/without taxanes	2.9% (n=6)
Transtumab with/without taxanes	2.9% (n=6)
Cyclophosphamide, methotrexate, and fluorouracil	2.4% (n=5)
Gefetinib	1.5% (n=3)
Low-dose cisplatin and 5-fluorouracil	1.5% (n=3)
Vinorelbine	1.0% (n=2)
Oxaliplatin and 5-fluorouracil/leucovorin	1.0% (n=2)
Oral capecitabine	1.0% (n=2)
Others	3.4% (n=7)

Fig. 1 Results



information and decision-making, nutrition, economic problems or daily activities.

Results

During this study interval, of 211 patients who newly started chemotherapy, 5 patients refused to complete the screening questionnaire (compliance rate, 98%). Each patient completed a median of 3.0 screening questionnaires during this study period (range 0–15) and we obtained 1,000 questionnaires from 206 patients. The percentages of missing values ranged from 2.7% (appetite loss) to 7.0% (distress thermometer). Table 1 summarizes the patient backgrounds.

Of 206 patients who completed the initial questionnaire, 38 (18%) were referred to the palliative care team due to newly recognized problems via the screening tool, in addition to 10 patients who consulted the palliative care team due to well-recognized problems (Fig. 1). The percentage of patients receiving the specialized palliative care service was thus 23% of all patients by treating physicians (48/206).

The main reasons for the referral via the screening tool were: psychological distress (58% of 38 patients, n=22), appetite loss/nausea/constipation (26%, n=10), pain (24%, n=9), numbness (13%, n=5), fatigue (13%, n=5), and dyspnea/cough (5.3%, n=2). On the other hand, the main symptoms of the patients who consulted the palliative care team due to well-recognized problems were: pain (40% of 10 patients, n=4), dyspnea (30%, n=3), delirium (20%, n=2), and psychological distress (10%, n=1).

For the questionnaire level (Table 2), frequently identified problems were oral problems (20%), insomnia (20%), help with information and decision-making (16%), psychological distress (defined as the distress thermometer ≧6; 14%), severe fatigue (9.0%), and severe appetite loss (8.8%). As a whole, problems were identified in half of all questionnaires (Fig. 1).

Discussion

The first important finding of this study was the feasibility of our clinical intervention. The percentage of patients who completed the screening questionnaire at instruction was over 90%. The percentages of missing values in each screening item were below 7.0%. These findings demonstrated that this intervention was feasible for the majority of cancer patients receiving chemotherapy as part of the routine clinical practice.

The second important finding was the potential usefulness of our intervention in identifying patients with under-

Table 2 Problems identified in 1,000 questionnaires

	Prevalence (%)[a]			Mean±SD (median)[b]
Physical problems				
MDASI items	Severe	Moderate	Total	
Fatigue	9.0	16	25	2.4±2.5 (2.0)
Appetite loss	8.8	11	20	1.9±2.6 (0.0)
Constipation	5.6	13	19	1.7±2.3 (1.0)
Somnolence	4.9	14	19	1.8±2.2 (1.0)
Pain	4.9	9.9	15	1.6±2.1 (1.0)
Numbness	6.0	7.5	14	1.4±2.3 (0.0)
Dyspnea	2.9	7.5	11	1.2±1.9 (0.0)
Nausea	3.4	6.9	10	1.1±2.0 (0.0)
Oral problems			20	
Fever			6.0	
Psychological problems				
Insomnia			20	
Distress thermometer			14	
Concern				
Information and help with decision-making			16	
Nutrition			6.8	
Daily activities			5.6	
Economic problems			2.9	

[a] The percentages of responses with moderate (4–6) and severe (7–10) symptom intensity for the MDASI items. The percentages of the score ≥6 for the distress thermometer. The percentages of problem presence for the other items.

[b] Mean values calculated for the MDASI items only.

recognized palliative care needs and referring them to the specialized palliative care service when patients wished for. Among the half of the patients who received chemotherapy and reported physical or psychological problems or concerns at the questionnaire level, 23% of all cancer patients were newly referred to the palliative care team with the primary aim of improving their quality-of-life. Despite clear limitation of the lack of control group, this finding strongly indicates that our intervention could provide specialized care for patients with profound symptoms irrespective of the disease extent.

The additional but third important finding was the clarification of the types of symptoms and concerns observed in heterogeneous cancer outpatients receiving chemotherapy. In this study, psychological issues (insomnia, distress), concern about information and decision-making, nutrition-related issues (oral problems and appetite loss), and fatigue were major concerns for patients. Consistent with the previous findings from Western countries, this finding indicates that developing systematic intervention strategies targeting psychosocial distress, decision-making, nutrition, and fatigue is of great importance and an emerging task for Japanese palliative care specialists [34–39].

In addition, this study revealed a considerable difference between the symptom patterns of the patients referred via the screening system and those from the treating physicians. While pain, dyspnea, and delirium were major reasons for the referral from the treating physicians, the screening system identified a broader range of patient distress, such as psychological distress, appetite loss, numbness, and fatigue. The result indicates that the screening system could be useful in identifying the patients with serious psychological distress, appetite loss, numbness, and fatigue, which are often overlooked by physicians.

This was a descriptive study of routine clinical experience and thus had considerable limitations. First, we did not formally measure the changes in the symptoms and concerns after consulting the palliative care team and we cannot conclude whether referral to the specialized palliative care service actually provided a benefit for the patients. Second, as the patients were a heterogeneous sample of their primary tumor sites, stages, and chemotherapy regimens, the results might not be automatically generalized to specific target populations. We believe this is not a fatal flaw of this study because we need to develop a useful system for heterogeneous outpatients receiving chemotherapy. Third, as this was a single institution study where the palliative care unit and palliative care team have been regarded as an essential function of the hospital [27, 28], the results could not be generalized to other institutions. Finally, because we had not decided to explore solid cutoff points, the most appropriate cutoff points for the screening and the definition of moderate and severe symptom intensities should be further studied.

In conclusion, the combined intervention of introducing the specialized palliative care service, using screening tools, and providing on-demand specialized palliative care service when starting chemotherapy as a part of routine clinical practice was feasible and could be useful in identifying patients with underrecognized palliative care needs and referring them to specialized palliative care service. To evaluate the accurate effects of this intervention, controlled trial is promising.

Appendix

Screening questionnaire

A. What is your greatest concern?

B. Physical symptoms. During the last week, how severe were your symptoms on the average?

	Not present ←									→ As bad as you can imagine
Pain	0	1	2	3	4	5	6	7	8	9	10
Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
Nausea	0	1	2	3	4	5	6	7	8	9	10
Lack of appetite	0	1	2	3	4	5	6	7	8	9	10
Drowsy (sleepy)	0	1	2	3	4	5	6	7	8	9	10
Fatigue (tiredness)	0	1	2	3	4	5	6	7	8	9	10
Constipation/Diarrhea	0	1	2	3	4	5	6	7	8	9	10
Numbness or tingling	0	1	2	3	4	5	6	7	8	9	10

Oral problems YES NO Fever YES NO Sleep Difficulty YES NO

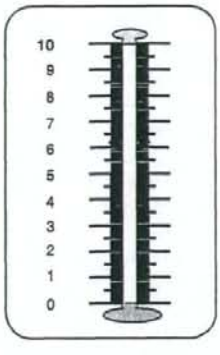
C. In the past week...

	Very poor ←						→ Excellent
1) Overall quality of life	0	1	2	3	4	5	6	7

2) Body Weight ( ) kg

3) How distressed are you?

Extreme distress



No distress

D. Do you need some help with...

- ☐ Information about the treatment and help with decision making
- ☐ Economic problems
- ☐ Nutrition
- ☐ Daily activities (house work, work, toilet...)

E. Do you wish for specialized palliative care (see the reverse side for detailed information)

→ WISH NOT wish

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SUPPORTIVE CARE INTERNATIONAL

Quality of end-of-life treatment for cancer patients in general wards and the palliative care unit at a regional cancer center in Japan: a retrospective chart review

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Abstract
Goals In Japan, most cancer patients die in the hospital. The aim of this study was to assess the quality of end-of-life treatment for dying cancer patients in general wards and palliative care unit (PCU).
Materials and methods A retrospective chart review study was conducted. The following data on cancer patients who died in general wards (N=104) and PCU (N=201) at a regional cancer center were collected: do-not-resuscitate (DNR) decisions, treatments in the last 48 h of life, and aggressiveness of cancer care for dying patients.
Main results DNR orders were documented for most patients (94% in general wards, 98% in PCU, p=0.067) and families usually consented (97%, 97%, p=0.307). Comparison of general wards with PCU showed that, in the last 48 h of life, significantly more patients in general wards received life-sustaining treatment (resuscitation, 3.8%, 0%, p=0.001; mechanical ventilation, 4.8%, 0%, p=0.004), large volume hydration (>1,000 ml/day, 67%, 10%, p<0.001) with continuous administration (83%, 5%, p=0.002) and fewer palliative care drugs (strong opioids, 68%, 92%, p< 0.001; corticosteroids, 49%, 70%, p<0.001; nonsteroidal anti-inflammatory drugs, 34%, 85%, p<0.001). Regarding aggressiveness of cancer care, patients received a new chemotherapy regimen within 30 days of death (3.0%), chemotherapy within 14 days of death (4.3%), and intensive care unit admission in the last month of life (3.3%).
Conclusion We found that families, not patients, consented to DNR, and life-sustaining treatments were appropriately withheld; however, patients on general wards received excessive hydration, and the use of palliative care drugs could be improved. Application of our findings can be used to improve clinical care in general wards.

Keywords Quality of health care · Palliative care · Terminal care · Decision making · Retrospective study · Neoplasm · Japan

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Introduction

For cancer patients in the last days of life, there are a wide variety of issues, including distressing physical symptoms, psychological concerns, decreased physical and communication abilities, and the ethical considerations of treatment [1, 2]. Providing appropriate care for these patients is very important.

Unfortunately, poor-quality end-of-life care occurs in hospital settings. The SUPPORT study revealed substantial shortcomings in the care of seriously ill hospitalized adults: patients' preferences regarding resuscitation were unknown to their physicians (47%), do-not-resuscitate (DNR) orders were written within 2 days of death (46%), patients received mechanical ventilation (46%), and patients suffered moderate-to-severe pain in the last 3 days of life (50%) [3]. After publication of the SUPPORT study, many studies reported inadequacy of end-of-life treatment in general wards. Especially in the last 48 h of life, many patients received inappropriate life-sustaining treatment [4–9] and inadequate pain and symptom management [4–6, 9–11]. The current status of end-of-life treatment should be investigated to improve the clinical care of dying hospitalized patients. Recently, quality indicators (QIs) of end-of-life cancer care have been identified: intensive use of chemotherapy, low rates of hospice use, and interventions resulting in emergency room visits, hospitalization, or intensive care unit (ICU) admissions [12]. These indicators were effectively utilized to assess the aggressiveness of cancer care using administrative data [13–15] and applied in a hospital setting [16].

In Japan, cancer is the leading cause of death (30% of all deaths), and 91% of cancer patients died in hospital in 2005 [17]. Palliative care developed from inpatient care for terminal cancer patients in Japan. In 1990, coverage for care in a palliative care unit (PCU) was included in National Health Insurance, and the number of PCUs has increased from 5 to 163 in 2007. Coverage for care provided by the palliative care team (PCT) began in 2002. These interdisciplinary teams cooperate with attending physicians to provide specialized care in general wards. Also in 2002, the Japanese Ministry of Health, Labor and Welfare designated a regional cancer center to provide standardized cancer diagnosis and treatment, which included palliative care. Only 5% of cancer patients died in PCU; therefore, a major task is to help staff on the general wards provide appropriate end-of-life care for dying cancer patients. This is also the case with Western countries. Previous studies investigated some aspects of quality of end-of-life care in Japan as follows: satisfaction of end-of-life care for cancer patients who died in PCUs [18], the efficacy of PCTs [19, 20], documentation of DNR orders in a teaching hospital [21], treatments and status of disclosure in the last 48 h of life in PCU and those provided in a geriatric hospital, where 42% of patients had cancer [22]. It is unclear who actually consents to DNR; however, in Japan, a cultural feature is that the family plays a greater role in this type of decision making [23–25]. There is also limited information about the comprehensive aspects of end-of-life treatment provided for dying cancer patients in general wards, and there are no data regarding QIs because of underdeveloped cancer registries in Japan. Improvements in the end-of-life treatment in general wards can be made by comparing practices that occur in PCU. In addition, understanding the aggressiveness of cancer care can be accomplished by using QIs.

The aim of this study was to assess quality of end-of-life treatment for dying cancer patients in general wards and the PCU at a regional cancer center in Japan. In particular, we focused on DNR decision making, treatments in the last 48 h of life, and aggressiveness of cancer care for dying patients.

Materials and methods

Patients and settings

Data were collected retrospectively on cancer patients who died in general wards and the PCU from September 2004 to February 2006 at Tsukuba Medical Center Hospital in Ibaraki Prefecture, Japan. The inclusion criteria were as follows: (1) died from cancer; (2) aged 20 years or older at the time of death; and (3) hospitalized for 3 days or more. The cancer sites could not be matched between settings because various clinical departments including respiratory medicine, general thoracic surgery, gastroenterology, gastroenterological surgery, general medicine, and palliative medicine participated in this study. These departments represented 88% of all cancer deaths in general wards and 100% in PCU during the study period. The exclusion criteria were as follows: (1) recruited by other study for bereaved family members; (2) bereaved family members would suffer serious psychological distress as determined by the attending physician; (3) cause of death was treatment or injury related; and (4) no bereaved family member aged 20 years or older.

Tsukuba Medical Center Hospital is a regional cancer center, in the suburbs of Tokyo. It has 409 beds (6 ICU beds and 20 PCU beds) and plays a central role in cancer treatment, community health care, and emergency medical care in Ibaraki Prefecture, Japan. PCU was certified in 2000 and provides specialized palliative care for patients in PCU and consultation, as requested, for general wards. During the study period, 188 patients died in general wards, and 242 patients died in PCU.

Procedure

We mailed a letter to identified bereaved families to inform them about the study. They were instructed to check and return the form in the enclosed envelope if they refused to participate in the chart review study in October 2006. The chart review was conducted between October and December 2006. Data were excluded for unknown addresses or if bereaved families declined to participate. A qualified research nurse (K.S.) reviewed all medical charts under the supervision of a PCU doctor. Initially, 20 medical charts were randomly selected and independently abstracted by two researchers (K.S. and M.M., also a licensed research nurse) to assure inter-rater reliability. The average rate of accordance was 93% between the reviewers; therefore, good inter-rater reliability was assured. The Ethics Committee of Tsukuba Medical Center Hospital approved this study.

Measures

Data were collected on five major categories: (1) patients' characteristics; (2) DNR decisions; (3) treatments in the last 48 h of life; (4) palliative care drugs in the last 48 h of life; and (5) QIs of end-of-life cancer care. Content validity was checked by two palliative care doctors and two research nurses before the medical chart review. A data collection sheet was utilized for documentation.

Patients' characteristics included information about sex, age, primary cancer site, cancer stage, and experience of cancer treatment (surgery, chemotherapy, and radiotherapy), length of time since cancer diagnosis, length of hospital stay, palliative care referral, length of time since palliative care referral, and length of PCU stay. Information concerning DNR decisions included: documentation of DNR order, patient or family consent to DNR, and length of time between documentation and death. Treatments in the last 48 h of life were comprehensively surveyed in reference to previous studies (see Table 4) [1, 4–6, 11]. We reviewed whether palliative care drugs were used in the last 48 h of life. They included ten classes of drugs which Nauck et al. [26] reported to be the most common in PCU (see Table 5). In addition, use of strong opioids, types of opioids in Japan (i.e., morphine, fentanyl, and oxycodone), methods [routine and as required (PRN)], and routes of administration were surveyed. We used QIs which Earle et al. [12] had identified and were available for our hospital setting to assess aggressiveness of cancer care near the end of life. QIs were identified during the chart review: new chemotherapy regimen within 30 days of death, chemotherapy within 14 days of death, more than 14 days hospital stay in the last month, admitted to the ICU in the last month, and 3 or fewer days PCU stay in the last month of life.

Data analysis

First, we calculated the relative frequency for categorical variables and the median, mean, and standard deviation (SD) for quantitative variables. For patients' characteristics,

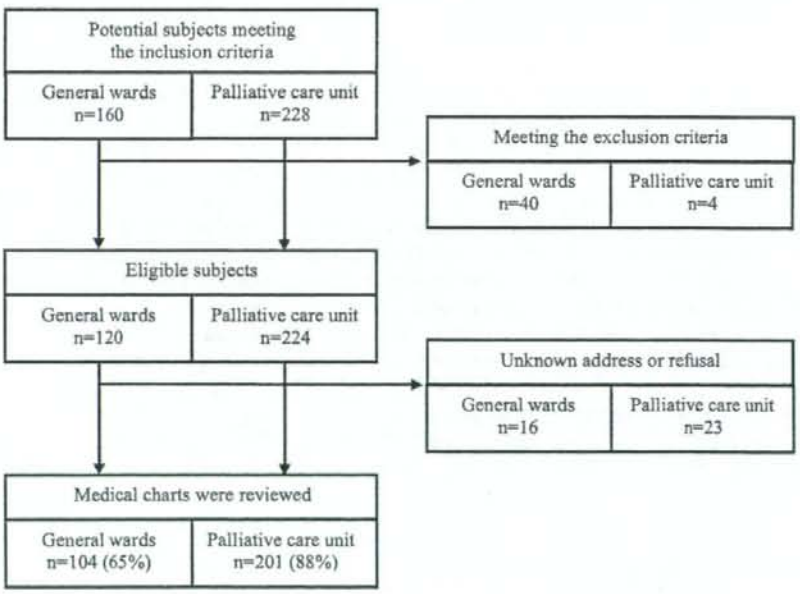

Fig. 1 Flow chart showing the patients' entry into the study

we separately calculated results from general wards and PCU and then compared the differences between the settings. For DNR decisions and treatments and palliative care drugs in the last 48 h of life, we also separately calculated results and then compared the differences to examine quality of end-of-life treatment for dying cancer patients in general wards. For aggressiveness of cancer care for dying patients, the calculated results combined for all settings were used to examine quality of end-of-life treatment throughout the hospital because these indicators were unsuited for comparing the aggressiveness between general wards and PCU. Statistical tests included Fisher's exact test, Cochran–Armitage exact trend test, or Wilcoxon test, as appropriate. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SAS version 9.1 for Windows (SAS Institute, Cary, NC).

Results

The patients' entry into the study is shown in Fig. 1. During the study period, patients who died in general wards (n=160) and PCU (n=228) were identified as potential subjects meeting the inclusion criteria. Among potential subjects, 44 were excluded due to participation in the other study (n=23 in general wards, n=0 in PCU), serious psychological distress as determined by the attending physician (n=8, n=0), treatment- or injury-related deaths (n=3, n=1), or no bereaved adult members (n=2, n=2). Subjects were also excluded if the bereaved family had no known address (n=3, n=8) or refused to participate (n=13, n=15). Finally, 104 (65%) medical charts from general wards and 201 (88%) from PCU were reviewed.

Patients' characteristics

Patients' characteristics are shown in Table 1. Among patients whose charts were reviewed, 71 and 55% were male and mean age was 71±9 and 68±12 years old in general wards and PCU, respectively. Primary cancer sites were lung (41% in general wards, 15% in PCU), hepatobiliary and pancreatic (28%, 17%), gastric (11%, 16%), and colorectal (6.7%, 17%).

In comparing patients' characteristics in general wards with those in PCU, significant findings include: more males

Table 1 Patients' characteristics

	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Sex, male	74	(71)	110	(55)	0.007**
Age, years (mean±SD)	71±9		68±12		0.100
Primary cancer site					
Lung	43	(41)	30	(15)	<0.0001***
Hepatobiliary and pancreatic	29	(28)	34	(17)	
Gastric	11	(11)	32	(16)	
Colorectal	7	(6.7)	35	(17)	
Head and neck	0	(0)	16	(8.0)	
Breast	1	(1.0)	15	(7.5)	
Other	13	(13)	39	(19)	
Cancer stage					
Local	7	(6.7)	2	(1.0)	0.002**
Regional	19	(18)	26	(13)	
Distant	74	(71)	171	(85)	
Experience of cancer treatment					
Surgery	26	(25)	118	(59)	<0.0001***
Chemotherapy	52	(50)	131	(65)	0.014*
Radiotherapy	45	(43)	93	(46)	0.630
Length of time since cancer diagnosis, months (median, mean±SD)	7, 14±27		18, 32±39		<0.0001***
Length of hospital stay, days (median, mean±SD)	27, 37±37		30, 45±65		0.296
Palliative care referral[a]	25	(24)	–		–
Length of time since palliative care referral, days (median, mean±SD)[b]	20, 31±27		61, 108±152		<0.0001***
Length of palliative care unit stay, days (median, mean±SD)	–		23, 37±60		–

Several total percentages are not 100% due to missing values.
SD Standard deviation
*p<0.05
**p<0.01
***p<0.001
[a] Palliative care referral to provide specialized care by PCT in general wards
[b] Median, mean, and SD calculated from patients with palliative care referral

(p=0.007), primary cancer sites were different (p<0.001), cancer stage was less advanced (p=0.002), fewer experienced surgical treatments (p<0.001) or chemotherapies (p=0.014), fewer with shorter length of time since cancer diagnosis (p<0.001), and shorter length of time since palliative care referral (p<0.001).

DNR decisions

Information about DNR decisions is shown in Table 2. DNR orders were documented for most patients (94% in general wards, 98% in PCU). Families (not patients) usually consented to DNR (97%, 97%). Median length of time between documentation of DNR and death was 8 days for general wards and 7 days for PCU. There was no significant difference between settings.

Treatments in the last 48 h

Treatments provided in the last 48 h of life are shown in Table 3. There were significant differences between general wards and PCU for the following: patients received life-sustaining treatment (resuscitation, 3.8% in general wards, 0% in PCU, p=0.001; mechanical ventilation, 4.8%, 0%, p=0.004; intubation, 3.8%, 0.5%, p=0.048); and had diagnostic testing (radiography, 27%, 14%, p=0.013; laboratory examination, 44%, 24%, p<0.001; electrocardiogram 63%, 1.5%, p<0.001). Meanwhile, significantly less palliative sedation (4.8%, 24%, p<0.001) was provided in general wards. Other treatments did not show significant differences between settings: oxygen inhalation (91%, 88%, p=0.556); intratracheal suction (41%, 37%, p=0.460); urinary catheter (61%, 50%, p=0.090); and therapeutic drainage (gastrointestinal fluids, 6.7%, 7.5%, p=1.000; percutaneous transhepatic cholangiole drainage, 3.8%, 3.0%, p=0.739).

Table 2 DNR decisions

	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Documentation of DNR order	98	(94)	197	(98)	0.067
Consent to DNR order[a]					
Patient	0	(0)	4	(2.0)	0.307
Family (not patient)	95	(97)	192	(97)	
Length of time between documentation and death, days (median, mean±SD)[a]	8, 17±29		7, 20±55		0.893

Several total percents are not 100% due to missing values
SD Standard deviation
[a] Percentage, median, mean, and SD calculated from patients with DNR orders

Approximately half of patients were given oral medicine (40% in general wards, 48% in PCU, p=0.185), and most received parenteral medication (98%, 97%, p=1.000); however, route of administration was significantly different. More patients had central venous access (21%, 4.6%, p<0.001), and fewer had peripheral venous access (71%, 81%, p=0.027) or continuous subcutaneous infusion (44%, 83%, p<0.001). Vasopressors (21%, 0.5%, p<0.001), antibiotics (48%, 31%, p=0.006), and intravenous hyperalimentation (10%, 1.5%, p=0.002) were used significantly more in general wards. In addition, 88% in general wards and 87% in PCU received artificial hydration, while significantly more patients received large volume hydration (>1,000 ml/day, 67%, 10%, p<0.001) with continuous administration (83%, 5%, p=0.002).

Palliative care drugs in the last 48 h of life

Use of palliative care drugs in the last 48 h of life is shown in Table 4. Significantly more patients took eight of ten drugs such as strong opioids (68% in general wards, 92% in PCU, p<0.001), gastric protections (54%, 76%, p<0.001), corticosteroids (49%, 70%, p<0.001), nonsteroidal anti-inflammatory drugs (NSAIDs, 34%, 85%, p<0.001), neuroleptics (17%, 52%, p<0.001), and sedative/anxiolytics (15%, 47%, p<0.001), while fewer took antiemetics (20%, 8.0%, p=0.003) in general wards than in PCU. Among those patients taking strong opioids, morphine (92%, 74%, p=0.375) was used most frequently, followed by fentanyl (15%, 42%, p<0.001) and oxycodone (4.2%, 4.9%, p=0.757). Strong opioids, PRN, were used significantly less in general wards (58%, 76%, p=0.006).

Aggressiveness of cancer care near the end of life

Table 5 shows the QIs used to assess aggressiveness of cancer care near the end of life: new chemotherapy regimen within 30 days of death (3.0%, n=9), chemotherapy within 14 days of death (4.3%, n=13), more than 14 days in hospital in the last month of life (72%, n=221), admitted to the ICU in the last month of life (3.3%, n=10), and length of stay of 3 or fewer days in PCU (4.5%, n=9).

Among those patients who received chemotherapy near death and died in PCU, all new chemotherapy regimens were started before admission to PCU, and five of seven chemotherapy treatments were actually done in PCU. All were oral chemotherapy: three hormonal and two molecular targeted. Regarding proportion, for those with more than 14 days in hospital, 19 patients who died within 2 days of hospitalization were not included in the denominator because of the study criteria. Among those patients who were admitted to the ICU, five of ten patients died in ICU.