Practical considerations for the integration of subcutaneous targeted therapies into the oncology clinic

by Angela Boudreau

ABSTRACT

The oncology clinic is changing, with an increasing number of cancer therapies becoming available as formulations for subcutaneous (SC) injection. Using targeted therapies, such as alemtuzumab, bortezomib, rituximab or trastuzumab, via SC injection can be advantageous for patients, healthcare professionals, and healthcare systems. However, their use can also present challenges, and nurses have a unique opportunity to positively influence the integration of SC agents in the clinic. This article summarizes practical suggestions for optimal administration of SC targeted therapies, and provides pragmatic considerations for managing the change process related to their adoption.

INTRODUCTION

Oncologic treatment has advanced exponentially over the past two decades. While the majority of therapies are delivered by intravenous (IV), the development of subcutaneous (SC) formulations has been steadily increasing. Since 2012, the IV targeted therapies alemtuzumab, bortezomib, rituximab and trastuzumab have been developed as SC formulations (Stilgenbauer et al., 2009; Janssen Inc., 2018; Hoffmann-La Roche Ltd., 2018a; b). The benefits of SC for the patient, healthcare professional, and healthcare system include preference, cost-savings, time-savings, and capacity improvements compared to the original IV formulations (Jackisch, Müller, Maintz, Hell, & Ataseven, 2014; Martin, Beegle, Zhu, & Hanisch, 2015; Davies et al., 2017; Dent et al., 2019). One of the challenges of administering SC targeted therapies is the potential for pain or other administration-related reactions (ARRs).

Successful integration of SC therapies into the clinic requires both practical knowledge of their optimal administration, as well as thoughtful consideration and planning from a management perspective.

PRACTICAL GUIDANCE

The decision to use a SC targeted therapy affects many aspects of the clinic. For scheduling, flexibility in IV chair time may be required in case a switch from SC back to IV is necessary. A private setting or full resuscitation facilities may be advised. Additionally, staffing schedules could rotate nurses administering SC injections to reduce potential physical strain from repeated injections.

Formulation of SC treatments has been challenging due to the resistance of the SC extracellular matrix; injecting volumes greater than 2 mL can lead to tissue distortion and pain (Haller, 2007). This has been overcome by dividing injections into smaller volumes (e.g., azacitidine), developing more concentrated solutions (e.g., bortezomib), or co-formulating with the enzyme hyaluronidase (e.g., rituximab, trastuzumab) (Table 1) (Leveque, 2014). Hyaluronidase temporarily degrades hyaluronan, allowing for larger volumes of fluid to be administered (Haller, 2007).

Pre-administration

Nurses support the assessment of patients considering SC oncology treatment by reviewing medical history, prior adverse reactions, and family and lifestyle priorities. Pre-administration counselling should include reinforcement of treatment decisions, tailored patient education, and setting realistic expectations to alleviate anxiety (Table 2).

The safety profiles of IV and SC formulations of the same drug are generally similar and in some cases improved. Patients should continue to be counselled on possible medication adverse events (AEs) regardless of the route of administration. One main difference relates to reactions that are administration related. Hypersensitivity and infusion-related reactions are common AEs associated with IV administration. With SC administration, local cutaneous AEs (SC-ARRs) are more common. SC-ARRs are generally mild to moderate in severity, resolve without treatment, and tend to diminish in likelihood with subsequent administration (Hoffmann-La Roche Ltd., 2018a; b; Janssen Inc., 2018; Lundin et al., 2002).

Administration

Because good administration technique can reduce the incidence of SC-ARRs, nurses play a critical role in the success of SC therapy (Martin et al., 2015). Injection sites vary by product (Table 1) but should, if possible, be rotated. Subsequent injections should be given at least 2.5 cm from the previous site. Avoid injecting into skin that is red, bruised, tender, hard, or where there are moles, scars or birthmarks. Any other SC medications should be injected at a different site (Hoffmann-La Roche Ltd., 2018a; b; Janssen Inc., 2018).

Bringing syringes to room temperature can reduce viscosity and facilitate injection (MacDonald et al., 2017). Attaching a fresh needle prior...
to injection avoids leaving an irritating injection track of drug (Martin et al., 2015). When using longer needles (> 1/4 inch), injecting at a 45o angle into the skin fold can prevent intramuscular injection (Kurtin et al., 2012; Martin et al., 2015). Select a needle gauge of 25 or 27 to align with that used in clinical trials; do not use a larger gauge for larger volumes (Carlson et al., 2015; MacDonald et al., 2017). Slower rates of SC injection reduce ARRs experienced by patients (Martin et al., 2015).

Another technique to reduce SC-ARRs is the use of an air-sandwich within the syringe (Figure 1) (Kurtin et al., 2012). Pulling air into the needle, followed by drug, followed by air into the bottom of the syringe barrel effectively seals in the medication and prevents leakage (Kurtin et al., 2012; Martin et al., 2015). Consider implementing the air sandwich for all SC injections to standardize the approach.

### Table 1. Key features of and considerations for oncologic SC targeted therapies

<table>
<thead>
<tr>
<th></th>
<th>Alemtuzumab* (Lundin et al., 2002; Stilgenbauer et al., 2009)</th>
<th>Bortezomib (Janssen Inc., 2018)</th>
<th>Rituximab (Hoffmann-La Roche Ltd., 2018b)</th>
<th>Trastuzumab (Hoffmann-La Roche Ltd., 2018a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Off-label: CLL</td>
<td>MM and MCL</td>
<td>NHL and CLL</td>
<td>HER2+ BC</td>
</tr>
<tr>
<td>SC formulation</td>
<td>Off-label: 30 mg vial for IV injection</td>
<td>Single-use vial, for reconstitution: 3.5 mg</td>
<td>Single-dose vials, ready to use: 1400 mg and 1600 mg‡</td>
<td>Single-dose vial, ready to use: 600 mg‡</td>
</tr>
<tr>
<td>SC dose</td>
<td>Fixed, following initial escalation</td>
<td>Variable, based on body surface area†</td>
<td>Fixed, following successful IV administration</td>
<td>Fixed, no loading dose required</td>
</tr>
<tr>
<td>Stability in syringe</td>
<td>Not reported</td>
<td>8 hrs at 25°C in normal indoor lighting</td>
<td>48 hrs at 2-8°C, then 8 hrs at 30°C in diffused daylight</td>
<td>48 hrs at 2-8°C, then 6 hrs at ambient temperature in diffused daylight</td>
</tr>
<tr>
<td>Duration of SC injection</td>
<td>Not reported</td>
<td>Not specified; Survey: majority 3-10 sec/mL (Martin et al., 2015)</td>
<td>5 to 7 min</td>
<td>2 to 5 min</td>
</tr>
<tr>
<td>Volume of SC injection</td>
<td>≤ 1 mL</td>
<td>Average &lt;1 mL (Martin, 2013)</td>
<td>11.7-13.4 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>Site of SC injection</td>
<td>Thigh Abdomen (BC Cancer Agency, 2015)</td>
<td>Thigh Abdomen</td>
<td>Abdomen</td>
<td>Thigh (Möbus et al., 2018)</td>
</tr>
</tbody>
</table>

*SC use is not approved (Sanofi Genzyme, 2018); refer to local guidelines for common use
†different concentration than IV
‡contains rHuPH20

### Table 2. Patient counselling points for SC targeted therapy. (BC Cancer Agency, 2015; Carlson et al, 2015; Kurtin et al, 2012; MacDonald et al, 2017)

**Pre-Administration**
- Reinforce treatment decisions
- Review differences versus IV
- Review any pre-medications
- Prepare for injection: avoid lotions and wear non-restrictive clothing that allows access to the injection site.

**Administration**
- Remind patient about injection duration
- Make conversation to reduce anxiety

**Post-Administration**
- Avoid friction to the site and monitor daily
- Show visuals of potential skin reactions
- Most resolve in 1-2 days; report to oncology healthcare team if not resolving
- Topical steroid and/or cool compress may be used after 4 hours
- Acetaminophen or anti-histamine for mild reactions
- Inform patient when to contact physician or visit emergency
- Review any unreported reactions before next injection
In the event of pain during administration, the injection can be paused; keep the needle in place, check placement, and consult colleagues before removing, repositioning, or resuming (MacDonald et al., 2017). If interrupted, administration should be restarted at another location (Carlson et al., 2015).

Medications containing hyaluronidase can be more difficult to push and, given the duration of injection, the patient and nurse should be positioned properly. With consideration to privacy, the patient should be comfortable and the injection site accessible, while the nurse sits with a straight posture and feet flat on the floor. The nurse should apply even pressure and push the syringe using the palm of his/her hand. While using a butterfly needle can increase space between the patient and nurse, and improve ergonomics, this has not been investigated in clinical trials and care is advised to ensure the full dose is administered (Carlson et al., 2015; MacDonald et al., 2017). For trastuzumab, an injection device has been trialled but not marketed, and the use of others may be cost restrictive (De Cock et al., 2016; Pivot et al., 2017).

Post-administration

Once complete, the site can be covered and the patient observed (Carlson et al., 2015). A small case series reported the efficacy of topical evening primrose oil in alleviating SC-ARRs (Platzbecker et al., 2010). Serious ARRs can be treated with an analgesic/antipyretic or antihistamine (Hoffmann-La Roche Ltd., 2018a). Patients should be counselled on how to manage reactions including what, when, and to whom to report (Table 2).

CHANGE MANAGEMENT

For successful integration of SC therapies into the clinic, it is important to recognize common reasons for failure in change implementation and proactively consider remedies (Barrow & Toney-Butler, 2019; Davidson, 2015).

1. Planning: Create a working group to review all functions, systems and processes that may be impacted by the change, including: order entry (paper or computerized), medication storage, medication preparation/dosing, scheduling, clinical protocols, and supportive educational materials (Dent et al., 2019; Martin et al., 2015).
2. Motivation: Ensure all staff are aware of the personal, patient, and system benefits of switching SC: chemotherapy and clinic nurses, administrative staff, pharmacists, pharmacy technicians, and all physicians (including inpatient). Proactively address concerns regarding capacity shifts and occupational health. Consider sharing motivators of change such as practice or clinical guidelines, best practices from other centres, or patient experiences (Martin et al., 2015).
3. Communication: Develop a cross-functional team to guide the vision, solicit feedback, and keep all stakeholders informed. Educate and train each stakeholder, including patients, with practical information relevant to their role.
4. Change frequency: Consider what amount of change is tolerable. Ease transitions by identifying barriers and implementing solutions.

CONCLUSION

Understanding the key considerations for administration and using effective change management techniques can help the healthcare team maximize the benefits and minimize the challenges associated with integrating SC targeted therapies into clinical practice.

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