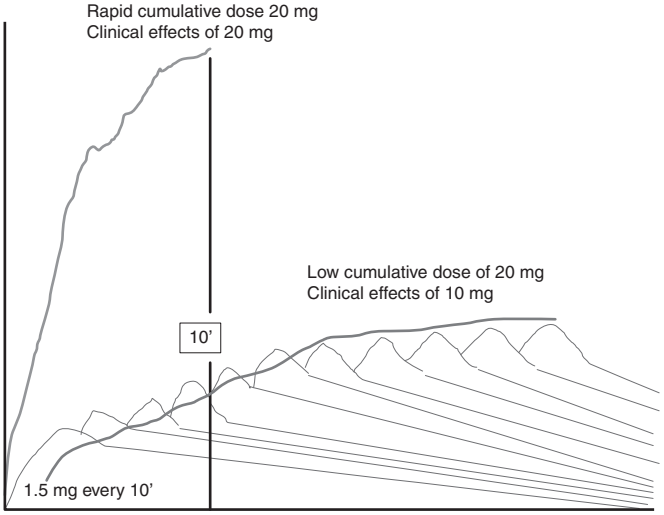

Figure 1. Rapid titration versus slow titration.

confuse the real needs, in relation to the calculation of the i.v.–oral conversion ratio, producing a series of overlapping curves providing poor effective drug concentration (Figure 1). For example, while a morphine dose of 20 mg administered within 10 min, produces a rapid effect from which clinical judgment can be derived, the same dose administered to spaced small boluses is unable to achieve an effective blood concentration. From the previously reported series, the maximum dose of 34.5 mg corresponds to 23 boluses of 1.5 mg repeated every 10 min, i.e. 215 min. During this phase, most of the morphine administered with the first boluses will have been eliminated, and the effective dose will be difficult to calculate. This observation explains the subsequent misleading conversion ratio of 1 : 1.

Intravenous titration is indicated only for patients experiencing excruciating pain, receiving opioids at different doses, unsuccessfully, as this group of patients requires a more intensive approach, commensurate with the circumstances of severe distress. Boluses proportional to the previous level of tolerance, administered in a short time, are safe and effective, and allow a better calculation of the subsequent needs [3].

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References

1. Fallon M, Giusti R, Aielli F et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29(Suppl 4): iv166–iv191.
2. Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med 2003; 17(3): 248–256.
3. Mercadante S, Villari P, Ferrera P et al. Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion. Cancer 2002; 95(1): 203–208.

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Reply to the letter to the editor 'Small repeated boluses are unreliable to provide rapid analgesia with intravenous morphine titration and mislead conversion ratio to oral morphine' by Mercadante S.

Dear Editor,

We would like to thank Dr Sebastiano Mercadante [1] for his thoughtful comments regarding our recent *Annals of Oncology* article about the latest ESMO recommendations on the management of cancer pain [2]. We also recognize the best expertise on the management of rapid i.v. opioid titration as reported in several published papers. In the latest ESMO guidelines, we suggested i.v. morphine administration for rapid opioid titration in cases of severe pain according to previous reported randomized controlled study from Harris et al. [3] in which patients with moderate or severe pain (NRS $\geq$ 5) were randomized to 1.5 mg i.v. bolus doses of morphine every 10 min versus oral morphine 5 mg doses (if opioid-naive) or 10 mg (if already on weak opioid) four-hourly. In the same study, the ratio of initial i.v. morphine dose to the regular four-hourly oral morphine dose after 2 days varied between 1 : 0.5 and 1 : 3.3, and the median ratio was 1 : 0.95 (mean/1 : 1.16). These results can explain the suggested conversion ratio from i.v. to oral route. To our knowledge, this study represents the only randomized controlled trial on this topic with good level of evidence (II—small randomized trial) and grade of recommendation (B—moderate evidence for efficacy but with a limited clinical benefit, generally recommended) according to the ESMO Guidelines Committee.

Clinical experience reported by Mercadante et al. [4] demonstrates a better knowledge of morphine pharmacokinetics and clinical approach for rapid morphine titration in several cancer pain emergencies reported as NRS $\geq$ 7. According to the author, several differences in the definition of cancer pain emergency have been reported in the literature and data are not clear [5]. Despite the low level of evidence for this recommendation (a single center prospective observational study, without control group), we agree that the practice of i.v. morphine titration with boluses proportional to the previous level of tolerance administered in a short time, are safe and effective, and allow a better calculation of the subsequent needs. This also represents an important clinical research question to empower nonpain and

palliative care specialists to practice this approach with confidence.

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References

1. Mercadante S. Small repeated boluses are unreliable to provide rapid analgesia with intravenous morphine titration and mislead conversion ratio to oral morphine. Ann Oncol 2018; 29(10): 2147–2148.
2. Fallon M, Giusti R, Aielli F et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29(Suppl 4): iv166–iv191.
3. Harris JT, Suresh Kumar K, Rajagopal MR. Intravenous morphine for rapid control of severe cancer pain. Palliat Med. 2003; 17(3): 248–256.
4. Mercadante S, Villari P, Ferrera P et al. Rapid titration with intravenous morphine for severe cancer pain and immediate oral conversion. Cancer 2002; 95(1): 203–208.
5. Kumar KS, Rajagopal MR, Naseema AM. Intravenous morphine for emergency treatment of cancer pain. Palliat Med. 2000; 14(3): 183–188.

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